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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

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**MEMORANDUM**

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

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This memorandum describes the materials OPP is providing for review by the Human Studies Review Board (HSRB or Board) at the meeting scheduled for October 21-22, 2008. At this meeting EPA will ask the Board to address scientific and ethical issues surrounding:

1. A slightly revised scenario design and three protocols from the Agricultural Handlers Exposure Task Force (AHETF), describing proposed research to monitor exposure of subjects who apply pesticide sprays to orchard and trellis crops using airblast equipment drawn by vehicles with closed cabs.
2. A new scenario design and three associated protocols from AHETF, describing proposed research to monitor exposure of subjects who apply pesticide sprays to orchard and trellis crops using airblast equipment drawn by vehicles with open cabs.
3. The report of a completed field study, LNX-001, conducted by Carroll-Loye Biological Research (CLBR) to evaluate the mosquito repellent efficacy of two registered products containing 20% picaridin.

In addition, EPA will report on its progress in revising its Guidelines for Product Performance Testing of Skin-Applied Insect Repellents. Each of these topics is discussed further below.

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

The HSRB has previously considered 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. The Board has addressed this kind of research in its meetings in June 2006, June 2007, April 2008, and June 2008. In its two most recent meetings the HSRB favorably reviewed proposals for handler exposure research submitted by AEATF (April) and by AHETF (June).

At its June 2008 meeting the Board favorably reviewed the proposal by the AHETF to collect data on the exposure of subjects applying liquid pesticides using closed-cab airblast equipment. At the October meeting EPA will present proposals from the AHETF for the three additional field studies required to fulfill this scenario design. These protocols are very similar to those reviewed by the Board in June, but involve monitoring workers making pesticide applications to different crops in different regions. In addition, these protocols incorporate numerous refinements agreed to by EPA and the AHETF shortly after the June HSRB meeting.

The three new protocols involve monitoring applications of surrogate pesticides to Michigan cherry orchards (AHE57), California vineyards (AHE-58), and Washington apple orchards (AHE59). Together with the data generated under the two field study protocols reviewed by the Board in June, 2008, these will fulfill the design of the Closed-Cab Air Blast application scenario. Because of the widespread use of chlorothalonil on Michigan cherries, the scenario design has been revised to add several formulations of this active ingredient to the list of permissible surrogate pesticides. The sampling design and other key elements in the scenario design are unchanged.

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 proposed research 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 Closed-Cab Airblast scenario modified to include Chlorothalonil as a surrogate pesticide, and the three associated protocols AHE57,

AHE58, and AHE59, and has concluded that, with minor revisions, they are 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 early in 2009, and since EPA finds that the protocols can be revised to meet applicable scientific and ethical standards, EPA is presenting this protocol for review by the HSRB at its October 2008 meeting.

1. EPA is providing the following materials concerning the AHETF Closed-Cab Airblast Scenario

a. Volume I: Closed Cab Airblast Scenario Design (8/14/08)

*Defines the closed-cab airblast scenario, documents 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. It has been modified from documents reviewed by the HSRB in June 2008 to provide for use of chlorothalonil as a surrogate pesticide in addition to carbaryl and malathion.*

b. Volume II: Protocol AHE57: Michigan Cherries (8/14/08)

c. Volume III: Protocol AHE58: California Grapes (8/14/08)

d. Volume IV: Protocol AHE59: Washington Apples (8/14/08)

*Each volume includes the protocol, IRB-approved consent forms and recruiting flyers in English and Spanish, and all supporting materials including IRB correspondence.*

e. EPA Science and Ethics Review: AHE57 (9/23/08)

f. EPA Science and Ethics Review: AHE58 (9/23/08)

g. EPA Science and Ethics Review: AHE59 (9/23/08)

*Each review addresses the content of the study-specific volume and relevant aspects of the scenario design.*

Charge Questions:

If proposed closed-cab airblast application field study protocols AHE57, AHE58, and AHE59 are revised as suggested in EPA's reviews and if the research is performed as described:

1. Is the research 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?
2. Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

## **2. Proposed AHETF Research on Exposure of Subjects Applying Pesticide Sprays to Orchard and Trellis Crops Using Open-Cab Airblast Equipment**

EPA will present a proposal from the AHETF for field studies for another scenario involving application of liquid pesticide sprays to orchard and trellis crops using conventional airblast sprayers drawn by open-cab tractors. The three proposed field study protocols are similar to those the Board reviewed for the closed cab airblast scenario, appropriately modified to monitor additional exposure, especially to the head, resulting from use of open cab equipment. A previous AHETF study, AHE-07A, conducted before promulgation of EPA's human research rule, provided 15 MUs meeting contemporary standards of scientific validity and then-prevailing standards of ethical conduct. The AHETF proposes to use the data from this earlier study in its generic database, and to supplement it with 15 more MUs, obtained through three additional field studies.

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 this proposed research 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 minor revisions, they are 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 early in 2009, 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 October 2008 meeting.

