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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

December 19, 2006

MEMORANDUM

SUBJECT: Ethics Review of EMD-004 Reports of Completed Efficacy Studies for Mosquito Repellents Containing IR-3535

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

TO: Linda Hollis, Chief
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

REF: Carroll, S. (2006) Test of Personal Insect Repellents (Lotion). Unpublished study conducted by Carroll-Loye Biological Research under Project No. EMD-004.1. 143 p. (MRID 46979003)

Carroll, S. (2006) Test of Personal Insect Repellents (Pump Spray). Unpublished study conducted by Carroll-Loye Biological Research under Project No. EMD-004.2. 140 p. (MRID 46979004)

Carroll, S. (2006) Test of Personal Insect Repellents: Study EMD-004.1: Replacement for MRID 46979003. Unpublished study conducted by Carroll-Loye Biological Research under Project No. EMD-004.1. 134 p. (MRID 47007703)

Carroll, S. (2006) Test of Personal Insect Repellents Study EMD-004.2: Replacement for MRID 46979004. Unpublished study conducted by Carroll-Loye Biological Research under Project No. EMD-004.2. 135 p. (MRID 47007704)

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced documents, which describe a single execution of the protocol EMD-004, a field test of the efficacy of IR-3535 formulations in repelling mosquitoes.

Background

After its first review and approval by the cognizant IRB, the Independent Investigational Review Board (IIRB) of Plantation FL, this protocol was initially submitted to EPA by Carroll-Loye Biological Research in the Spring of 2006. Both EPA and the HSRB found the protocol to require significant revision before it could be approved. Following the HSRB discussion of EMD-003 in June, 2006, the Principal Investigator, Dr. Scott Carroll, revised it substantially, resubmitted it to the IIRB (who approved it again) and resubmitted it to EPA. After this revision EPA found the protocol to meet all ethical requirements of 40 CFR 26 subparts K and L. The HSRB reconsidered EMD-003 at its October 2006 meeting, and concurred with EPA's assessment, with one suggestion, discussed below.

As reviewed, the protocol called for testing three different formulations of the repellent ingredient IR-3535: a lotion, a pump spray, and an aerosol. Testing of all three formulations was initiated on October 23, 2006. An error in formulation of the aerosol was discovered, however, that led to cancellation of testing of the aerosol, and to removal of the blind for the Principal Investigator. The documents within the scope of this review address only the lotion and pump spray formulations. Although a reformulated aerosol has subsequently been tested, the reports of that research arrived at EPA only on December 13, too late to be considered in this review.

Scope of Review

Reports of testing of the lotion and pump spray formulations were initially submitted to EPA by the sponsor, EMD Chemicals, Inc., on November 9, 2006. A separate report was submitted for each formulation tested, notwithstanding that the protocol had called for testing multiple formulations. After an exchange of Email with the EPA science reviewer, both reports were revised, and EMD Chemicals, Inc., submitted replacements for the original reports to EPA on December 15, 2006. The revised submission provided little new information relevant to this ethics review.

This review covers both the original and revised submissions of the reports of executing protocol EMD-003 with the lotion and pump spray formulations. The following specific documents were considered:

- Initial study submissions of November 9, 2006: MRIDs 46979003 and 46979004
- Revised study submissions of December 15, 2006: MRIDs 47007703 and 47007704
- EPA's Protocol Review of September 15, 2006

  Carley, J., and Fuentes, C. (2006) Science and Ethics Review of Protocol for Human Study of Mosquito Repellent Performance. Memorandum to Sheryl Reilly dated 9/15/2006. 13 p.

- Final Draft Report of October 18-19, 2006 Meeting of the Human Studies Review Board

Completeness of Submissions

The standard of completeness for documenting ethical conduct of completed research submitted to EPA under the pesticide laws is defined by 40 CFR §26.1303. This passage tracks closely to the standard for documenting protocols, but requires only submission of materials "not previously provided to EPA." Most of the requirements of this regulation were satisfactorily addressed at the time of protocol submission, and need not be addressed again.

The completed studies, however, are not accompanied by a record of correspondence between the sponsors or investigators and the IIRB after the October HSRB meeting, or an explanation for its absence. Since revisions were made to both the protocol and the Informed Consent Material after the HSRB meeting, reconsideration by the IIRB was required. In addition, the discovery of the mis-formulated aerosol and the decision to abort that part of the research should also have been reported to the IRB. Absent records of this correspondence it is hard to reconstruct the exact sequence of events. The IRB approval letter, dated November 1, 2006, cites two additional documents: a "Site letter" of 10/30/06, and an Informed Consent Form version of 10/24/06. Neither is provided.

