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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 27, 2007

MEMORANDUM

Subject: Transmission of materials for review by the Human Studies Review Board for its October 2007 Meeting

To: Paul 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 materials being provided by the Office of Pesticide Programs for review by the Agency's Human Studies Review Board (HSRB or Board) at the meeting scheduled for October 24-26, 2007. This meeting will address, among other topics, scientific and ethical issues surrounding:

- A published report (Black et al. 1954) of a completed clinical trial measuring the effects on blood pressure in human subjects of single and repeated treatments with sodium azide. Sodium azide is also a pesticidal active ingredient proposed as a replacement for the fumigant methyl bromide. [A]

- Three interrelated product-specific reports of a single completed field study (SCI-001) by Carroll-Loye Biological Research of the mosquito repellent efficacy of four pesticides, all containing Deet. [B]

- A report of a completed field study (WPC-001) by Carroll-Loye Biological Research of the mosquito repellent efficacy of a registered product containing Oil of Lemon Eucalyptus. [C]

- A research proposal (SPC-001) from Carroll-Loye Biological Research to evaluate the field efficacy against mosquitoes of two registered repellent sprays containing the active ingredient picaridin, and of one lotion formulation including both picaridin and a sunscreen, for which an application for registration is pending. [D]

- A research proposal (SPC-002) from Carroll-Loye Biological Research to evaluate the laboratory efficacy in repelling ticks of three registered products containing picaridin. [D]

- A research proposal (A 117) from Insect Control & Research, Inc., to evaluate the laboratory efficacy in repelling mosquitoes of the genus *Culex* of two registered products containing picaridin. [E]

Each of these topics is described more fully below.

In addition to the topics listed above, the Board will review and comment on a draft document entitled "Scientific and Ethical Approaches for Observational Exposure Studies," presented by Drs. Fortmann and Cupitt from EPA's Office of Research and Development. They will provide the Board will a separate memorandum explaining the context for the Board's review, describing the materials they are providing for Board review, and presenting the charge questions.

Finally, the agenda for the October meeting includes two other substantive topics. First, the Board has requested input from expert consultants on certain scientific issues involving the design of field studies to evaluate the efficacy of mosquito repellents, particularly the factors influencing the frequency and duration of mosquito landings on treated subjects. The consultants will respond to specific questions posed by the Board and then engage in further discussion with the Board. Second, OPP will provide an update to the Board on recent actions taken to address issues surrounding the design of sampling strategies for pesticide handler exposure research. OPP is working with independent experts on the design of sampling strategies and with representatives of the Agricultural Handlers Exposure Task Force and the Antimicrobials Exposure Assessment Task Force to reach a position on the issues about sampling design raised at the June 2007 HSRB meeting. OPP is not providing either any advance materials or charge questions for these two topics.

A. Completed Oral Therapeutic Study with Sodium Azide

In its registration program EPA reexamines the safety of pesticides being proposed for new or amended registration. The Agency is currently reviewing an application for registration of the active ingredient, sodium azide, as a limited replacement for the fumigant, methyl bromide. The application seeks to register sodium azide for commercial production of ornamental cut flowers and pre-plant application via drip tape irrigation on beds under plastic mulch; for sod farms with pre-plant application

to soil with tarping after application; and for golf course turf area renovation with pre-plant application and immediate tarping.

Sodium azide also has been used for many years as a laboratory reagent and as a raw material for production of azide-containing compounds. It has been used as a pharmaceutical intermediate and as a preservative of blood, laboratory reagents, and biological fluids. It has been used as a gas generant in automotive airbags, and was commonly used in early inflator designs. During the 1990s, however, airbag propellants containing NaN_3 were phased out in favor of more efficient, less expensive and less toxic alternatives. In the past, NaN_3 was also used as a pharmaceutical to treat high blood pressure and as an anti-neoplastic agent.

EPA has identified a study published in 1954 in which human subjects received oral doses of sodium azide to assess its potential for lowering blood pressure. The Agency intends to use this study in its hazard assessment to derive a "point of departure" (POD) for assessing acute and chronic toxicity resulting from both acute and chronic exposures to this chemical.

