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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

June 12, 2006

MEMORANDUM

Subject: Transmittal 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: Jack E. Housenger
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The Agency's Human Studies Review Board (HSRB) is scheduled to meet June 27 through 30, 2006, to hear a report on plans for an EPA / ORD workshop on conducting observational research with human subjects; and to address scientific and ethical issues surrounding a human toxicity study involving one pesticide active ingredient-chloropicrin; guidelines for conducting insect repellant efficacy testing; protocols for conducting two insect repellent efficacy studies; and protocols for conducting five occupational handler exposure monitoring studies.. By this memo the Office of Pesticide Programs (OPP) is transmitting to the HSRB the documents discussed below.

On March 21, 2006, the Agency sent to the HSRB materials containing background information regarding EPA review policies and approaches and the newly-effective amended rules for protecting human subjects of research. These materials may also be useful in preparing for this HSRB meeting. Please refer to this package for additional information.

DOCUMENTS PROVIDED TO THE HUMAN STUDIES REVIEW BOARD (HSRB) FOR THE JUNE 27-30, 2006 MEETING

Introduction

The Pesticide Registration Improvement Act (PRIA) requires that EPA complete its decision-making process on certain types of applications to register a pesticide product within specified amounts of time after receiving the application for registration. In addition, PRIA established deadlines for EPA to complete "reregistration" of pesticide active ingredients that are contained in pesticide products initially registered before 1984. Reregistration involves the systematic reexamination of these older pesticides, applying contemporary scientific and regulatory standards. When a pesticide active ingredient is approved for use on food, EPA combines reregistration with the tolerance reassessment process mandated by the Food Quality Protection Act of 1996 (FQPA).

Chloropicrin is undergoing reevaluation in the reregistration process. As part of the review of the available toxicity data on chloropicrin, EPA has identified a study involving intentional exposure of human subjects which EPA intends to use in its risk assessment. In accordance with 40 CFR 26.1602, EPA is seeking HSRB review of this study.

EPA regulates pesticides intended for use on skin to repel arthropod pests. As part of the application for registration of a new repellent, EPA requires data to demonstrate that the product is effective. The Agency has developed a guideline for the conduct of such studies, and is presenting it to the Board for comment. The Agency has also received protocols for two insect repellent efficacy studies, and as required by the recently promulgated regulation, EPA is required to submit the protocols to the HSRB for its review and comment. See 40 CFR 26.1601.

In addition, EPA routinely considers the human health risks of occupational handlers of pesticides in both in its reregistration program and as part of its review of an application for registration pending under FIFRA and PRIA. EPA has received five protocols for conducting new research involving human subjects to collect data on the levels of exposure received by people when mixing, loading, and applying pesticides under various conditions. In accordance with 40 CFR 26.1601, EPA is seeking HSRB review of these proposed protocols.

Finally, observational research such as that conducted by the Office of Research and Development is also routinely used by the Agency as part of the risk characterization process through the comparison of situational monitoring to the results of its scenario-driven risk assessments. ORD will report on its plans to hold a workshop to develop a "best practices" document for the design and conduct of observational research with human subjects.

Types of Documents Provided to the Human Studies Review Board (HSRB) for the May 2 - 4, 2006 Meeting

For the human studies or guidelines under consideration, the Agency has provided the Board members with the complete study report or associated protocols and any supplements available to the Agency. Similarly, guideline documents are included with appropriate background information. Completed studies are assigned a unique identifier (e.g., the Master Record Identifier-MRID), which OPP uses to manage documents. When a company submits multiple documents pertaining to a single study, each document is typically assigned a unique tracking number.

For each study, protocol or guideline to be evaluated, the Agency has provided a review of the ethical conduct. Each ethics review identifies any deficiencies which were identified compared to appropriate ethical standards. EPA has intentionally deferred making a final determination of whether the chloropicrin study satisfies the ethical standards for acceptability in 40 CFR sections 26.1704 – 26.1706, pending the advice of the Board.

