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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

***September 29, 2011***

**MEMORANDUM**

**SUBJECT:** Ethics Review of Completed Carroll-Loye Mosquito Repellent Field Efficacy Study No Mas 003

**FROM:** Kelly Sherman
Human Research Ethics Review Officer
Office of the Director
Office of Pesticide Programs

**TO:** Linda Hollis, Chief
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs

**REF:** Carroll, S. (2011) Field Efficacy Test of a PMD and Lemongrass oil-Based Repellent 'No Mas' Against Mosquitoes. Unpublished study prepared by Carroll-Loye Biological Research under Project No. No Mas 003. 411p. (MRID 48577201)

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 No Mas 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 No Mas 003 was initially submitted to EPA for review in August 2010. The protocol and EPA's review dated October 1, 2010, were discussed by the HSRB on October 27, 2010. The HSRB concluded in its December 13, 2010, final report of the October meeting that "the protocol submitted for review, if modified in accordance

with Agency and HSRB recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."

Following HSRB review, the protocol and consent form were modified through Amendment 1 (dated November 15, 2010). This amendment incorporated changes responsive to the comments of EPA, HSRB, and the California Department of Pesticide Regulation (CDPR), as well as additional corrections initiated by the investigators and/or sponsor. The Independent Investigational Review Board, Inc. granted approval to Amendment 1 on November 16, 2010.

Because the study was to be conducted in California, CDPR approval was also required before the study could be initiated. CDPR granted final approval of the amended protocol and supporting documents on March 21, 2011.

A total of 32 subjects participated in the study. They were selected randomly from a pool of 92 subjects. Ten subjects participated in the dosimetry determination phase, which was conducted on July 5-7, 2011, at the Arthropod Behavior Laboratory of Carroll-Loye Biological Research. A total of 22 subjects participated in the field testing at one or both of the study sites. Six subjects were enrolled as alternates. Details about subject participation in each of the phases of the research are provided on p. 27 of the study report.

Subjects were enrolled between July 1 and July 24, 2011, and the field research was conducted on July 23-24, 2011, at two field sites in the Central Valley of California (Glenn County and Butte County). The field sites were chosen to represent different habitat types and based on mosquito and virus surveillance data compiled weekly by the California State Department of Public Health.

At each site, ten subjects – five female and five male – exposed a treated limb (arm at Site 1; leg at Site 2) to mosquitoes for one minute every 15 minutes, until product failure or cessation of the test. At the same time, one male and one female untreated control subject exposed their arm (Site 1) or leg (Site 2) in the same manner, in order to assess mosquito biting pressure.

The study report was completed on August 14, 2011, and submitted to EPA on August 15, 2011. A full chronology appears as Attachment 2 to this review.

**Completeness of Submission:**

The checklist used by EPA to verify satisfaction of the requirements of §26.1303 as they apply to the report of No Mas 003 appears as Attachment 1 to this review. All requirements of §26.1303 were satisfactorily addressed.

CLBR should take care in future studies to have better document version control. The final version of the protocol, which was approved by IIRB on 11/16/10, bears the date 7/15/10, although it should have been re-dated before it was re-submitted to IIRB.

**Protocol Deviation:**

One deviation from the amended protocol is reported on p. 157-159: the laboratory manager reformatted the lotion dosimetry data form to match data entry format prior to data gathering to reduce data entry error and the time involved in proofing data entry. This format change was not reported to IIRB prior to the form being used by the researchers. I agree with the investigator that this deviation had no effect on data quality or subject safety. I did not note any unreported deviations in my review of the study report.

**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*

The protocol for this study received favorable reviews from EPA and the HSRB in 2010. EPA concluded in its review dated October 1, 2010, that the protocol described research that, if conducted as proposed, would comply with the applicable ethics standards in 40 CFR 26 and FIFRA 12(a)(2)(P). The HSRB concluded in its December 13, 2010, final report that "the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."

