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

OFFICE OF
PREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

March 19, 2007

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 describes the materials being provided for review by the Agency's Human Studies Review Board (HSRB or Board) at the meeting scheduled for April 18 - 20, 2007. This meeting will address scientific and ethical issues surrounding:

- The results of two completed insect repellent efficacy studies on an aerosol formulation of the active ingredient IR3535, studies on which the Agency intends to rely in making registration decisions. One is a laboratory study with ticks (EMD-003.3); the other is a field study with mosquitoes (EMD-004.3). The Board initially commented on the protocols for these studies at it June 2006 meeting and then favorably reviewed the revised protocols for these studies at its October 2006 meeting.

- A research proposal to evaluate the efficacy of products containing oil of lemon eucalyptus in repelling mosquitoes in the field.

- Completed studies of human skin irritation and skin sensitization on two formulations of a pesticide product whose use would involve extensive dermal exposure.
- An EPA draft "Best Practices Framework" concerning the process for recruiting and enrolling subjects in studies of occupational exposure.

- EPA's approach to assessing the need for new research on the exposures received by occupational handlers who mix, load, or apply agricultural or antimicrobial pesticides.

Each of these topics is described more fully below.

In addition, at the Board's request, EPA will discuss it approach to interpreting and applying the standard in 40 CFR §26.1705: ". . . 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 [EPA's human studies rules]."

A. Completed IR3535 Insect Repellent Efficacy Studies

Description. In two previous meetings the HSRB reviewed and commented on materials relating to two insect repellent efficacy protocols from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. These two protocols described proposed research to evaluate the efficacy of three new formulations of repellent products containing the active ingredient IR-3535. The protocol identified as EMD-003 described a laboratory study of efficacy of the test formulations against ticks. The protocol identified as EMD-004 described a field study of efficacy of the test formulations against mosquitoes.

The HSRB offered extensive comments on the two protocols at its June 2006 meeting. Following that meeting, Dr. Carroll revised the protocols to address comments from the HSRB. EPA reviewed Dr. Carroll's revised protocols and concluded that they appeared 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. When the HSRB reconsidered the revised protocols at its October 2006 meeting, it concurred with EPA's assessment and suggested some minor additional refinements. Dr. Carroll proceeded to conduct the research and has submitted the results to EPA for review.

The Board reviewed the results of the research on two of the formulations, a lotion and a pump spray, at its January 2007. The report on the study with the third formulation, an aerosol, arrived too late to permit its review at the January meeting. Thus, EPA is presenting the results of the aerosol testing 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 not yet submitted an application to register these products, but with Agency concurrence

submitted the completed studies ahead of the applications so that HSRB review would not compromise EPA's ability to review the application within the time allowed by statute. The Agency expects to receive such an application in the near future. In order to facilitate timely review of the application, EPA has reviewed the studies, applying the standard in 40 CFR §26.1705. That provision 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.

The Agency's reviews concluded that the data are scientifically sound and that the research was conducted in a manner that deviates at least technically from some of the requirements of subparts K and L of EPA's final rule establishing Protections for Subjects in Human Research—the only subparts of the rule which apply to third-party research. The Agency seeks the Board's advice on whether the available information supports a determination of "substantial compliance" with the applicable rules. Assuming a potential determination of substantial compliance, and because EPA would like to rely on these data to support an application for registration of these formulations, EPA is presenting these studies for review at the Board's April 2007 meeting

EPA is providing the following materials to the HSRB in the folder identified as "Insect Repellent Efficacy Studies EMD-003 and EMD-004":

Completed Repellent Efficacy Studies of IR3535 Aerosol

a. Read this first – Annotated Bibliography:

In addition this folder contains two subfolders.