Section 26.1303(c) requires "[c]opies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research." While the study reports do contain copies of the Informed Consent Document as approved by the IIRB on November 1, it is not clear what records were actually used to document subject consent, since data collection in both the dosimetry and repellency phases of the research had been completed before the date of IIRB approval of the ICF included in the report. The approval letter states "[a]ll current subjects and future volunteers must sign the revised consent form." Although the study reports state "[s]ubjects . . . signed the IRB approved Informed Consent Form," it is not reported which generation of the approved form was signed, or how many generations of the form were signed, or when they were signed.

The checklist used by EPA to verify satisfaction of the requirements of §26.1303 appears as Attachment 1 to this memorandum.

Protocol Deviations

Several minor deviations from the protocol are reported in Appendix 5. None affected the integrity of the research or the safety of the subjects.

Although it was not reported as a deviation from the protocol, data collection was initiated before either QA review of the protocol or IRB approval of the final round of changes to the protocol and Informed Consent Form. This is discussed further below.

Applicable Ethical Standards

Because this research 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 provide the protocol to the HSRB for review.

The final draft report of the October 18-19, 2006 HSRB meeting stated the Board's concurrence with EPA's finding that the protocol as revised met all ethical requirements of 40 CFR 26 subparts K and L, and made one specific suggestion:

- "Carroll-Loye Biological Research also may wish to designate a specific physician to be contacted in the event that any adverse side effects are seen."

Because this research 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 provide the protocol to the HSRB for review.

Because this research was conducted 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, Section 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 §26.1125 for prior submission of the protocol to EPA and of §26.1601 for HSRB review of the protocol were met.

- Revisions to the protocol and Informed Consent Form.

  Subsequent to the October 18 HSRB discussion of this protocol the Investigator expanded the discussion of "Research Related Injuries" in the Informed Consent Form to note that in the event of an injury, "a consulting physician who is aware of the study will be contacted immediately by telephone." In addition, changes were made to the protocol itself responsive to the Board's discussion.

  The revised protocol and Informed Consent Form were submitted to the Independent Investigational Review Board as proposed changes to previously approved research, probably on October 24, and approved, apparently after submission of additional information (the "Site letter of 10/30") to IIRB, on November 1.

  The procedures of the IIRB governing "Modifications of Ongoing Research" require the investigator to report changes promptly, and to await Board approval before implementing modifications unless they are necessary to eliminate immediate hazards.

  The Carroll-Loye QA unit conducted its protocol review on October 26. The protocol (Section 13, Quality Assurance) states in pertinent part:

  > Protocol Review and Comments must take place before data collection commences.

  The dates on the data recording forms presented with the study reports show that the dosimetry phase of data collection was initiated on October 23, before either the IIRB approval of modifications and QA review of the revised protocol, and that the repellency testing phase of data collection was conducted on October 25 and November 1, spanning the date of QA review of the protocol, and ending on the date of IIRB approval of the modifications to the protocol and Informed Consent Form.

- Ban on research involving pregnant or nursing women or children

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

- Compliance with 40 CFR 26 subparts A through L

  Section 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.

  As is noted above, data collection for this research was both initiated and completed by the date of IIRB approval of the final round of changes in the protocol and Informed Consent Form. Subpart K, §26.1108(a)(4), reads in pertinent part:

  > In order to fulfill the requirements of this subpart each IRB shall:
  >
  > (a) Follow written procedures:

(4) For ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

The procedures of the IIRB, cited above, were not effective in ensuring that changes in approved research were not initiated without IRB review and approval. In this case the changes were not necessary to eliminate apparent immediate hazards to subjects. They had at most a very minor effect on the quality of information provided to subjects, or on the safety of the subjects.

The failure to submit full documentation of correspondence between the IIRB and the investigator following the October HSRB meeting, or to submit the Site letter of 10/30/06 and the Informed Consent Form version of 10/24/06 cited in the IIRB approval letter, falls short of the requirement of §26.1303(b), and by reference of §26.1125(e).

- 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.

Conclusion

I find this study to meet most applicable ethical standards for the protection of human subjects of research, but I am concerned by the gaps in the required documentation and the investigator's both initiating the research before receiving IIRB approval and his failure to acknowledge doing so in the reports of the research. These deficiencies represent at least "technical noncompliance" with the cited passages of subpart K. I defer to the HSRB for their advice on whether the available evidence constitutes "adequate information to determine that the research was conducted in substantial compliance" with subparts K and L.

Attachment: §26.1303 completeness check

§ 26.1303 Submission of Completed Human Research for EPA Review
EMD-004.1 and EMD-004.2
MRIDs 46979003/04 and 47007703/04

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	Satisfied with protocol submission
	§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	Satisfied with protocol submission
	§1115(a)(3): Records of continuing review activities.		n/a	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		N	Correspondence since October HSRB meeting not provided
	§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	Satisfied with protocol submission
	§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	Satisfied with protocol submission
	§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.		N	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	Final approval reported in MRID 46979003 p. 70
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			N	MRID 46979003 pp. 71-79 shows ICF approved 11/1; data collection began 10/23. Unclear what ICF was actually used.
(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	No explanation of missing elements