The Agency's regulation, 40 CFR §26.1602, requires EPA to seek HSRB review of an EPA decision to rely on the results of any study if the research was "initiated before April 7, 2006, and the research was conducted for the purpose of identifying or measuring a toxic effect." EPA has reviewed the study, applying the standards in 40 CFR §§26.1703 and 26.1704. Those provisions state:

> **§26.1703 Prohibition of 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 involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a 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 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.

The Agency's reviews concluded that the data are scientifically sound and that there is no clear and convincing evidence that the conduct of the research was

fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. Nor is there evidence to show that the subjects included nursing or pregnant women or children.

Review materials. EPA is providing the following materials to the HSRB in the folder identified as "Sodium Azide Study":

a. MRID 47221401 Black et al 1954

Black, M.; Zweifach, B.; Speer, F. (1954) "Comparison of Hypotensive Action of Sodium Azide in Normotensive and Hypertensive Patients." *In* Proceedings of the Society for Experimental Biology and Medicine, Jan 1954, pp. 11-16. MRID 47221401.

b. MRID 47221401 Data Evaluation Record

c. EPA WOE Sodium Azide 9-18-07

Memorandum from Nancy McCarroll to Jack Housenger, Associate Director Health Effects Division, "Human Studies Review Board: Weight of Evidence Discussion for Sodium azide (NaN_3)." September 18, 2007.

d. EPA Ethics Review MRID 47221401 9-27-07

Charge Questions

1. Black et al. oral therapeutic study on sodium azide

a. The Agency has concluded that this study contains information sufficient for assessing human risk resulting from potential acute and chronic exposure. Please comment on whether the study is sufficiently sound, from a scientific perspective, to be used as the point of departure to estimate a safe level of acute and chronic exposure to sodium azide.

b. Please comment on the following:

(1) Is there clear and convincing evidence that the conduct of the study was fundamentally unethical?

(2) 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. Completed Insect Repellent Efficacy Study (SCI-001) of DEET Formulations

Description. In its January 2007 meeting the HSRB reviewed and commented on materials relating to a comparative insect repellent efficacy protocol from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. The proposal, identified as SCI-001, described a study to evaluate the efficacy of four repellent formulations containing the active ingredient DEET. (One formulation included two other active ingredients as well.) The study was designed to measure the efficacy against mosquitoes under field conditions of three test formulations as compared to one "comparison article"—the US military standard repellent. The HSRB offered comments on the protocol at its January 2007 meeting. Following that meeting, Dr. Carroll revised the protocol to address comments from the HSRB. Dr. Carroll conducted the research in July 2007, and has submitted the results to EPA for review. EPA is presenting the results of this testing for review at this meeting.

Although the protocol SCI-001 was executed only once, the results are presented in three separate volumes, each one addressing a single test formulation as compared to the military standard repellent. Most of the material presented in each report is duplicated in the other two reports, but there are unique elements in each volume.

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 applications for amendment of two of the test materials citing these data, but the third test material (LipoDEET 3434) is not registered, nor is it the subject of any application. EPA has reviewed the research, 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.

Dr. Carroll conducted the research covered by SCI-001 at the same times and at the same locations as the research covered by protocol WPC-001, described below. Because these two protocols were executed concurrently, in the same field locations, with the same untreated controls, and with overlapping sets of treated subjects, EPA believes that the conduct of WPC-001 study may affect the results of SCI-001, and vice versa. Thus EPA has conducted a single ethics review addressing both studies, and will present both studies together at the HSRB meeting.

The Agency's science review raises questions about whether the data are scientifically sound. In addition, EPA's ethics review raises a questions about whether the research under SCI-001 was conducted in substantial compliance with 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. EPA seeks the Board's advice on whether the research data are scientifically sound and whether the available information supports a determination of "substantial compliance" with the applicable rules. If it is concluded that the data are scientifically sound and the research substantially complied with the applicable requirements, EPA would rely on these data in support of applications for new or amended registration of the test materials.