EMD-003.3: Laboratory Tick Repellency of IR3535 Aerosol Subfolder

a. EPA Review of EMD-003 protocol 9/15/06

This is EPA's combined science and ethics review of the protocol, provided to the HSRB for the October meeting.

b. Final HSRB Report on EMD-003 protocol 1/21/07

This is the section of the final HSRB report on the discussion of this protocol at the October HSRB meeting. This passage appears in the full report on pages 18-22.

c. Draft Final HSRB Report on EMD-003.1/2 completed studies

This is the section of the draft final HSRB report dated March 2, 2007, on the discussion at the January 2007 HSRB meeting of the reports of completed studies executing this protocol with two other IR3535 formulations. It appears in the full draft final report on pages 10-16.

c. EMD-003.3 Aerosol MRID 47045901 Revised 2-3-07

This is the report of the completed study. This version was edited after the January HSRB discussion and submitted on February 5, 2007. It includes the transmittal document as well as relevant IRB correspondence and other supporting information.

e. EMD-003.3 Science Review 3/9/07

This review addresses MRID 47045901, supplemented by an exchange of email between Clara Fuentes, the EPA reviewer, and Scott Carroll, the Principal Investigator.

f. EMD-003.3 Ethics Review 3/14/07

This review addresses MRID 47045901.

EMD-004.3: Field Mosquito Repellency of IR3535 Aerosol Subfolder

a. EPA Review of EMD-004 protocol 9/15/06

This is EPA's combined science and ethics review of the protocol, provided to the HSRB for the October meeting.

b. Final HSRB Report on EMD-004 protocol 1/21/07

This is the section of the final HSRB report on the discussion of this protocol at the October HSRB meeting. This passage appears in the full report on pages 22-26.

c. Draft Final HSRB Report on EMD-004.1/2 completed studies

This is the section of the draft final HSRB report dated March 2, 2007, on the discussion at the January 2007 HSRB meeting of the reports of completed studies executing this protocol with two other IR3535 formulations. It appears in the full draft final report on pages 16-22.

d. EMD-004.3 Aerosol MRID 47049502 Revised 2-5-07

This version of the study report was edited after the January HSRB discussion and submitted on February 5, 2007. It includes relevant IRB correspondence.

e. EMD-004.3 Science Review 3/1/07

This review addresses MRID 47045902, supplemented by an exchange of email between Clara Fuentes, the EPA reviewer, and Scott Carroll, the Principal Investigator.

f. EMD-004.3 Ethics Review 3/14/07

This review addresses MRID 47045902.

Charge Questions.

1. *EMD-003.3: Tick Repellency with Aerosol Spray Formulations:*

   a. Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against ticks?

   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?

2. *EMD-004.3: Mosquito Repellency with Aerosol Spray Formulations:*

   a. Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against mosquitoes?

   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?

B. Oil of Lemon Eucalyptus Insect Repellent Efficacy Protocol WPC-001

Description. EPA requires data from efficacy studies using appropriate insect species to support claims of greater efficacy than have previously been approved.

An applicant for new or amended registration typically conducts such research prior to submitting an application. In this instance, however, EPA approved a conditional registration for the product with a label claim for repellency lasting "up to 6 hours." EPA required the company as a condition of continued registration to conduct a field study to support the label efficacy claim.

EPA's regulation, 40 CFR §26.1125, 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.

Dr. Scott Carroll has submitted a description of proposed research to be performed by Carroll-Loye Biological Research. The proposal, identified as WPC-001, describes a study to evaluate the field efficacy against wild mosquitoes of a repellent product containing the active ingredient Oil of Lemon Eucalyptus. The proposal bears many similarities to the protocols EMD-004 and SCI-001 that the HSRB has previously reviewed. EPA has reviewed Dr. Carroll's protocol and has concluded that, with some required refinements, it appears 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.

EPA has identified some relatively easily corrected deficiencies in the protocol, which must be corrected before execution. In the interest of providing a thorough and timely response to the proposal, and since EPA finds the protocol generally meets applicable scientific and ethical standards, EPA is presenting this protocol for review at the Board's April 2007 meeting.

EPA is providing the following materials to the HSRB in the folder identified as "Insect Repellent Efficacy Protocol WPC-001":

WPC-001 (Mosquito repellency study)

a. WPC-001 1-16-07:
The protocol as approved by the IIRB on 1/23/07 and submitted to EPA on 1/30/07.

b. EPA Science & Ethics Review WPC-001 3/13/07
This review addresses the protocol as submitted.

