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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 18, 2006

MEMORANDUM

Subject: Transmission 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: William L. Jordan
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Office of Pesticide Programs (7501P)

This memorandum transmits the materials for review by the Agency's Human Studies Review Board (HSRB or Board) at the meeting scheduled for October 18-19, 2006. This meeting will address scientific and ethical issues surrounding:

- a completed human toxicity study, evaluating the allergic contact dermatitis response in individuals with known sensitivity to hexavalent chromium to repeated exposure to a wood treatment solution containing hexavalent chromium;

- two revised research protocols to evaluate the efficacy of new formulations of the repellent IR3535 against ticks and mosquitoes (the Board reviewed and commented on earlier versions of these revised protocols at its June 2006 meeting); and

- a draft EPA guidance document informing the public about how and when to submit materials concerning research involving human subjects for EPA and HSRB review.

Each of these topics is described more fully below.

The Agency notes that materials we sent to the HSRB for previous meetings contain information which may provide useful background for the topics scheduled for review in the October 2006 meeting. In particular, we refer the Board to the FIFRA Scientific Advisory Panel (SAP) report on how to evaluate the level of exposure to hexavalent chromium, below which exposure does not elicit allergic contact dermatitis in a specified percentage of individuals with known sensitivity to hexavalent chromium; and to the Agency's draft guidelines for the conduct of insect repellent efficacy research and the SAP's report on a draft of those guidelines. These materials may be found at: www.epa.gov/osa/hsrb/meetings.htm (May 2-3, 2006 meeting) for chromium, and http://www.epa.gov/osa/hsrb/backgrounddocuments.htm for insect repellent efficacy research.

A. Chromium Repeat Open Application Test (ROAT)

Description. The Agency has received a report on a study involving repeated open dermal application of a wood treatment solution containing hexavalent chromium to human subjects with known sensitivity to hexavalent chromium. This study was initiated prior to the effective date of EPA regulation in 40 CFR Part 26, subparts K – Q, but submitted after the effective date of subpart M, which requires documentation of ethical conduct. The Agency has reviewed the study and supplemental materials concerning its ethical conduct and determined that the study meets the applicable provisions of the EPA regulations and deems the study ethically acceptable. EPA has also concluded the report provides scientifically sound information that can be used to estimate a level of exposure to hexavalent chromium (together with confidence limits), below which exposure would be unlikely to elicit an allergenic response in a specified percentage of individuals with a preexisting sensitivity to hexavalent chromium. The Agency's regulation, 40 CFR § 26.1602, requires EPA to seek HSRB review of EPA's decision to rely on the results of this study.

The hexavalent chromium study has been submitted in connection with a pending application to register a wood preservative product that contains Acid Copper Chromate (ACC). By statute, EPA must make a decision on this application before the next scheduled HSRB meeting. Accordingly, EPA regards HSRB review of this study as a priority for the October 2006 meeting.

Materials. EPA is providing the following types of material to the HSRB:

- MRID 46884001: Proctor, D.; Gujral, S.; Fowler, J. (2006) Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as CopperShield®: Risk Assessment for Dermal Contact with Cr(VI). Unpublished study conducted by Dermatology Specialists, PSC, and Exponent under Project No. FPRL #012506. 324 p.

- MRID 46922901: Proctor, D.; Gujral, S.; Fowler, J. (2006) Supplemental Information to the Final Report Titled "Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as CopperShield®: Risk Assessment for Dermal Contact with Cr(VI)." Unpublished document dated August 24, 2006. Project No. FPRL #012506. 347 p.

- MRID 46930701: Proctor, D.; Gujral, S.; Su, S.; Fowler, J. (2006) Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as Potassium Dichromate: Risk Assessment for Dermal Contact with Cr(VI). Unpublished study conducted by Dermatology Specialists, PSC, and Exponent under Project No. FPRL #012406. Includes Supplemental Information documenting ethical conduct of the research. 664 p.

- EPA Data Evaluation Record (DER) of the ROAT study

- EPA ethics review of the ROAT study dated 9/12/06

The folder identified as "Chromium ROAT Study" contains these materials. The folder includes a file named "Read this first," which identifies each of the individual files in the folder.

Charge Questions.

Hexavalent chromium is a component of a pesticide product intended to be used as a wood preservative. Members of the general public may experience dermal exposure to residues of hexavalent chromium remaining on wood treated with a wood preservative. Because chromium has caused allergic contact dermatitis (ACD) in occupational settings, EPA has determined that it should assess the potential for ACD in the general public resulting from exposure to hexavalent chromium on wood treated with acid copper chromate (ACC).

1. *Scientific considerations:*

   The Agency has concluded that the study contains information sufficient for assessing human risk resulting from potential dermal exposure to wood treated with ACC, containing hexavalent chromium.

   Please comment on whether this study is sufficiently sound, from a scientific perspective, to be used to estimate a safe level of repeated dermal exposure to residues of ACC on treated wood.

2. *Ethical considerations:*

The Agency requests that the Board provide comment on the following:

a. Is there clear and convincing evidence that the conduct of the hexavalent chromium ROAT study was fundamentally unethical?

b. Is there clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted?

B. IR3535 Insect Repellent Efficacy Protocols

Description. EPA requires data from efficacy studies using appropriate insect species to support an application for registration of a new product making insect repellency claims. An applicant for registration typically conducts such research prior to submitting an application. If such a study is to be initiated after April 7, 2006, the Agency's regulation, 40 CFR § 261125, requires the sponsor or investigator to submit to EPA, before conducting the study, 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.

