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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 7, 2008

MEMORANDUM

SUBJECT: Ethics Review of Reports of Completed Carroll-Loye Field Mosquito Repellent Efficacy Studies SCI-001.4 and SCI-001.5

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

TO: Marion Johnson, Chief
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REF: Carroll, S. (2007) Test of Dermaegis LipoDEET 302 Personal Insect Repellent: EPA Reg. #82810-1. Unpublished study prepared by Carroll-Loye Biological Research under Project No. SCI-001.4. 180 p. (MRID 47323501)

Carroll, S. (2007) Test of Coulston's Duranon Personal Insect Repellent (EPA Reg. #50404-8). Unpublished study prepared by Carroll-Loye Biological Research under Project No. SCI-001.5. 180 p. (MRID 47322401)

Carroll, S. (2008) Letter of 3/5/2008 to John M. Carley transmitting supplemental correspondence between Carroll-Loye Biological Research and Independent Investigational Review Board, Inc., concerning SCI-001, with enclosures. 27 p.

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced documents, which describe the re-execution of Carroll-Loye protocol SCI-001, using two of the original four test repellents.

The protocol SCI-001 was reviewed favorably by the Human Studies Review Board at its meeting in January 2007, and initially executed in July 2007. Reports of the initial execution were submitted to EPA and reviewed unfavorably by the Human Studies Review Board at its meeting on October 25, 2007, because potentially significant amendments had been made to the protocol without prior review and approval by the IRB. Just before that meeting, on October 24,

the Principal Investigator notified the IRB of deviations in the July field studies. Just after the HSRB meeting the Principal Investigator provided to the IRB a progress report, submitted the two amendments implemented on July 2, and requested approval of a further amendment to permit re-execution of the protocol using only two test repellents. All three amendments and an appropriately revised consent form were approved by the IRB on November 6, 2007, and the protocol was re-executed between November 7 and 11.

I have reviewed the two separately submitted reports of SCI-001 as a single study. The study reports are closely similar, reporting a single execution of the protocol with two test repellents at each of two field sites.

Scope of Review:

This review reflects consideration of the two separate sub-study reports cited above, and the following additional documents:

- EPA's protocol review of December 20, 2006
- The HSRB's April 16 report of its January 2007 discussion of SCI-001
- The March 5, 2008 letter from Scott Carroll of Carroll-Loye Biological Research to EPA, transmitting supplemental records of correspondence between C-LBR and the Independent Investigational Review Board, Inc., and the final Consent Form as approved by IIRB on November 6, 2007.

Completeness of Submission:

Most of the 180 pages in each of the two sub-study reports are duplicative. I have highlighted below where the information unique to each sub-study can be found.

With the exception of the title, pages 1-5 of both volumes are identical. The content of the Information Summary and "Testing Materials and Methods" on pp. 6-11 differs only where the test material is named (paragraph 3 and Table 1 on p. 6, two references to the test material on p. 9, and one reference to the test material on p. 10.) The content in the sections headed "Test Results" and "Summary and Conclusions" on pages 12-17 is repellent-specific. Table 1 on the following page shows how the appendices of the two reports differ.

The two study reports as submitted do not include the final consent form approved by the IIRB on November 6, 2007 and used in the conduct of the research. Both reports include an incomplete record of correspondence between the investigators and the IIRB after the October 2007 HSRB meeting. In response to a request from EPA on February 26, Carroll-Loye Biological Research submitted on March 5 additional correspondence and the missing consent forms. The checklist used by EPA to verify satisfaction of the requirements of §26.1303 as they apply to the reports of SCI-001.4 and SCI-001.5 appears as Attachment 1 to this review.