Charge Question.

1. Protocol WPC-001 from Carroll-Loye Biological Research:

a. If the proposed research described in Protocol WPC-001 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes?

b. If the proposed research described in Protocol WPC-001 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the

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

C. Completed Skin Irritation and Skin Sensitization Patch Test Studies

Description. EPA requires applicants for registration of pesticide products that are intended for extensive contact with human skin to provide scientific data evaluating the potential for such products to cause irritation and sensitization. Although many products rely on the results of studies conducted with laboratory animals, generally rats, mice, guinea pigs, or rabbits, EPA has also accepted the results of such studies when conducted with humans.

EPA uses the results from dermal irritation and dermal sensitization studies to assign a product to a hazard category and to require label statements appropriate to the category. EPA can also use the data to determine whether potential exposure of people who handle a pesticide poses a risk and whether those risks can be mitigated by labeling requirements, such as warning statements or requirements for actions that could reduce exposure such as using protective equipment.

The Agency has received an application for registration of a product that is intended to be applied directly to human skin. The applicant / sponsor has submitted the results of two studies, a 48 hour dermal irritation patch study and a repeated insult patch test sensitization study. Each of these two studies was conducted with two different formulations containing the same active ingredient. The studies were initiated before EPA's Human Studies regulation took effect, and therefore they are subject to review under §§ 26.1703 and 26.1704 of 40 CFR. Those sections provide:

§26.1703 Prohibition on reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women or children.

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, EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or child.

§26.1704 Prohibition on reliance on unethical research with non-pregnant, non-nursing adults conducted before 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 before April 7, 2006, if there is clear and convincing evidence that the conduct oft 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.

The Agency has reviewed the studies in connection with the application and has concerns regarding the design and conduct of the research. Because EPA has not previously received HSRB views on these kinds of research, EPA will wait to make conclusions on the acceptability of these studies pending the HSRB's comments on the scientific and ethical merit of these studies. Assuming that the studies are scientifically sound and ethically acceptable, EPA intends to rely on them in reaching its decision on the pending application. The Agency believes these studies are ready for review by the HSRB at its April meeting.

The following materials are included in a folder named "Completed Skin Irritation and Sensitization Patch Tests."

a. Read this first: annotated bibliography

b. Redacted supplement responding to EPA Questions.

This document, submitted March 2, 2007, addresses EPA questions raised in emails of November 16, 2006 and January 30, 2007. The questions and the responses concern both the 48-h Irritation Study and the Repeated Insult Patch Test (RIPT) for sensitization. Although multiple copies were submitted directed to different EPA case files, their content is identical, and only one copy is provided here.

WHO Monographs on Repellent Active Ingredients.

These three monographs, from the series "WHO Specifications and Evaluations for Public Health Pesticides", address the three principal active ingredients used in repellents. They may assist the members of the HSRB to understand the properties and effects of these materials. Because the composition of the products tested in these patch studies is subject to a claim of confidentiality EPA cannot identify the active ingredient in the products, but it does appear in currently registered repellent products. WHO has issued full evaluations in the format used for IR3535 and Picaridin only since 2002. The information concerning DEET is more limited.

c. WHO Picaridin Evaluation October 2004

d. WHO IR3535 Evaluation April 2006

e. WHO DEET Specification December 1999.

f. EPA DEET RED Fact Sheet April 1998.

In addition there are two subfolders:

48-h Irritation Study Subfolder.