In its June 2006 meeting, the HSRB reviewed and commented on materials relating to two proposed insect repellent efficacy protocols from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. The two protocols described research to evaluate the efficacy of new formulations of repellent products containing the active ingredient, IR 3535. One study would be conducted under laboratory conditions to measure the efficacy of the test formulations against ticks. The second study would measure the efficacy of the test formulations against mosquitoes under field conditions. The HSRB offered extensive comments on the two protocols. Following the June 2006 meeting, Dr. Carroll revised the protocols to address comments from the HSRB. EPA has reviewed Dr. Carroll's revised protocols and has concluded that 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 of the extent of the revisions to Dr. Carroll's earlier protocols, the Agency has decided to ask the HSRB to review the protocols again.

The Board has already reviewed Dr. Carroll's research proposals, and EPA believes Dr. Carroll has made a diligent, good faith effort to revise the protocols to address the Board's recommendations. Since EPA attempts to provide timely review and responses to sponsors who seek Agency review and since EPA thinks these protocols meet applicable scientific and ethical standards, EPA is presenting these protocols for review at the Board's October 2006 meeting.

Materials. EPA is providing the following materials to the HSRB:

EMD-003 (Tick repellency study)

- "READ THIS FIRST": an annotated bibliography of the other materials in the subfolder
- Transmittal EMD-003 9/10/06
- EMD-003 with IRB approval 9/12/06
- EMD-003 Errata 9/14/06
- Training Materials for subjects
  - Tick Handling Training Materials
  - Dosimetry Training Materials (Same as for EMD-004)
- IRB Review of EMD-003
- IRB Correspondence Record (Same as for EMD-004)
- EPA Science & Ethics Review of EMD-003: 9/15/06

EMD-004 (Mosquito repellency study)

- "READ THIS FIRST": an annotated bibliography of the other materials in the subfolder
- Transmittal EMD-004 9/10/06
- EMD-004 with IRB approval 9/12/06
- EMD-004 Errata 9/14/06
- Training Materials for subjects
  - Mosquito Aspiration Training Materials
  - Dosimetry Training Materials (Same as for EMD-003)
- IRB Review of EMD-004
- IRB Correspondence Record (Same as for EMD-003)
- California DPR Approval of EMD-004
- EPA Science & Ethics Review of EMD-004: 9/15/06

The folder identified as “IR 3535 Protocols” contains these materials, orgainized in two subfolders for the two different protocols. Each subfolder includes a file named “Read this first,” which identifies each of the individual files in the folder.

Charge Questions.

1. *Study EMD-003 from Carroll-Loye Biological Research*

   a. Does the proposed research described in Study EMD-003 from Carroll-Loye Biological Research appear likely to generate scientifically reliable data, useful for assessing the efficacy of a test substance for repelling ticks?

b. Does the proposed research described in Study EMD-003 from Carroll-Loye Biological Research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

2. Study EMD-004 from Carroll-Loye Biological Research

a. Does the proposed research described in Study EMD-004 from Carroll-Loye Biological Research appear likely to generate scientifically reliable data, useful for assessing the efficacy of a test substance for repelling mosquitoes?

b. Does the proposed research described in Study EMD-004 from Carroll-Loye Biological Research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

3. Review format

Please comment on the format used for EPA's science and ethics reviews of Dr. Carroll's protocols in terms of:

a. whether future use of this format is likely to produce reviews that adequately explain the basis for EPA's position regarding the ethical and scientific acceptability of the proposed research; and

b. whether presentation of future EPA reviews in such a format will assist the Board's review of proposed protocols.

C. Draft EPA Guidance on the Submission of Materials Concerning Proposed New Human Research

Description. As noted above, the Agency's regulation at 40 CFR §26.1125, requires a sponsor or investigator to submit specified materials to allow EPA and the HSRB to review the scientific and ethical aspects of the conduct of certain types of proposed human research before the research is initiated. Based on its experience with early submissions of protocols and associated materials since this provision took effect, EPA believes the public would benefit from guidance explaining what materials should be presented, how they would be most effectively organized, how EPA would approach the review of a submission, and how long EPA would expect to take to complete its review of the material and to prepare the materials for submission to the HSRB. Accordingly, EPA has drafted a guidance document, referred to as a PR Notice, containing recommendations for researchers who might submit materials under 40 CFR §26.1125.

EPA believes the most efficient process for review of proposals for covered human research would be for submitters to transmit to EPA a complete

package which could be sent to the HSRB, without EPA having to make any changes to the organization of the materials. Since such an approach would mean that the Board would usually be reviewing materials in the form they were originally submitted, EPA will ask the Board whether the guidance for form and content of protocol submissions suggested in the draft guidance represents an acceptable way of presenting researchers' materials for HSRB review. (Of course, in addition to the materials as submitted, EPA would provide to the Board its own reviews of submitted protocols.)

While not required to undergo HSRB review, EPA regards this draft guidance as an important step toward improved quality and completeness of protocol submissions and toward increased efficiency of both EPA and HSRB reviews of proposed new research. Thus, EPA regards HSRB review of the draft guidance as a priority for the October 2006 meeting.

Materials. EPA is providing a draft PR Notice to the HSRB. The folder identified as "Draft Guidance on Human Research" contains this document.

Charge Question.

Please comment on the approach, as described in EPA's draft PR Notice, to organizing materials submitted under 40 CFR § 26.1125 for EPA and HSRB review. In particular, please address whether this approach is appropriate for anticipated types of studies involving intentional exposure of human subjects, and whether EPA should provide different guidance for various types of research.