Table 1
Content of Appendices to Study Reports SCI-001.4 and SCI-001.5

App No.	Content of Appendix	Pages	Comments
1	Subject Tracking Spreadsheets	18-20	P. 20 is same. P. 19 excludes subjects treated only with the other repellent
2	Dosimetry, Dosage and Treatment Allocation		
	2a. Dosimetry Data Spreadsheet	21-23	Repellent-specific; no overlap
	2b. Completed Dosimetry Data Capture Forms	24-34	Repellent-specific; no overlap
	2c. Completed Limb Measurement Forms	35-59	Overlaps, but each volume excludes subjects treated only with the other repellent
3	Treatment Allocation and Dosing	60-62	Identical
4	Efficacy		
	4a. Repellency Data Spreadsheet	63-64	Repellent-specific; no overlap
	4b. Completed Repellency Data Capture Forms	65-69	Identical
5	Environmental Records	70-72	Identical
6	Mosquito Identifications and Viral Assays	73-74	Identical
7	Study Protocol SCI-001 and Informed Consent		
	7a. Study Protocol SCI-001	76-129	Identical. Protocol of 12/29/06 approved by IIRB 1/2/07, corrected CF 1/22/07, as reviewed by HSRB in Jan 07
	7b. Amendments to Protocol SCI-001		
	1(c) to re-execute with only 2 materials	131	Identical; amendment dated 11/2/07
	1(b) to change test materials	132	Identical; amendment dated 7/2/07
	1(a) to add viral assay	133	Identical; amendment dated 7/2/07
	7c. IRB Approvals, Informed Consent Form		
	11/6/07 approval of progress report	135	Identical
	11/6/07 approval of amendment 1(c) and revised consent form	136	Identical
	10/30/07 approval of amendments 1(a), (b) and protocol deviations	137	Identical
	7d. Deviations from the Protocol & their Consequences	139	Identical
	7e. Correspondence with IRB	141-143	Identical
8	Additional Protocol Materials:		
	Label/MSDS Insect-Guard II	145-149	Identical (and irrelevant)
	Label/MSDS Duranon	150-157	Identical
	Label/MSDS LipoDEET 302	158-166	Identical
	Label/MSDS Ultrathon	167-178	Identical (and irrelevant)
9	Physical plan of Carroll-Loye Laboratory	179-180	Identical

Protocol Deviations

Three deviations from the protocol are reported on p. 139 in both sub-studies:

- With the Study Director's consent, subjects did not always cover treated limbs between exposures when it was straightforward to avoid mosquitoes in the interim periods by entering the screen house.

  I concur with the Study Director that "this deviation probably reduced abrasion of the Test Materials by the coveralls, without significantly increasing the risk of biting from mosquitoes."

- During dosimetry, the stipulated number of practice applications quickly proved excessive, and so was reduced from two to one or zero for most subjects.

  I concur with the Study Director that "subject exposure to the insect repellent was reduced, and the quality of the data set is not seriously affected."

- To reduce the risk of artificially truncating data records as has occurred in prior efficacy tests, the Study Director scheduled treatment applications *before* subjects went to the field.

  The Study Director comments that "subjects were transported for 150-180 minutes before initial exposure, during which time they were instructed to remain vigilant about avoiding abrasion of their treated surfaces. Subjects were protected from LIBes until, at a minimum, the twenty-second exposure after initiation. The prolonged delay in LIBes after initial exposure suggests that the data records accurately represent the temporal distribution of protection." I take no exception to these comments, but note the unacknowledged inconsistency of this choice with the statement in the consent form that the first field exposure would occur "approximately 15 minutes after you have had the test repellent applied."

Events similar to all three reported deviations have occurred in previous similar studies conducted by Carroll-Loye Biological Research, and provision for these changes should be incorporated into future protocols.

Field trials were conducted on consecutive days (November 10-11) using many of the same subjects on both days. Consistent with the interpretation discussed at the October 2007 HSRB meeting, I do not consider participation by the same subjects on consecutive days to imply a deviation from the exclusion criterion that disallows use of insect repellent "within one day preceding the study" (protocol §9.1.3.5, p. 92 in each volume) or "within a day prior to the start of the study" (11/6/07 consent form, p. 6 of 10, in supplement of 3/5/08).