An animal test of acute dermal irritation is a standard require-ment for registration of end-use pesticide products. This human study was submitted as an alternative to the required animal test. It was conducted with five test materials, and reported separately for each of two of the five. No information is available to EPA concerning the remaining three test materials.

a. **Redacted 48-h Irritation-Product A.** This is the revised redaction reflecting the narrowing of the scope of CBI claims to cover only the sponsor, the product name, and the product composition. This document reports results only for Product A, one of five included in the research; it is otherwise identical to the report below.

b. **Redacted 48-h Irritation-Product B.** This is the revised redaction reflecting the narrowing of the scope of CBI claims to cover only the sponsor, the product name, and the product composition. This document reports results only for Product B, one of five included in the research; it is otherwise identical to the report above.

c. **Science Review: 48-h Irritation.** This review addresses the common elements in the two reports, and the results for both products A and B.

d. **Ethics Review: 48-h Irritation.** This review addresses the ethical conduct of the study, without regard to the specific products tested. Page references are to the report for Product A.

Repeated Insult Patch Test (RIPT) Study Subfolder.

An animal test of skin sensitization is a standard requirement for registration of end-use pesticide products. This human study was submitted as an alternative to the required animal test. It was conducted as two sub-studies, one involving 14 test materials and the other involving 15 test materials. At least Products A and B were tested in both sub-studies; no information is available to EPA concerning the remaining test materials. Each of the submitted reports covers one test material, including the results of both sub-studies.

a. **Redacted RIPT Product A.** This is the revised redaction reflecting the narrowing of the scope of CBI claims to cover only the sponsor, the product name, and the product composition. This document reports results only for Product A, one of 15 materials included in the research; it is otherwise identical to the report below.

b. Redacted RIPT Product B. This is the revised redaction reflecting the narrowing of the scope of CBI claims to cover only the sponsor, the product name, and the product composition. This document reports results only for Product B, one of 15 materials included in the research; it is otherwise identical to the report above.

c. Science Review: RIPT Study. This review addresses the common elements in the two reports, and the results for both products A and B.

d. Ethics Review: RIPT Study. This review addresses the ethical conduct of the study, without regard to the specific products tested. Page references are to the report for Product A.

e. European Commission Scientific Committee on Consumer Products (2005) Memorandum: Classification and categorization of skin sensitizers and grading of test reactions. This is another supplemental resource, laying out how the EC assesses consumer products for skin sensitization potential.

f. OECD Scientific Issue Paper on Strong vs. Weak Sensitizers

Charge Questions.

1. 48 hour Dermal Irritation Patch Study

a. Is this study sufficiently sound, from a scientific perspective, to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to irritate human skin?

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

2. Repeated Insult Patch Test Sensitization Study

a. Is this study sufficiently sound, from a scientific perspective, to be used to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to cause sensitization of human skin?

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

D. Draft "Framework" Concerning Best Practices for Recruiting and Enrolling Subjects in Studies of Occupational Exposure

The Agency has been working with two industry task forces–the Agricultural Handlers Exposure Task Force (AHETF) and the Antimicrobial Exposure Assessment Task Force (AEATF)–planning to conduct research to measure exposure received by pesticide handlers when mixing, loading, or applying agricultural or antimicrobial pesticides. In June 2006 the Board reviewed 5 proposed protocols developed by the AHETF. The Board raised questions and made numerous comments on both scientific and ethical aspects of the proposals.

Since June, EPA and the Task Forces have been addressing the issues identified by the HSRB. Both the AHETF and AEATF are preparing extensively expanded justifications for their proposed research, and expect to submit to EPA protocols and related materials for new research that they plan to conduct in the winter of 2007–2008 (AEATF) or during the pesticide use season in 2008 (AHETF). Since EPA regards the proposed studies as "research involving intentional exposure of human subjects," EPA regulations require the Agency and the Board to review these proposals before the investigators initiate the studies.

Although EPA and the Task Forces do not expect HSRB review of specific protocols to occur until the Board's October 2007 meeting, EPA believes that it would be useful for EPA and the Board to provide guidance on selected, fundamental matters affecting all of the protocols before they are submitted for review. In particular, EPA thinks it would be helpful to offer guidance on best practices that investigators could employ to recruit and enroll subjects into this kind of research. Since it is especially important that subjects participating in the research be representative of the larger handler population, it is likely that some of the potential subjects will have characteristics that require careful consideration and special procedures to ensure a recruitment and enrollment process consistent with Subpart K. For example, potential subjects may not speak English well, so the informed consent process may need to be conducted in a language other than English. Potential subjects may also have limited education and will need informed consent materials presented simply enough so they can understand them. Potential subjects may be in the U.S. illegally, and investigators will need to address their legitimate privacy concerns.