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

Completed Repellent Efficacy Study with Four DEET Formulations (SCI-001)

a. EPA Ethics Rvw SCI-001 & WPC-001 9-26-07

This review addresses both this study and the concurrently conducted WPC-001.

b. MRID 47211901 SCI-001.1 LipoDEET 302

Carroll, S. (2007) Test of Dermaegis LipoDEET 302 Personal Insect Repellent: EPA Reg. #82810-1. Unpublished study prepared by Carroll-Loye Biological Research under Project No. SCI-001.1. 219 p.

c. MRID 47208401 SCI-001.2 LipoDEET 3434

Carroll, S. (2007) Test of Dermaegis LipoDEET 3434 Personal Insect Repellent. Unpublished study prepared by Carroll-Loye Biological Research under Project No. SCI-001.2. 222 p.

d. MRID 47211801 SCI-001.3 Coulston's Duranon

Carroll, S. (2007) Test of Coulston's Duranon Personal Insect Repellent (EPA Reg. #50404-8). Unpublished study prepared by Carroll-Loye Biological Research under Project No. SCI-001.3. 217 p.

e. CLBR Supplement Re LipoDEET 3434

Carroll-Loye Biological Research's September 24, 2007 response to EPA's request for additional information about LipoDEET-3434 and the rationale for the amendment by which it became one of the test repellents

f. EPA Protocol Review SCI-001 12-20-06

g. 4-16-07 HSRB Report of Jan 07 discussion of SCI-001

h. SCI-001 Science Review 9-27-07

Charge Questions.

2. *SCI-001Mosquito Repellency with Four DEET Formulations:*

   a. Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes? Please comment specifically on:

      (i) Whether participation in field testing by several subjects on the day after they had been treated with a different test repellent is likely to have affected the validity of the results for those subjects on those days.

      (ii) The effects of changes to the experimental design resulting in evaluation of repellents using fewer than ten subjects per treatment per day, followed by pooling of results by site for statistical analysis.

   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? Please comment specifically on:

      (i) The decision to use a different test formulation in place of one of the test materials described in the protocol reviewed by the IRB, EPA and the HSRB.

      (ii) How to assess the ethical conduct of an insect repellency study involving multiple test formulations when there is an ethical deficiency in the conduct of the study with respect to one of the test formulations. If the ethical deficiency warrants not relying on the results of the testing with regard to one test formulation, under what circumstances (if any) does the ethical deficiency affect the acceptability of the results from testing the other formulations?

C. Completed Insect Repellent Efficacy Study with Oil of Lemon Eucalyptus (WPC-001)

Description. In the June 2007 meeting the HSRB reviewed and commented on materials relating an insect repellent efficacy protocol from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. The protocol described proposed research to evaluate the efficacy of a conditionally registered repellent product containing the active ingredient Oil of Lemon Eucalyptus (OLE). The protocol, identified as WPC-001, described a field study of efficacy of the test formulation against mosquitoes.

The HSRB offered comments on the protocol at its June 2007 meeting. Following that meeting, Dr. Carroll revised the protocols to address comments from the HSRB, conducted the study, and submitted the results. EPA is presenting the results of this research for HSRB 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. EPA has reviewed the study, 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.

As noted above, the principal investigator conducted the research covered by WPC-001 at the same times and at the same locations as the research covered by protocol SCI-001. Because these two protocols were executed together, EPA has questions about whether and how this fact affects the review of the separate reports.

The Agency's science review raises questions about whether the data are scientifically sound. In addition, depending on whether the study covered by WPC-001 is considered separate from the study covered by SCI-001, EPA's ethics review (discussed above under the heading of SCI-001) raises a question about whether the research under WPC-001 was conducted in a manner that substantially complies 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 research is scientifically sound and whether the available information supports a determination of "substantial compliance" with the applicable rules. If it is concluded that the data are scientifically sound and the research substantially complied with the applicable requirements, EPA would rely on these data to satisfy the data requirement imposed as part of the conditional registration of this product.

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

Completed Repellent Efficacy Studies of OLE

a. MRID 47217601 WPC-001 OLE

Carroll, S. (2007) Test of an Oil of Lemon Eucalyptus-Based Personal Insect Repellent: EPA Reg. #305-62. Unpublished study prepared by Carroll-Loye Biological Research under Project No. WPC-001. 225 p.

b. CLBR Supplement Re: Consent Documentation

Carroll-Loye Biological Research's September 20, 2007 response to EPA's request for additional information concerning which subjects signed which version(s) of the consent document on what date(s)

c. EPA Protocol Review WPC-001 3-13-07

d. 6-13-07 HSRB Report of Apr 07 discussion of WPC-001

e. WPC-001 Science Review 9-27-07

Charge Questions.