2. EPA is providing the following materials concerning the AHETF Open-Cab Airblast Scenario

a. Volume I: Open Cab Airblast Scenario Design (8/14/08)

*Defines the open-cab airblast scenario, documents the general patterns of use of airblast application equipment, describes the monitoring data available from the pre-rule AHETF study AHE-07A, and documents the rationale for the sample size proposed for the additional monitoring data still needed to fulfill the scenario design, the initial purposive choices leading to selection of crops and growing areas, and the multi-tiered plan for selecting workers to monitor.*

b. Volume II: Protocol AHE62: California Trellis Crops (8/14/08)

c. Volume III: Protocol AHE63: New York Grapes (8/14/08)

- d. Volume IV: Protocol AHE64: Oklahoma Pecans (8/14/08)

*Each volume includes the protocol, IRB-approved consent forms and recruiting flyers in English and Spanish, and all supporting materials including IRB correspondence.*

- e. EPA Science and Ethics Review: AHE62 (9/23/08)  
f. EPA Science and Ethics Review: AHE63 (9/23/08)  
g. EPA Science and Ethics Review: AHE64 (9/23/08)

*Each review addresses the content of the study-specific volume and relevant aspects of the scenario design.*

Charge Questions:

If proposed open-cab airblast application field study protocols AHE62, AHE63, and AHE64 are revised as suggested in EPA's reviews and if the research is performed as described:

3. Is the research 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?
4. Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

**3. Completed CLBR Mosquito Repellent Field Study LNX-001**

In its June 2007 meeting the HSRB favorably reviewed protocol LNX-001 from Carroll-Loye Biological Research (CLBR) for a field study to evaluate the mosquito repellent efficacy of two conditionally registered products, a cream and a spray, both containing 20% picaridin as the active ingredient.

Following that meeting CLBR revised the protocol to address EPA and HSRB comments. IRB approval of final amendments occurred on 28 April 2008. CLBR executed the research in May-June 2008, and the sponsor submitted a report to EPA in August. EPA is presenting this report of the execution of protocol LNX-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 these data to support continued registration of the two test materials. EPA has reviewed the research, applying the standard in 40 CFR §26.1705, which states:

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 there is adequate information to determine that the conduct of the study was in substantial compliance with EPA's rules for the protection of human subjects of research. OPP proposes to accept and rely on the results in support of the registrations of the two products tested.

3. EPA is providing the following materials on the completed Carroll-Loye insect repellent efficacy study LNX-001:

- a. MRID 47506401 LNX-001 Primary Report (8/5/08)

*The primary report of the study, with appendices including the final IRB-approved protocol and consent form and IRB approval letters*

- b. EPA Science and Ethics Review of LNX-001 (date)

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

- c. HSRB Report of Review of LNX-001 (12/18/07)

*This is an extract from the HSRB final report of the June 2007 meeting, including all comments and recommendations concerning this protocol.*

- d. EPA Science Review: LNX-001 (9/23/08)

*EPA's ethics review of the completed study*

- e. EPA Ethics Review: LNX-001 (9/23/08)

*EPA's science review of the completed study*

Charge Questions:

5. Is the CLBR study LNX-001 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the tested formulations against mosquitoes?
6. Does available information support a determination that study LNX-001 was conducted in substantial compliance with subparts K and L 40 CFR Part 26?

#### 4. Guidelines for Product Performance Testing of Skin-Applied Insect Repellents

In order to improve the quality and reliability of data submitted to the Agency, EPA issues non-binding guidance documents, referred to as “Test Guidelines,” describing the scientific methodology recommended by EPA to develop data required to support applications to register pesticide products. EPA’s test guidelines typically contain detailed information about many aspects of the study design – for example, the test material, the use of control groups, the nature and number of data points, and the content of study reports.

The Agency has been working to revise its Product Performance Test Guidelines OPPTS 810.3700: Insect Repellents for Human Skin and Outdoor Premises since it was published as a “public draft” in December 1999. A revised draft addressing only repellents for human skin was presented to and discussed by the HSRB in June, 2006. Since then the HSRB has reviewed and commented on numerous proposals for insect repellent efficacy studies and several reports of completed studies. Over the course of these reviews the Board has made many suggestions for strengthening the scientific and ethical conduct of this kind of research, and has encouraged EPA to further revise and publish its guidelines for researchers considering this type of study.

EPA has extensively revised its insect repellent efficacy test guideline in response to many helpful suggestions from the HSRB and others. This new guideline of September 23, 2008 contains many new sections addressing the ethical considerations affecting the design and conduct of repellent efficacy studies. EPA has also expanded and revised the sections dealing with scientific aspects of this kind of study. The Agency presentation will describe the changes made, with particular emphasis on how the draft addresses previous advice from the Board.

EPA will soon announce in the Federal Register the availability of the new draft of the guideline. The Agency plans to designate the new version as an “interim guideline” for immediate use by investigators, but subject to further refinement in light of future comments from the HSRB and the public.