Analysis by Subject Number

Both sub-study reports include on p. 20 a spreadsheet tracking by individual subject all key events in the re-execution of SCI-001. This spreadsheet confirms the accuracy of this statement from p. 8 in each study report:

> Females were negative in pregnancy tests conducted immediately before dosimetry or, if they did not participate in dosimetry, immediately before they participated in efficacy testing, and stated that they were not lactating.

From the spreadsheet it is apparent that:

- Two female subjects participated in dosimetry testing. Subject 38 was tested for pregnancy on Day 1 and participated in dosimetry testing on Day 1; she did not participate further in the study. Subject 50 was tested for pregnancy on Day 2 and participated in dosimetry testing on Day 2; she also participated in field testing on both Days 4 and 5, but was not re-tested for pregnancy after Day 2.

- Four female subjects (7, 20, 37, and 59) participated in repellent testing on only one day and were tested for pregnancy on the same day. None of these subjects were tested for pregnancy on the day of their first visit for orientation and limb measurement.

- Six female subjects (1, 39, 49, 53, 65, and 75) were tested for pregnancy on day 4, and participated in repellent testing on both days 4 and 5, without additional pregnancy tests on day 5. None were tested for pregnancy on the day of their first visit for orientation and limb measurement.

No female subject was tested for pregnancy more than once. Five were tested on the only day they participated; six were tested on the first of two consecutive days on which they participated; one was tested on her first day of participation, and participated further two and three days later.

The discussions of timing of pregnancy testing in the protocol and consent form are unclear. The protocol excludes female candidates known to be pregnant or lactating, and states in §9.1.3.7 that "pregnancy will be self-checked by each female volunteer ***on the morning of the repellent test***." Since exposure to repellents was involved in both the dosimetry and repellency phases of the research, this could be interpreted to mean any or all of the days of participation in the test.

The consent form tells candidates "If you are a female, you will perform a pregnancy test . . . ***in the morning prior to the start of each of the two study visits***." These two study visits are described elsewhere in the consent form as "Visit 1 for Orientation and determining Dosage" and "Visit 2 for the Field Test against Mosquitoes". Ten of the twelve female subjects did not participate in dosimetry testing, and were not tested for pregnancy during their initial orientation and training visit to the laboratory.

Female subjects were checked for pregnancy only once, either before they participated in dosimetry or before their first day of field testing. Testing before dosimetry may be inconsistent with the protocol (although there is little reason to test before taking limb measurements and learning to use an aspirator.) Testing only before visit 1 without retesting on the day of field testing (visit 2) is inconsistent with the consent form. Testing only on the first day of field testing, but not on the initial visit to the laboratory is also inconsistent with the consent form.

These discrepancies in wording among the protocol, the consent form, and the study reports are not indicative of a substantive problem. The Investigator exercised due diligence in trying to ensure that pregnant females were not enrolled as subjects in the research. Future protocols and consent forms, however, should be crafted to be both consistent with each other and unambiguous concerning when pregnancy testing will be conducted.

Applicable Ethical Standards

Both sub-studies were initiated after April 7, 2006, so 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 provide the protocol to the HSRB for review. Suggestions made in EPA and HSRB reviews, and the investigator's response to them, are noted for each protocol below.

EPA and HSRB Comments in Prior Reviews of SCI-001

EPA noted the following ethical deficiencies in its December 20, 2006 review of SCI-001:

- The protocol does not describe how the "experienced" subjects who will serve as untreated controls 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.

  No changes were made in the SCI-001 protocol or consent document in response to this comment before initial execution in July 2007 or before re-execution in November 2007.

- Risks from exposure to the test materials themselves are mischaracterized in the Informed Consent Form, which refers to test materials intended for spray application and containing alcohol. This passage must be replaced by a description of the risks associated with exposure to the test materials—all of which are lotions not containing alcohol.

  This was corrected in the consent form approved by IIRB on January 2, 2007, corrected by IIRB January 22, 2007, and further revised in November 2007 and approved by IIRB on November 6, 2007.

