

US EPA ARCHIVE DOCUMENT



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 27, 2008

MEMORANDUM

SUBJECT: Materials for review by the Human Studies Review Board for its June 2008 Meeting

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

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

This memorandum describes the materials OPP is providing for review by the Human Studies Review Board (HSRB or Board) at the meeting scheduled for June 24-25, 2008. At this meeting the Board will address scientific and ethical issues surrounding:

1. The scenario design and two associated protocols from the Agricultural Handlers Exposure Task Force (AHETF), which describe proposed research to monitor exposure of subjects who apply liquid pesticides to orchard and trellis crops using airblast equipment drawn by vehicles with closed cabs, accompanied by revised versions of the AHETF Governing Document and selected AHETF Standard Operating Procedures.
2. The report of a laboratory study conducted by ICR, Inc., (ICR) to evaluate the efficacy of two registered products containing picaridin in repelling mosquitoes of the genus *Culex*.

Each of these topics is discussed more fully below.

1. Proposed AHETF Research on Exposure of Subjects Applying Liquid Pesticide to Orchard and Trellis Crops Using Closed-Cab Airblast Equipment

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. In response to concerns 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 surrounding handler exposure research at its January 2007 meeting. The Office of Pesticide Programs presented the results of the SAP review and additional issues at the April and June 2007 HSRB meetings. In response to the SAP and HSRB reviews the Task Forces have extensively reworked their research proposals.

At its April 2008 meeting the Board favorably reviewed proposals by the AEATF. At the June meeting we will present a proposal from the AHETF for two field studies, both of which will contribute to the closed-cab airblast application scenario.

In earlier discussions with the HSRB the design of the sampling strategies to be used by the Task Forces, has drawn particular attention. As OPP reported at the April 2008 meeting, OPP has consulted with experts both within and outside EPA, and has carefully considered information presented by the Task Forces. After thoughtful consideration of all these inputs, OPP has decided to accept data developed through “hybrid” sampling strategies, i.e., strategies that use a purposive design but which incorporate random elements whenever feasible.

The AHETF has submitted two proposed protocols, each for a different field study involving pesticide application to orchard trees by airblast sprayers while the applicators are within a vehicle with a fully enclosed cab. Both field studies would provide monitoring data for the same scenario; the AHETF and EPA expect to present the protocols for the remaining three field studies associated with this scenario at a future HSRB meeting. When all five field studies have been conducted, data collection for this scenario will be complete.

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 scientific and ethics reviews. In addition, EPA’s regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the proposed research. 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 AHETF 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. Because the AHETF would like to conduct these field studies as soon as possible, and since EPA finds that the protocols can meet applicable scientific and ethical standards, EPA is presenting this protocol for review by the HSRB at its June 2008 meeting.

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

1. Documents specific to the Closed-Cab Airblast Scenario

a. Volume 1 General Information and Scenario Sampling Design (4/7/08)

Defines the closed-cab airblast scenario, describes the general patterns of use of airblast application equipment, the initial purposive choices leading to selection of crops and growing areas, and the multi-tiered plan for selecting workers to monitor

b. Volume 7 Documents cited in Scenario Sampling Design (4/7/08)

Includes reports of interviews with experts concerning use of airblast equipment for the crops and growing areas selected

c. Volume 2 Protocol AHE55: Citrus in Florida; primary documentation (4/7/08)

Includes the protocol itself and IRB-approved consent forms, product-specific risk statements, and recruiting flyers in English and Spanish

d. Volume 8 Protocol AHE55: Citrus in Florida; supporting documentation (4/7/08)

Includes initial and revised submissions of protocol and related materials to the IRB, all correspondence with the IRB, including notice of approval, selected SOPs, and other supporting documentation

e. Volume 3 Protocol AHE56: Pecans in Georgia; primary documentation (4/7/08)

Includes the protocol itself and IRB-approved consent forms, product-specific risk statements, and recruiting flyers in English and Spanish

f. Volume 9 Protocol AHE56: Pecans in Georgia; supporting documentation (4/7/08)

Includes initial and revised submissions of protocol and related materials to the IRB, all correspondence with the IRB, including notice of approval, selected SOPs (fewer than in Volume 8), and other supporting documentation

- g. EPA Science and Ethics Review: AHETF Protocol AHE55 (5/27/08)

Addresses the closed-cab airblast application scenario and the Florida Citrus protocol

- h. EPA Science and Ethics Review: AHETF Protocol AHE56 (5/27/08)

Addresses the closed-cab airblast application scenario and the Georgia Pecan protocol

2. General Documentation of the AHETF Monitoring Program

- a. Volume 4 AHETF Governing Document (4/7/08)

Substantially revised since the version reviewed by the HSRB in June 07, especially in sections 1, 9, 10, 14, and 16

- b. Volume 5 AHETF Governing Document (4/7/08; track changes)

This document is helpful in tracking minor changes, but less helpful where whole sections were replaced and the earlier text has been moved to the end of the document

- c. Summary of Changes to AHETF Governing Document

Table of Contents from AHETF Volume 4, annotated with comments concerning the scope of revisions since June 07

- d. Volume 6 AHETF Standard Operating Procedures (4/7/08)

This volume includes SOPs cited in other AHETF documents, including the Scenario Design and protocols. A complete list of AHETF SOPs appears on pp. 4-6 of this volume; any not included in this volume can be made available to the HSRB on request.

