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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

December 20, 2006

MEMORANDUM

Subject: Transmission of materials for review by the Human Studies Review Board.

To: Paul Lewis, Ph.D.
Designated Federal Officer
Human Studies Review Board
Office of Science Advisor (8105R)

From: William L. Jordan
Senior Policy Adviser
Office of Pesticide Programs (7501P)

This memorandum transmits the materials for review by the Agency's Human Studies Review Board (HSRB or Board) at the meeting scheduled for January 24, 2007. This meeting will address scientific and ethical issues surrounding:

- Two completed human studies, evaluating repellent efficacy of formulations containing the active ingredient IR3535. One is a laboratory study with ticks (EMD-003); the other is a field study with mosquitoes (EMD-004). The Board reviewed favorably the revised protocols for these studies at its October 2006 meeting.

- A research proposal to evaluate the efficacy in the field of multiple formulations of the repellent DEET against mosquitoes.

Each of these topics is described more fully below.

A. Completed IR3535 Insect Repellent Efficacy Studies

Description. In its last two meetings the HSRB has reviewed and commented on materials relating to two insect repellent efficacy protocols from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. These two

protocols described proposed research to evaluate the efficacy of new formulations of repellent products containing the active ingredient IR-3535. The protocol identified as EMD-003 described a laboratory study of efficacy of the test formulations against ticks. The protocol identified as EMD-004 described a field study of efficacy of the test formulations against mosquitoes.

The HSRB offered extensive comments on the two protocols at its June 2006 meeting. Following that meeting, Dr. Carroll revised the protocols to address comments from the HSRB. EPA reviewed Dr. Carroll's revised protocols and concluded that they appeared likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L. When the HSRB reconsidered the revised protocols at its October 2006 meeting it concurred with EPA's assessment and suggested some minor additional refinements. Dr. Carroll proceeded to conduct the research and has submitted the results to EPA for review.

The Agency's regulation, 40 CFR §26.1602, requires EPA to seek HSRB review of an EPA decision to rely on the results of these studies. The sponsor has not yet submitted an application to register these products, but with Agency concurrence submitted the completed studies ahead of the applications so that HSRB review would not compromise EPA's ability to review the application within the time allowed by statute. The Agency expects to receive such an application in the near future. In order to facilitate timely review of the application, EPA has reviewed the studies, applying the standard in 40 CFR §26.1705. That provision states:

> **§ 26.1705 Prohibition on reliance on unethical research with non-pregnant, non-nursing adults conducted after April 7, 2006**
>
> Except as provided in §26.1706, in actions within the scope of § 26.1701, 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 . . . This prohibition is in addition to the prohibition in § 26.1703.

The Agency's reviews concluded that the data are scientifically sound and that the research was conducted in a manner that deviates at least technically from some of the requirements of subparts K and L of EPA's final rule establishing Protections for Subjects in Human Research—the only subparts of the rule which apply to third-party research. The Agency seeks the Board's advice on whether the available information supports a determination of "substantial compliance" with the applicable rules. Assuming a potential determination of substantial compliance, and because EPA would like to rely on these data to support an application for registration of these formulations, EPA is presenting these studies for review at the Board's January 2007 meeting

EPA is providing the following materials to the HSRB in the folder identified as “Insect Repellent Efficacy Studies EMD-003 and EMD-004”:

EMD-003 and EMD-004

a. Read this First: An annotated bibliography covering both study folders

b. MRID 46979000 Xmttl 11-9-06
The transmittal associated with the original submission of the four study reports to EPA on November 9. It explains why reports on the aerosol formulation were not included.

c. MRID 47007700 Xmttl 12-15-06
The transmittal associated with the resubmission of the four amended study reports on December 15. It summarizes the revisions made, and also cites the reports of retesting of the aerosol formulation, submitted separately on December 13.

d. E-mail Dec 18-19 Re Dates
E-mail exchange between John M. Carley (EPA) and Scott P. Carroll (Carroll-Loye) concerning discrepant dates in reports of EMD-003 and EMD-004, December 18-19, 2006

e. IRB_Corresp,_Rvsn_3
December 19 E-mail submission of 10/30 correspondence between Scott P. Carroll and Kim Lerner of IIRB transmitting revised protocol and Informed Consent Form for IIRB review.