For most studies and protocols, the Agency develops documents, called Data Evaluation Records (DERs), containing a scientific review, the Board has been provided with one or more DERs for chloropicrin, the two proposed insect repellent efficacy protocols, and each of the 5 Agricultural Handlers Exposure Taskforce (AHETF) protocols. DERs contain summaries of the study design, methods and results, describe potential deficiencies, and provide conclusions about the usefulness of the study in risk assessment.

In addition to the DERs, OPP has prepared or included several other background documents which address various elements of the issues to be reviewed by the HSRB. For example, for the AHETF protocols, a number of types of documents have been provided including includes transmittal documents and the charge questions, general background information pertaining to the manner in which the Agency completes exposure/risk assessments; the AHETF protocols themselves and various documents that the AHETF has developed related to the manner in which it intends to conduct studies; the background documents related to the AHETF protocol review by the Washington Institutional Review Board; and the EPA science and ethics reviews of these protocols. [Note: A complete list of the documents which have been provided is included below corresponding to Agenda items that the HSRB is to review.]

Table of contents

- Published Journal Articles (2 documents)
- EPA Science Reviews (2 documents)
- EPA Ethics Review (1 document)

2. Information on the Conduct of Insect Repellent Efficacy Studies

- 31 Documents

- **EPA Guidelines (4 documents)**

EPA Product Performance Test Guidelines (PUBLIC DRAFT), OPPTS 810.3700, Insect Repellents for Human Skin and Outdoor Premises, dated December 1999. [OPPTS 8103700]

Scientific Advisory Panel ("SAP") Report No. 00-02B, FIFRA SAP Meeting – Insect Repellent Product Performance Testing Guideline Evaluation, dated August 2, 2000. [SAP Report No002B]

Presentation of the Draft Insect Repellent Product Performance Testing Guideline 810.3700 to the Human Studies Review Board, dated June 9, 2006. [Final Brief on GL 6-9-06]

Product Performance of Skin-Applied Repellents of Insects and Other Arthropods, dated June 12, 2006. [OPPTS 810.3700 repellent 6-9-06]

- **Protocol Transmittal <u>(1 document)</u>**

Submission Cover Letter from Scott P. Carroll to William Jordan, dated May 15, 2006. [Submission_Cover_Letter]

- **Protocol C-L-001 (Template for Test of Personal Insect Repellents) <u>(4 documents)</u>**

Test of Personal Insect Repellents Protocol, Protocol Number C-L-001, dated March 30, 2006 (the "Template Protocol"). [Protocol_C-L-001]

IIRB Approval Letter regarding Template Protocol, from Anita McSharry, Vice-Chairman of the IIRB, to Scott Carroll, Principal Investigator, dated March 30, 2006. [810-3700_Repellent_T#131581]

Ethics Review of Protocol Template for Human Studies of Arthropod Repellent Performance by John M. Carley, Program Analyst, dated June 5, 2006. [CL-001 Review 6-5-06]

Product Performance Protocol Review by Kevin Sweeney, Senior Entomologist, dated June 9, 2006. [Science review 6-9-06]

- **Protocol EMD-003 (Laboratory, Tick Repellent Efficacy Study) (9 documents)**

Efficacy Test Protocol, Study EMD-003, dated April 13, 2006. [Test_Protocol_EMD-003]

Informed Consent Authorization to Participate as a Research Study Subject, Study EMD-003, and Letter approving clinical research protocol for EMD-003, from Anita McSharry, Vice-Chairman of the IIRB, to Scott Carroll, Principal Investigator, both dated April 18, 2006. [Informed_Consent_EMD-003]

Material Safety Data Sheet, Product EUS 26-15 – Insect Repellent Spray, dated January 26, 2006. [Insect repellent_EUS26-15_msds]

. Material Safety Data Sheet, Product EUS 26-16 – Insect Repellent Aerosol, dated January 26, 2006. [Insect repellent_eus26-16_msds]

Material Safety Data Sheet, Product EUS 29-01 – Insect Repellent Lotion, dated January 26, 2006. [Insect repellent_wv29-01_msds]