EPA has prepared a document that identifies the major elements of the recruitment and enrollment processes that should be considered by investigators as they prepare protocols for handler exposure research. In addition, the document discusses broad principles which should be considered in the course of research design. In future, through a participatory process involving investigators, workers, and other stakeholders EPA intends to add to the document specific best practices and identify publicly available resources that contain additional discussion, information, and guidance relevant to the implementation of general ethical principles in occupational exposure research. In order to ensure the Task Forces have timely advice for use in drafting their protocols for subsequent review, the Agency is seeking HSRB review of the draft framework for this effort at its April meeting.

The following document is included in a folder named "Draft Framework for Best Practices."

Draft Framework for Best Practices

Charge Questions.

1. What additional elements of the process of recruiting and enrolling subjects in handler exposure research should be addressed in a "Best Practices Framework"?

2. For each of the elements in the "Best Practices Framework," please identify any additional sources of guidance that could be useful for an investigator who is designing a process for recruiting and enrolling subjects in handler exposure research.

E. Assessing the Need for New Research on Pesticide Handler Exposure

As noted above, EPA has been working with two Task Forces that are planning to conduct research to measure the exposure received by people who handle agricultural and antimicrobial pesticides. In June 2006, EPA asked the HSRB to review 5 protocols developed by one of these Task Forces, the Agricultural Handlers Exposure Task Force (AHETF). One of the fundamental issues identified by the Board about these proposals was whether there was a need for the new data that would result from the proposed research.

In response to scientific concerns raised by the HSRB, EPA analyzed the existing handler exposure database, as well as relevant scientific literature. The Agency presented its analysis to the FIFRA Scientific Advisory Panel (SAP) in January 2007. The Agency asked the SAP to comment on, among other topics, the "limitations [of existing data] and on EPA's conclusion that additional data could improve significantly EPA's ability to estimate worker exposure." The SAP is still drafting its report, which is expected to be released by the end of March.

EPA will address, in general terms, the threshold question of whether new handler exposure research could produce data that would be valuable for EPA risk assessments. Much of the information in these presentations is adapted from materials EPA presented to the SAP.

The following document is included.

ExposureSAP.Jan2007.v121206.

This document provides the background information for the SAP panel discussion previously held on January 9-2. It includes a summary presentation of the methods that the Agency currently uses for calculating worker exposures. It also includes the background information and Agency analyses related to the charge questions considered by the SAP. It also introduces the industry groups who are

going to be developing a large amount of the occupational monitoring data that are to be used by the Agency. The key topics addressed in the document include the data currently used by the Agency, a discussion of monitoring techniques based on passive methods and biological monitoring as well as how they compare with one another, an examination of hand sampling methods which has been a key concern for the Agency, a discussion about how applicable exposure estimates are across varied situations in agriculture, and a discussion of the research plans proposed by the industry task forces including inter- and intra-worker variability and the needed numbers of samples.

In addition, EPA expects to provide the Board with the report of the FIFRA Scientific Advisory Panel for the January 9-12 Meeting as soon as it is available. Board members interested in additional information can review all of the materials provided to the SAP for its January meeting on the EPA website at: www.epa.gov/scipoly/sap/index.htm under the heading "Meetings for the Year 2007:" January 9-12.

Charge Question.

1. Please comment on EPA's conclusions that:

   a. the Pesticide Handlers Exposure Database (PHED) has significant limitations with respect to the quality and quantity of data contained in the database which limits EPA's ability to fully characterize the range, magnitude, and variability of potential exposures of pesticide handlers, and

   b. EPA needs additional data beyond the information available in PHED to improve its ability to assess potential exposure of pesticide handlers.