EMD-003 (Tick repellency study)

a. EPA Review of EMD-003 protocol 9/15/06
The review provided to the HSRB for the October meeting.

b. Final Draft HSRB Report on EMD-003 protocol 12/8/06
The section of the final draft HSRB report addressing this protocol.

c. EMD-003.1 Lotion MRID 46979001
d. EMD-003.2 Pump Spray MRID 46979002
The original 11/9 submissions of the two reports for EMD-003

e. EMD-003 Science Rvw 12/14/06
This review addresses the initial reports for both formulations

f. EMD-003.1 Lotion Rvsd MRID 47007701
g. EMD-003.2 Pump Spray Rvsd MRID 47007702

The revised 12/15 submissions of the two reports for EMD-003, which arrived too late to be addressed in the EPA science review listed above.

h. EMD-003 Ethics Rvw 12/19/06
This review addresses both the initial and the revised submissions of the reports for both formulations

EMD-004 (Mosquito repellency study)

a. EPA Review of EMD-004 protocol 9/15/06
The review provided to the HSRB for the October meeting

b. Final Draft HSRB Report EMD-004 protocol 12/8/06
The section of the final draft HSRB report addressing this protocol.

c. EMD-004.1 Lotion MRID 46979003
d. EMD-004.2 Pump Spray MRID 46979004
The original 11/9 submissions of the two reports for EMD-003

e. EMD-004 Science Rvw 12/14/06
This review addresses the initial reports for both formulations

f. EMD-004.1 Lotion Rvsd MRID 47007703
g. EMD-004.2 Pump Spray MRID 47007704
The revised 12/15 submissions of the two reports for EMD-004, which arrived too late to be addressed in the EPA science review listed above.

h. EMD-004 Ethics Rvw 12/19/06
This review addresses both the initial and revised reports for both formulations

Charge Questions.

1. *EMD-003.1 and EMD-003.2: Tick Repellency with Lotion and Pump Spray Formulations:*

a. Are these studies sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against ticks and mosquitoes?

b. Does available information support a determination that these studies were conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

2. *EMD-004.1 and EMD-004.2: Mosquito Repellency with Lotion and Pump Spray Formulations:*

a. Are these studies sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against ticks and mosquitoes?

b. Does available information support a determination that these studies were conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

B. DEET Insect Repellent Efficacy Protocol

Description. EPA requires data from efficacy studies using appropriate insect species to support claims of greater efficacy than have previously been approved.

An applicant for new or amended registration typically conducts such research prior to submitting an application. If such a study is to be initiated after April 7, 2006, EPA's regulation, 40 CFR §26.1125, requires the sponsor or investigator to submit to EPA, before conducting the study, materials describing the proposed human research in order to allow EPA to conduct scientific and ethics reviews. In addition, EPA's regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the research proposal.

Dr. Scott Carroll has submitted a description of proposed research to be performed by Carroll-Loye Biological Research. The proposal, identified as SCI-001, describes a study to evaluate the efficacy of four formulations of repellent products containing the active ingredient DEET. (One formulation includes two other active ingredients as well.) The study would measure the efficacy of three test formulations and one "comparison article"—the US military standard repellent—against mosquitoes under field conditions. The proposal bears many similarities to the protocol EMD-004 that the HSRB has previously reviewed. EPA has reviewed Dr. Carroll's protocol and has concluded that, with some required refinements, it appears likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L.

EPA has identified some relatively easily corrected deficiencies in the protocol, which must be corrected before execution. In the interest of providing a thorough and timely response to the proposal, and since EPA finds the protocol generally meets applicable scientific and ethical standards, EPA is presenting this protocol for review at the Board's January 2007 meeting.

EPA is providing the following materials to the HSRB in the folder identified as “Insect Repellent Efficacy Protocol SCI-001”:

SCI-001 (Mosquito repellency study)

a. Read this First: this annotated bibliography

b. SCI-001 v.1 11-02-06:
The protocol as submitted on 11/8/06 and addressed by the EPA review of December 19, 2006

c. Carroll-Loye–IIRB Email Correspondence 11/3/06 – 11/8/06
Submitted with the protocol, v.1 on 11/8/06

d. Carroll–Carley Email 11/8/06 – 12/14/06
Emails exchanged between Scott P. Carroll of Carroll-Loye Biological Research and John M. Carley of EPA concerning this protocol

e. Site Questionnaire: SCI-001 11/3/06
Part of the original Carroll-Loye submission to the IIRB, submitted in response to EPA’s request on 11/17/06

f. Roogow–Carley Email 11/15/06

g. IIRB Minutes 11/7/06 Re SCI-001
The Email from Robert Roogow of IIRB transmits the minutes of the IIRB discussion of SCI-001, and reports no changes in IIRB membership or procedures since those were previously reported to EPA.

h. EPA Review SCI-001 v.1 12/20/06
This review addresses the protocol as submitted on November 8 and supplemented by all additional materials submitted before December 14.

i. SCI-001 v.2 12-14-06:
Revised version of the protocol responding to preliminary comments from EPA, to be reviewed in detail by EPA before the HSRB meeting.

j. SCI-001 Lbls + MSDS 12-14-06:
“Supporting Documents” submitted with revised SCI-001 protocol; includes labels with associated correspondence, and an MSDS for each product, all of which were previously included within the v.1 protocol.

Charge Questions.

1. *Protocol SCI-001 from Carroll-Loye Biological Research:*

    a. If the proposed research described in Protocol SCI-001 from Carroll-Loye Biological Research is revised as suggested by EPA, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes?

    b. If the proposed research described in Protocol SCI-001 from Carroll-Loye Biological Research is revised as suggested by EPA, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?