Formulation Examples for EUS 26-15, 26-16 and 29-01. [Formulation Examples]

IIRB Site Questionnaire, EMD-003 dated January 10, 2006 (revised). [Questionnaire 003]

Ethics Review of Protocol for Human Study of Tick Repellent Performance by John M. Carley, Program Analyst, dated June 9, 2006. [EMD-003 Review 6-9-06]

Science Review of Protocol EMD-003 by Kevin Sweeney, Senior Entomologist, dated June 9, 2006, page 4. [Science review 6-9-06]

- **Protocol EMD-004 (Field, Mosquito Repellent Efficacy Study) (5 documents)**

Efficacy Test Protocol, Study EMD-004, dated April 13, 2006. [Test_Protocol_EMD-004[1]]

Informed Consent Authorization to Participate as a Research Study Subject, Study EMD-004, and Letter approving clinical research protocol for EMD-004, from Anita McSharry, Vice-Chairman of the IIRB, to Scott Carroll, Principal Investigator. dated April 18, 2006. [Informed_Consent_EMD-004]

IIRB Site Questionnaire, EMD-004 dated January 10, 2006 (revised). [Questionnaire 004]

Ethics Review of Protocol for Human Study of Mosquito Repellent Performance by John M. Carley, Program Analyst, dated June 9, 2006. [EMD-004 Review 6-9-06]

Science Review of Protocol EMD-004 by Kevin Sweeney, Senior Entomologist, dated June 9, 2006, page 7. [Science review 6-9-06]

- **General IRB Information (6 documents)**

Letter summarizing IIRB information required pursuant to 40 C.F.R. § 26.1115, and attaching brief resumes of IIRB members, from Kim Lerner, Chairman of the IIRB, to Scott Carroll, Principal Investigator, dated May 12, 2006. [Lerner_May12]

Email correspondence between IIRB officials and Scott Carroll, Principal Investigator, associated with the review of EMD-003 and EMD-004. [email correspondence]

EPA Protocol Checklist. [EPA Protocol Checklist]

ICFChecklist[1].form5-06. [ICFChecklist[1].form5-06]

Summary Outline of 40 CFR § 26.1115, Containing Information and Commentary Addressing the Requirements of Each Subsection. [SummaryOutline1115]

Summary Outline of 40 CFR § 26.1125, Containing Information and Commentary Addressing the Requirements of Each Subsection. [SummaryOutline1125]

- **IR3535 Information (2 documents)**

EPA Fact sheet regarding IR3535, available at http://www.epa.gov/oppbppd1/biopesticides/ingredients/factsheets/factsheet_113509.htm. [EPA Fact Sheet]

Document entitled “Data Requirements in Fulfillment of § 408 of the Federal Food, Drug and Cosmetic Act.” [IR3535_Tox_summary]

EPA Technical Document regarding IR3535, available at http://www.epa.gov/oppbppd1/biopesticides/ingredients/tech-_docs/tech_113509.htm. [EPA Technical Document]

World Health Organization, Specifications and Evaluations for Public Health Pesticides, IR3535. [WHO IR3535]

- **References**

  To be e-mailed separately

3. Information on AHETF Occupational Exposure Protocols

- 3 Overview documents ("Read this first" primer, charge questions & copy of this transmittal memo) and 8 directories that contain various information including (there are a total of 154 documents included):
  - AHETF Analytical Method Validation Reports (5 documents)
  - AHETF Misc. Documents (4 documents)
  - AHETF SOPs (Standard Operating Procedures) Applicable To Study Conduct (32 documents)
  - AHETF Protocols & Institutional Review Board documentation (5 Subdirectories, one for each protocol, 85 documents). Each subdirectory includes:
    - Protocol AHE-XX
    - Initial Review Submissions To WIRB (Washington Institutional Review Board)
    - Approval Documentation From WIRB
  - EPA Science Review Documents (6 documents)
  - EPA Ethics Review Document (1 document)
  - EPA Guidance Documents (14 documents)
  - Primers For Occupational Exposure Assessment (4 documents)