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

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 2009 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 20-21, 2009. At this meeting EPA will ask the Board to address scientific and ethical issues surrounding these topics, each of which is discussed further below:

1. Two published reports of completed, pre-rule research on the effects of exposure to pesticides containing pyrethrins/pyrethroids.

2. A proposal for new research to be conducted by Carroll-Loye Biological Research to evaluate in the laboratory the repellent efficacy to ticks of two registered products containing 20% picaridin.

3. A new scenario design and associated protocol from the Antimicrobials Exposure Assessment Task Force II (AEATF-II), describing proposed research to monitor at three sites the exposure of professional janitorial workers who apply an antimicrobial pesticide formulated as an aerosol spray.

1. Published reports of completed, pre-rule research on pyrethrins/pyrethroids

In response to a published analysis asserting a recent increase in the number and severity of human incidents involving pyrethrins and pyrethroids, EPA has recently completed a thorough review of animal toxicity data and human incident and epidemiological data for pyrethrins and pyrethroids. The focus of this review has been whether these data show an association between exposure to products containing pyrethrins or pyrethroids and asthmatic or allergic responses. This overall weight-of-evidence review is reported in the EPA White Paper, among the background documents transmitted to the HSRB under this memorandum.

In the course of its review EPA identified several additional studies which involved intentional exposure of human subjects. These studies were not included in the scope of the review reported in the White Paper pending review by the HSRB. Some of these studies involved intentional exposure of children under 18 or of pregnant or nursing women; consistent with the prohibition in the rule at 40 CFR §26.1703, EPA does not propose to rely on these studies, and they have been set aside. Other studies did not involve intentional exposure of vulnerable populations, and these are being presented to the HSRB now.

These remaining studies are reported very briefly, making them difficult to review. An effort was made to contact the authors of each article to obtain more information about the work reported, but these efforts were not successful. Both studies involved intentional exposure of human subjects for the purpose of identifying or quantifying a toxic effect; both were conducted before the effective date of EPA's amended rule for the protection of human subjects of research:

- A study by Newton & Breslin (1983) of the respiratory responses of seven known asthmatics to an aerosol insecticide containing pyrethrins, tetramethrin, and synergists.

- A short communication by Lisi (1992) summarizing a study of irritant and allergic responses of 230 subjects to dermal exposures to 7 pyrethroids.

EPA requests the advice of the HSRB on the scientific merit, relevancy, and limitations of these studies, and on their ethical acceptability. EPA intends to incorporate into a future revision of the EPA White Paper a discussion of any of these studies deemed to be scientifically sound and relevant and ethically acceptable.

The Agency's regulation, 40 CFR §26.1602, requires EPA to seek HSRB review of an EPA decision to rely on the results of pre-rule studies such as these, which identify or quantify a toxic effect. EPA has reviewed the research, applying the standard in 40 CFR §26.1704, 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 before April 7, 2006, if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. This prohibition is in addition to the prohibition in §26.1703.

OPP has determined that these two studies bear on the question of a possible relationship between pyrethrins/pyrethroid exposures and asthma or allergic responses, and that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or significantly deficient relative to the standards of ethical research prevailing when each of the studies was conducted. OPP proposes to address these studies in its revised weight-of-the-evidence review of all available studies and incident data bearing on this question.

1. EPA is providing the following materials on the pre-rule pyrethrins/pyrethroid studies:

   a. EPA White Paper: A Review of the Relationship between Pyrethrins, Pyrethroid Exposure and Asthma and Allergies (Revised 9/21/09)

   b. Newton & Breslin (1983)

      (1) Newton, J.; Breslin, A. (1983) Asthmatic reactions to a commonly used aerosol insect killer. *Medical Journal of Australia* 1:378-380.

      (2) EPA Science Review of Newton & Breslin study (9/21/09)

      (3) EPA Ethics Review of Newton & Breslin study (9/16/09)

   c. Lisi, P. (1992)

      (1) Lisi, P. (1992) Short Communication: Sensitization risk of pyrethroid insecticides. *Contact Dermatitis* 26:349-350.

      (2) EPA Science Review of Lisi study (9/21/09)

      (3) EPA Ethics Review of Lisi study (9/16/09)

Charge Questions

1.1 Newton & Breslin (1983)

1.1.1 Is the Newton & Breslin study scientifically sound, providing reliable data?

1.1.2 If so, is the Newton & Breslin study relevant to an assessment of the proposition that exposures to pyrethrins/pyrethroids may be associated with asthmatic or allergic respiratory responses?

1.1.3 If so, what limitations of the Newton & Breslin study should be taken into account by EPA in assessing the proposition that exposures to pyrethrins/ pyrethroids may be associated with asthmatic or allergic respiratory responses?

1.1.4 Is there clear and convincing evidence that the conduct of the Newton & Breslin study was fundamentally unethical, or that its conduct was significantly deficient relative to standards prevailing when it was conducted?

1.2 Lisi (1992)

1.2.1 Is the Lisi study scientifically sound, providing reliable data?

1.2.2 If so, is the Lisi study relevant to an assessment of the proposition that exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses?

1.2.3 If so, what limitations of the Lisi study should be taken into account by EPA in assessing the proposition that exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses?

1.2.4 Is there clear and convincing evidence that the conduct of the Lisi study was fundamentally unethical, or significantly deficient relative to the standards of ethical research conduct prevailing when it was conducted?