- Either a revised Informed Consent Form covering both the untreated and treated subjects, or a separate form for the untreated controls, must be provided and approved by the IRB.

This was satisfactorily addressed in the consent form revised subsequent to EPA review, approved by IIRB January 2, 2007, corrected by IIRB January 22, 2007, and further revised in November 2007 and approved by IIRB on November 6, 2007.

In its April 16, 2007, final report of the January 24, 2007 meeting, the HSRB stated its concurrence with EPA's finding that if protocol SCI-001 were revised as suggested by EPA and the HSRB it would meet the applicable ethical requirements of 40 CFR 26 subparts K and L. The HSRB report also included the following specific suggestions:

- The investigator should collect mosquitoes during the field studies and subject them to serologic or molecular analysis to confirm absence of known pathogens.

  The protocol was amended on July 2, 2007 to incorporate viral assay of field-collected mosquitoes. This amendment was sent to IIRB on October 30, 2007, and approved on November 6, 2007.

- The protocol should clarify how untreated controls will be recruited.

  The protocol has not been changed in response to this comment..

- The informed-consent document (1) mischaracterizes the test materials as containing alcohol; (2) is structured so it doesn't apply to untreated control subjects; and (3) should say "up to 48 (10 exposed and 2 controls per arm of the study)" subjects will participate.

  Point (1) was corrected in the January 2, 2007 consent form. Point (2) was addressed by the January 2, 2007 consent form, which applied to both treated and untreated subjects. Changes to the consent form approved by IIRB November 6, 2007 did not affect this point. The consent document was not changed to address point (3); the actual number of participants in July was 37-41 subjects (37 uniquely identified by number; up to 4 more served as untreated controls on July 8 and 14, but were identified only by function). The actual number of participants in the November re-execution was 29.

- It is difficult to assess qualifications of IIRB; the Board would like to see some evidence of member training, IIRB accreditation, etc.

  No additional information about IIRB member qualifications or IIRB accreditation has been provided.

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 both EPA and HSRB calling for clarification of how "experienced subjects" would be recruited to serve as untreated controls were not implemented by changes to either the protocol or consent form after the January 2007 HSRB discussion.

  The HSRB comment that the consent form should be changed to project up to 48 subjects was not implemented. The actual number of subjects participating in the November re-execution of SCI-001 was 29.

  Other comments by EPA and HSRB were addressed responsively.

- *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 third-party research.

  The information provided meets the regulatory standards for completeness, and is adequate to support a determination that the research was conducted in substantial 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 requirement of 40 CFR §26 subpart M to document the ethical conduct of research involving human subjects has been met for SCI-001.4 and SCI-001.5.

- *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 both studies.

Conclusions

These studies report research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L, and meet all applicable ethical standards for the protection of human subjects of research. There is no regulatory barrier to EPA's reliance on them in actions under FIFRA or §408 of FFDCA.

Attachment 1: §26.1303 completeness check for SCI-001.4 and SCI-001.5

§26.1303 Submission of Completed Human Research for EPA Review
SCI-001.4 (MRID 47322501) and SCI-001.5 (MRID 47322401) and Supplement of 3/5/08

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. 131-133; progress report and approved Consent Forms in supplement. No reports of injuries to subjects
	§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	Initially satisfied with protocol submission; minutes of subsequent IIRB discussions of SCI-001 on 10/30 and 11/06 not provided.
	§1115(a)(3): Records of continuing review activities.		Y	IIRB request p. 141; CLBR response in supplement; IIRB approval p. 135.
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	pp. 141-143 and supplement
	§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	Satisfied with protocol submission
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	Satisfied with protocol submission
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Satisfied with protocol submission
		(5) The balance of risks and benefits of the proposed research.	Y	Satisfied with protocol submission
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	In protocol submission and supplement
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	Satisfied with protocol submission
	§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 with protocol submission
	§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. Final approvals pp. 135-137
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	Supplement
(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	