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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 10, 2008

MEMORANDUM

SUBJECT: Transmission of materials for review by the Human Studies Review Board for its April 2008 Meeting

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

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This memorandum describes the materials OPP is providing for review by the Agency's Human Studies Review Board (HSRB or Board) at the meeting scheduled for April 9-11, 2008. At this meeting the Board will address scientific and ethical issues surrounding:

1. Two product-specific reports from field studies of mosquito repellent efficacy of two pesticides containing DEET, conducted by Carroll-Loye Biological Research and reported as SCI-001.4 and SCI-001.5.

2. A research proposal (A382) from Insect Control & Research, Inc. to evaluate stable fly repellent efficacy of two conditionally registered products containing picaridin in the laboratory.

3. Two scenario design documents and associated protocols from the Antimicrobial Exposure Assessment Task Force II (AEATF) to monitor exposure of subjects who apply an antimicrobial pesticide by mopping or by wiping in one of two different ways.

Each of these topics is discussed more fully below.

1. Completed Insect Repellent Efficacy Studies (SCI-001.4 and SCI-001.5) of DEET Formulations

In its January 2007 meeting the HSRB reviewed protocol SCI-001 from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll, to test mosquito repellent efficacy of three controlled-release formulations of DEET in the field. The study was designed to measure the efficacy of the three test formulations and one "comparison article"—the US military standard repellent. The HSRB offered comments on the protocol at its January 2007 meeting.

Following that meeting, Dr. Carroll amended the protocol to address a comment from the HSRB and to substitute a new, unregistered repellent formulation for one of those proposed in the protocol. Dr. Carroll then proceeded to conduct the research according to the amended protocol in July 2007, and submitted the results to EPA for review. At it October 2007 meeting, the HSRB reviewed the results of the research, determined that there were both scientific and ethical issues with the conduct of the research, and advised EPA not to rely on the data. Dr. Carroll further amended the protocol, obtained IRB approval for both the original and subsequent amendments, and re-executed the research in November 2007, testing only two of the originally proposed test repellents and omitting the comparison positive control formulation. Reports of this testing have been submitted to EPA by the study sponsor, Scientific Coordination, Inc., under study numbers SCI-001.4 and SCI-001.5. EPA is presenting the results of the re-execution of protocol SCI-001 to the HSRB for review at this meeting.

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 submitted cited these data in support of applications for amended registration for the two test materials. In order to facilitate review of these applications within the time allowed by statute, EPA has reviewed the research, 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.

OPP has determined that the data are scientifically sound and that the research meets the standard in §26.1705. Therefore OPP proposes to rely on the results in considering the pending applications.

EPA is providing the following materials on the completed insect repellent efficacy studies SCI-001.4 and SCI-001.5 to the HSRB:

1. Insect Repellent Efficacy Studies SCI-001.4 and SCI-001.5

    a. MRID 47322501 SCI-001.4: Test of DermAegis LipoDEET 302

    b. MRID 47322401 SCI-001.5: Test of Coulston's Duranon

    c. Supplemental correspondence IIRB↔CLBR 3/5/08

    d. EPA Science and Ethics Review (Protocol) SCI-001 (12/20/06)

    e. Changes in consent form version of 11-6-07

    f. EPA Ethics Review: SCI-001.4 and SCI-001.5 (3/7/08)

    g. EPA Science Review: SCI-001.4 and SCI-001.5 (3/7/08)

Charge Questions.

1. SCI-001.4 and SCI-001.5 Mosquito Repellency Studies with DEET Formulations:

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

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

2. Proposed ICR Stable Fly Repellent Efficacy Study (A 382)

EPA requires submission of data from efficacy studies when a pesticide product is directed against organisms classified as public health pests. EPA's regulation, 40 CFR §26.1125, requires a sponsor or investigator to submit to EPA, before conducting a study involving intentional exposure of human subjects, materials describing the proposed human research in order to allow EPA to conduct science and ethics reviews. In addition, EPA's regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the research proposal.

Insect Control & Research, Inc. (ICR) has submitted a proposal for new research to evaluate the efficacy of two conditionally registered products containing picaridin, to be conducted by Dr. William Gaynor. ICR protocol number G4330108001A382 (A382)

describes a laboratory study of the efficacy of the test formulations against stable flies, a species classified as a public health pest.

EPA has reviewed ICR's protocol and has concluded that, with several required revisions, 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. The sponsor wishes to submit the data to EPA later this year in support of an application to amend the registration of these picaridin products in order to claim specifically that the products are effective at repelling stable flies. In the interest of providing a thorough and timely decision on such applications, and since EPA finds the protocol can meet applicable scientific and ethical standards, EPA is presenting this protocol for review at the Board's April 2008 meeting.

EPA is providing the following materials on the ICR repellent efficacy protocol A382 to the HSRB:

2. ICR Repellent Efficacy Protocol A382

    a. ICR Stable Fly Protocol A382 (Rvsd 2/1/08)

    b. EPA Science & Ethics Review (3/7/08)

Charge Questions.