*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 and/or HSRB Ethics-Related Comments | Addressed prior to initiation of the study? |
|---|---|
| 1. Exclude as permissible subjects employees of the sponsor. | **Yes** (p. 107, 127, 138) |
| 2. Add "child/minor" to the list of exclusion criteria. | **No.** However, there is an inclusion criterion in the protocol and a statement in the "Subject Selection" section of the consent form that specify that subjects must be between 18-55 years old. (pp. 106, 127, 138) |
| 3. The term "treatment" is used ambiguously throughout the protocol and informed consent form to describe both the application of the test materials and treatment for research-related injuries. Resolve this ambiguity through the use of a different term to describe the application of test materials. | Y**es** |
| 4. Modify the protocol to use more direct phrasing such as "Researchers may obtain informed consent from dosimetry subjects before repellency subjects" rather than "dosimetry subjects may be consented before repellency subjects. Untreated control subjects for the repellency phase (field study) are consented before the treated subjects for that phase…" | **Yes** (p. 108) |
| 5. Carroll-Loye should spell out the acronym "PMD" when it is first used in the protocol and consent form. | **No** (pp. 97, 126, 137) |
| 6. On page 2 of the consent form, the phrase "You have been offered an opportunity to participate in this research study because …" should be modified to be more neutral. An alternative might be: "We are asking you to participate in this research study because…" | **Yes** (pp. 126, 137) |
| 7. Add a description of the symptoms of heat stress and equine encephalitis to the consent form. | **Yes** (pp. 131-2, 143-4) |

- *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.

No deviations were reported or noted during my review. 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 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 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 No Mas 003
Attachment 2: Chronology of No Mas 003

## § 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
## CLBR Study No. No Mas 003: MRID 48577201

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<br>• all research proposals reviewed,<br>• scientific evaluations, if any, that accompany the proposals,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | Y<br>n/a<br>Y<br>Y | Initially addressed in protocol; Amendment 1 p. 362<br>Final approved CFs pp. 126, 137, 149<br>Progress Report p. 400 |
| | §1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution. | | Y | Minutes of IIRB review of Amendment 1 p. 410 |
| | §1115(a)(3): Records of continuing review activities. | | Y | pp. 398-408 |
| | §1115(a)(4): Copies of all correspondence between the IRB and the investigators. | | Y | pp. 274-411 |
| | §1115(a)(5):<br>• 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;<br>• 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 | Provided separately to EPA |
| | §1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b). | | Y | Provided separately 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 | Addressed in protocol, p. 97-102 |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | Addressed in protocol, p. 97-102 |
| | | (3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue; | Y | Addressed in protocol, p. 102 |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | Addressed in protocol, p. 97 |
| | | (5) The balance of risks and benefits of the proposed research. | Y | Addressed in protocol, p. 102 |
| | §1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB. | | Y | Original CFs: provided in protocol submission<br>Final approved CFs pp. 126-156 |
| | §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 | pp. 274-411 |
| | §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 Amdmt 1: p. 363 |
| (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. 126-156 |
| (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 No Mas 003 Completed Study

| | |
|---|---|
| 7/15/10 | Date of protocol submitted for EPA and HSRB review |
| 7/20/10 | Initial IIRB, Inc. protocol approval |
| 10/01/10 | Date of EPA science and ethics protocol review |
| 10/27/10 | HSRB protocol discussion |
| 12/13/10 | Final report of HSRB protocol review |
| 11/15/10 | Amendment 1 submitted<br>• Adjusts wording in the protocol and consent form, including but not limited to replacing the term "compensation" replaced with term "payment" as required by CDPR, replacing the words "treatment" and "treated," and replacing the terms "opportunity" and "consented"<br>• Corrects drafting errors noted by EPA and the HSRB<br>• Provides additional justification for the chose sample size and discussion of the data analysis approach<br>• Complete details are provided in the final report, pp. 309-362 |
| 11/16/10 | IIRB Approval of Amendment 1 |
| 3/21/11 | CDPR Final Approval of Protocol with Amendment 1 |
| 7/01/11 | First subject enrolled (Experimental Start Date) |
| 7/01/11 – 7/07/11 | Subject enrollment for dose determination phase |
| 7/05/11 - 7/07/11 | Dose determination testing |
| 7/01/11 – 7/18/11 | Subject enrollment for field efficacy phase |
| 7/07/11 | CLBR progress report submitted to IIRB |
| 7/13/11 | IIRB approves renewal for one year |
| 7/23/11 & 7/24/11 | Efficacy Field Testing |
| 7/08/11 | Protocol Deviation Report |
| 8/14/11 | Study Completion Date |
| 8/16/11 | Study Submission Date |