- e. List of AHETF SOPs Revised since June 2007

This lists the SOPs revised by the AHETF since the HSRB meeting in June 2007

3. Background documents on Sampling Strategy distributed to the HSRB on 12/5/07

These are the same documents the Board reviewed for the April 2008 meeting, included again for convenient reference

- a. Memorandum from William Jordan to Dr. Celia Fisher Re: "Design of Sampling Strategies in Proposed Handler Research"
- b. AHETF Study Design, Logistics, and Conduct (10-17-07) Power Point presentation by David Barnekow and Victor Cañez
- c. AEATF Introduction and Background (10-17-07) Power Point presentation by Hasmukh Shah
- d. AHETF Membership Benefits and Incentives (10-17-07) Power Point presentation by Victor Cañez and David Barnekow
- e. AHETF and AEATF Concepts, Objectives, and Sampling Issues (10-17-07) Power Point presentation by Larry Holden
- f. 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)
- g. 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)
- h. Summary of EPA/OPP Teleconferences with AHETF (11-28-07)

Charge Questions.

1. *AHETF's Proposed Closed-Cab Airblast Scenario Design and Protocols:*

If AHETF's proposed closed-cab airblast application scenario design, field study protocols AHE55 and AHE56, and supporting documentation are revised as suggested in EPA's reviews:

- a. does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply liquid pesticides using airblast equipment drawn by vehicles with closed cabs?
- b. does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

2. Completed Insect Repellent Efficacy Study (A117) of Picaridin Formulations

In its October 2007 meeting the HSRB favorably reviewed protocol A117 from Insect Control & Research, Inc. (ICR) to evaluate the efficacy in the laboratory of two registered products containing picaridin against *Culex* mosquitoes.

Following that meeting, ICR revised the protocol to address EPA and HSRB comments and then submitted the revised protocol for IRB approval. ICR executed the research and submitted a report to EPA. EPA is presenting the report of the execution of protocol A117 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 these data to support applications for amended registration for the two test materials. EPA has reviewed the research, applying the standard in 40 CFR §26.1705, which 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 although there were some irregularities in the conduct of recruitment, the study appears to meet the standard of §26.1705. Unless the HSRB advises that the conduct of the study was not in substantial compliance with EPA's rules for the protection of human subjects of research, OPP proposes to rely on the results in considering the pending applications for amended registration.

EPA is providing the following materials on the completed insect repellent efficacy study ICR A117:

4. Completed Insect Repellent Efficacy Study ICR A117
 - a. MRID 47397701 Primary Report of ICR A117

The primary report of the study, with appendices including the final IRB-approved protocol and consent form and IRB approval letters
 - b. MRID 47413801 Supplemental Information on Ethical Conduct of ICR A117 (4-8-08)

Includes a summary of changes made since the HSRB reviewed the protocol in October 2007, IRB correspondence, and the revised draft consent form submitted to the IRB for review.

- c. EPA Science and Ethics Review of ICR Protocol A117 (9/24/07)

This is the EPA Joint Science and Ethics Review of the protocol presented to the HSRB in October 2007, included for convenient reference

- d. toXcel response to EPA Science and Ethics Review (10/17/07)

This is the submitter's response to EPA's review, provided to the HSRB in October 2007

- e. toXcel summary of January 14, 2008 meeting with EPA (1/17/08)

This documents a meeting of EPA with ICR, toXcel, and Avon to discuss changes to the protocol and consent form

- f. toXcel 5/21/08 response to EPA E-mail request for clarifications

Clarifies reason for protocol deviation, number of subjects recruited, and sequence and timing of recruiting events

- g. EPA Ethics Review: A-117 (5/22/08)

EPA's ethics review of the completed study

- h. EPA Science Review: A-117 (5/22/08)

EPA's science review of the completed study

Charge Questions.

2. *ICR A117 Mosquito Repellency Study with Picaridin Formulations:*

- a. Is this study sufficiently sound, from a scientific perspective, to be used, in conjunction with other information, to assess the repellent efficacy of the formulations tested against mosquitoes of the genus *Culex*?
- 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?