2. Proposed CLBR Tick Repellent Study LNX-003 with Two Formulations of Picaridin

In earlier meetings the HSRB has reviewed proposals from Carroll-Loye Biological Research (CLBR) for field studies, designated LNX-001 and LNX-002, of mosquito or biting fly repellency of two formulations containing 20% picaridin. This new proposal, LNX-003, is for a laboratory study of the repellency of the same two products to two species of ticks.

LNX-003 is similar to previous Carroll-Loye tick studies reviewed by the Board, but differs in general format and organization. Carroll-Loye has substantially revised their protocol "template" to reflect the many changes made over the past three years to incorporate recommendations from EPA and the HSRB.

EPA's regulation at 40 CFR §26.1125 requires a sponsor or investigator to submit to EPA, before conducting a study involving intentional exposure of human subjects, a protocol and supporting materials describing the proposed human research. In addition, EPA's regulation at 40 CFR §26.1601 requires EPA to conduct science and ethics reviews of submitted proposals, and to seek HSRB review of the proposed research. Because the proposed research involves exposure of subjects that would not occur but for their participation in the research, it meets the regulatory definition of "research involving intentional exposure of a human subject," and thus these provisions of regulation apply to it.

EPA has reviewed both the scientific and ethical aspects of Carroll-Loye protocol LNX-003, and has concluded that, with minor revisions, it is 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.

2. EPA is providing the following materials on the proposed Carroll-Loye tick repellent efficacy study LNX-003:

   a. CLBR Protocol LNX-003 MRID 47836801 (7/27/09)

   b. Supplemental IIRB, Inc. Documentation

   c. CLBR Memorandum Explaining Planned Amendments (9/16/09)

   d. EPA Science and Ethics Review of LNX-003 (9/21/09)

Charge Questions:

If the proposed laboratory tick repellency study protocol LNX-003 is revised as suggested in EPA's review and if the research is performed as described:

2.1 Is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested materials in repelling ticks?

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

3. Proposed AEATF-II research on exposure of janitorial workers applying antimicrobial pesticides formulated as aerosol sprays

In several previous meetings the HSRB has considered the design and conduct of research to measure the levels of exposure received by professionals who mix, load, or apply pesticides using various types of equipment. Most of these discussions have been of agricultural pesticides; at its April 2008 meeting the Board considered proposals for monitoring janitorial workers applying antimicrobial pesticides using a mop or wipe. At this meeting the Board will consider another proposed handler exposure scenario involving janitorial workers who apply antimicrobial pesticides formulated as aerosol sprays. This proposal is generally similar to those the Board has seen before from the Antimicrobials Exposure Assessment Task Force II (AEATF-II), but incorporates numerous refinements responsive to earlier EPA and HSRB comments and recommendations, and addressing lessons learned in the field execution of the earlier mop and wipe studies.

This new proposal is to monitor the exposure of experienced janitorial workers as they apply antimicrobial pesticides formulated as aerosol sprays. The AEA04 protocol calls for collection of six Monitoring Events (MEs) from each of three clusters, each of which is to be sited in a different hotel/motel in the Fresno area, for a total of 18 MEs.

When the scenario is complete, the resulting data will be posted to the Biocide Handlers Exposure Database (BHED™). EPA intends to use these data generically to estimate daily dermal and inhalation exposures of pesticide handlers who apply aerosol antimicrobial pesticides. Data from this scenario addressing exposure from spraying only can be combined with data from the wiping scenario to estimate exposures of pesticide handlers who both apply aerosol sprays and then wipe down the treated surfaces.

Because the proposed research involves scripted exposure, it meets the regulatory definition of "research involving intentional exposure of a human subject" and thus is covered by subparts K and L of EPA's amended rule for the protection of human subjects of research. The rule at 40 CFR §26.1125 requires a sponsor or investigator to submit to EPA, before conducting a study involving intentional exposure of human subjects, the protocol and related materials describing the proposed human research. In addition, EPA's regulation at 40 CFR §26.1601 requires EPA to conduct science and ethics reviews of the submitted proposal and to seek HSRB review of the proposed research.

EPA has reviewed the AEATF Aerosol Application scenario and the associated protocol AEA04, 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. Since EPA finds that the protocols can be easily revised to meet applicable scientific and ethical standards, EPA is presenting this protocol for review by the HSRB at its October 2009 meeting.

3. EPA is providing the following materials concerning the AHETF proposal for monitoring mixers/loaders using water-soluble packaging:

    a. AEATF-II Aerosol Application Scenario: Rationale for Study Design (8/4/09)

    Defines the scenario, documents the general patterns of use of aerosol antimicrobial pesticides and the choice to focus on hard-surface treatments, the initial purposive choices leading to selection of the test material, cluster sites, and the multi-tiered plan for selecting workers to monitor.

    b. AEATF-II Aerosol Application Protocol AEA04 (8/4/09)

    Includes the protocol itself as approved by the IIRB, Inc., on July 22, 2009, and the records of IIRB, Inc., approval.

    c. Supplemental File of IRB Correspondence Re: AEA04 (8/4/09)

    d. AEATF-II SOPs (8/4/09)

    e. AEATF-II memos clarifying Aerosol Proposal

    f. EPA Science and Ethics Review: Aerosol Application Scenario and AEA04 (9/21/09)

Charge Questions:

If the proposed AEATF-II aerosol application scenario and field study protocol AEA04 is revised as suggested in EPA's review and if the research is performed as described:

3.1 Is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply antimicrobial pesticides formulated as aerosol sprays?

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