2. Insect Control & Research's Proposed Picaridin Protocol (A382):

a. If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, 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 ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

3. Proposed AEATF Research on Exposure of Subjects Using an Antimicrobial Pesticide in Mopping and Wiping Activities

The HSRB has previously considered issues related to the design and conduct of research to measure the levels of exposure received by people when handling (i.e., mixing, loading, or applying) pesticides. As most Board members will recall, two industry Task Forces, the Antimicrobials Exposure Assessment Task Force II (AEATF) and the Agricultural Handlers Exposure Task Force (AHETF), have previously submitted materials for HSRB review. Based on the issues raised by the Board at its meeting in June 2006, EPA asked its FIFRA Scientific Advisory Panel (SAP), an advisory

committee of independent expert scientific peer reviewers, to address a number of scientific issues at its January 2007 meeting. Drawing on the advice of the SAP, the Office of Pesticide Programs presented additional issues relating to the proposed handler research again at the April and June 2007 HSRB meetings. In response to those reviews the Task Forces have extensively reworked their research proposals.

One issue, the design of the sampling strategies to be used by the Task Forces, has drawn particular attention. To resolve this question OPP has consulted with experts both within and outside EPA, and has carefully considered information presented by the Task Forces. Based on these interactions, OPP has decided to accept data developed through "hybrid" sampling strategies, i.e., strategies that use a basic purposive diversity sampling design but which incorporate random elements whenever feasible. OPP provided background documents on these interactions on December 5, 2007 to a work group of the HSRB that has been considering this issue. Those same background documents are provided again in this transmittal for the Board's convenience in preparing for the April 2008 HSRB meeting.

The AEATF has submitted two proposals. Each includes both a scenario-specific design document and the associated field study protocol, along with supporting documentation, for EPA and HSRB review. One proposal would measure inhalation and dermal exposure of subjects applying an antimicrobial pesticide by mopping floors. The other would measure exposure of subjects who apply an antimicrobial pesticide by wiping vertical and horizontal hard surfaces in two distinct scenarios—one using a spray-and-wipe technique, and the other using ready-to-use impregnated wipes.

EPA's regulation, 40 CFR §26.1125, requires the sponsor or investigator to submit to EPA, before conducting a study involving intentional exposure of human subjects, 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. Because the research proposed by the AEATF involves scripted exposure, it meets the regulatory definition of "research involving intentional exposure of a human subject", and thus these cited provisions of regulation apply to it.

EPA has reviewed the AEATF proposals and has concluded that, with a number of required revisions, they appear 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 also concluded that the proposed hybrid sampling designs for all three proposed exposure scenarios effectively incorporate elements of randomization, consistent with EPA's guidance to the AEATF. Because the sponsor wishes to initiate testing pursuant to these protocols as soon as possible to meet regulatory requirements in other countries, and since EPA finds the protocols can meet applicable scientific and ethical standards, EPA is presenting this protocol for review at the Board's April 2008 meeting.

EPA is providing the following materials concerning the AEATF Exposure Monitoring Program to the HSRB:

3. AEATF Exposure Monitoring Program

   a. General Documents

      (1) Volume 5 AEATF Governing Document (Revised 2/13/08)

      (2) AEATF Governing Document (Revised 2/13/08; track changes)

      (3) Summary of Changes to Governing Document of 2/13/08

      (4) Volume 6 AEATF SOPs (Revised 2/25/08)

   b. Documents specific to the Mop Scenario

      (1) Volume 1 AEATF Mop Scenario Design/Protocol: Primary Documentation (Revised 2/25/08)

      (2) Volume 2 AEATF Mop Scenario Design/Protocol: Secondary Documentation (Revised 2/25/08)

      (3) EPA Science and Ethics Review: AEATF Mop Scenario (3/10/08)

   c. Documents specific to the Wipe Scenarios

      (1) Volume 3 AEATF Wipe Scenario Design/Protocol: Primary Documentation (Revised 2/25/08)

      (2) Volume 4 AEATF Wipe Scenario Design/Protocol: Secondary Documentation (Revised 2/25/08)

      (3) EPA Science and Ethics Review: AEATF Wipe Scenarios (3/10/08)

   d. Background documents on the Sampling Strategy Issue distributed to the HSRB on December 5, 2007

      (1) Memorandum from William Jordan to Dr. Celia Fisher Re: "Design of Sampling Strategies in Proposed Handler Research"

      (2) AHETF Study Design, Logistics, and Conduct (10-17-07) Power Point presentation by David Barnekow and Victor Cañez

      (3) AEATF Introduction and Background (10-17-07) Power Point presentation by Hasmukh Shah

(4) AHETF Membership Benefits and Incentives (10-17-07) Power Point presentation by Victor Cañez and David Barnekow

(5) AHETF and AEATF Concepts, Objectives, and Sampling Issues (10-17-07) Power Point presentation by Larry Holden

(6) Report of Dr. Tapabrata Maiti, Associate Professor of Statistics at Iowa State University, to EPA concerning sampling design issues in proposed handler exposure research (11-30-07)

(7) Letter from Debra Edwards, OPP director, to Hasmukh Shah, manager of the American Chemistry Council's Biocides Panel, concerning issues involving the AEATF's proposed handler research. (11-28-07)

(8) Summary of EPA/OPP Teleconferences with AHETF (11-28-07)

Charge Questions.

3. AEATF's Proposed Mop Scenario Design and Protocol:

a. If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by mopping?

b. If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

4. AEATF's Proposed Wipe Scenario Designs and Protocol:

a. If the proposed research described in AEATF's proposed wipe scenario designs, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by wiping?

b. If the proposed research described in AEATF's proposed wipe scenario designs, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?