4. WPC-001 Mosquito Repellency with OLE Formulation:

a. Is the research conducted under WPC-001 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against mosquitoes? Please comment specifically on whether participation in field testing by several subjects on the day after they had been treated with a different test repellent is likely to have affected the validity of the results for those subjects on those days..

b. Does available information support a determination that the research covered by WPC-001 was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26? If the conduct of any part of SCI-001 is deemed not to substantially comply with the requirements of subparts K and L, please comment specifically on how to assess the ethical conduct of research conducted under WPC-001 in light of the fact that it was conducted at the same times and at the same places as the research covered under protocol SCI-001.

D. Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Studies (SPC-001 & SPC-002)

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

EPA's regulation, 40 CFR §26.1125, requires the 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 research proposal.

In previous meetings the HSRB has reviewed and commented favorably on several proposed insect repellent efficacy protocols to be conducted by Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. Dr. Carroll has submitted proposals for new research to evaluate the efficacy of two registered repellent sprays containing the active ingredient picaridin, as well as one lotion formulation including both picaridin and a sunscreen, for which an application for registration is pending. The first research protocol, identified as SPC-001, describes a field study of the efficacy of the test formulations against mosquitoes. The second research protocol, identified as SPC-002, describes a laboratory study of the efficacy of the test formulations against ticks. Both proposals bear many similarities to protocols that the HSRB has previously reviewed favorably.

EPA has concluded that, with some refinements, these protocols 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. The sponsor wishes to submit the data to EPA later this year to satisfy the requirement to provide efficacy data imposed when it received a conditional registration for picaridin and to support the pending application for registration for the repellent / sunscreen product. In the interest of providing a thorough and timely response to the proposals, and since EPA finds the protocols generally meet applicable scientific and ethical standards, EPA is presenting these protocols for review at the Board's October 2007 meeting.

Review materials. EPA is providing the following materials to the HSRB in the folder identified as "Carroll-Loye Repellent Protocols SPC-001 and SPC-002":

a. IIRB Minutes 7-17-2007

This single document addresses IIRB review of both protocols.

SPC-001: Field test of mosquito repellency

b. Carroll-Loye Protocol SPC-001 7-13-07

c. EPA Science & Ethics Review SPC-001 9-24-07

SPC-002: Laboratory test of tick repellency

d. Carroll-Loye Protocol SPC-002 7-10-07

e. EPA Science & Ethics Review SPC-002 9-24-07

Charge Questions.

5. Protocol SPC-001 from Carroll-Loye Biological Research:

a. If the proposed research described in Protocol SPC-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 SPC-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?

6. Protocol SPC-002 from Carroll-Loye Biological Research:

a. If the proposed research described in Protocol SPC-002 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 SPC-002 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?

E. Proposed ICR Picaridin Insect Repellent Efficacy Study (A 117)

EPA requires data from efficacy studies with human subjects to support claims of efficacy of a new pesticide product intended to repel insects that transmit human diseases.

EPA's regulation, 40 CFR §26.1125, requires the 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 research proposal.

Dr. Niketas Spero has submitted a proposal for new research to evaluate the efficacy of two registered products containing picaridin, to be conducted by Insect Control & Research, Inc. (ICR). The research protocol, identified by Protocol ID G0590607001A117 describes a laboratory study of the efficacy of the test formulations against mosquitoes of the genus *Culex*.

EPA has reviewed ICR's protocol and has concluded that, with a number of required revisions, 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. The sponsor wishes to submit the data to EPA later this year in support of an application to amend the registration of these picaridin products in order to claim specifically that the products are effective at repelling the mosquito species that transmit West Nile Virus. In the interest of providing a thorough and timely decision on such applications, and since EPA finds the protocol can meet applicable scientific and ethical standards, EPA is presenting this protocol for review at the Board's October 2007 meeting.

Review materials. EPA is providing the following materials to the HSRB in the folder identified as "Insect Control & Research Inc. Repellent Efficacy Protocol A117":

a. ICR Protocol A117 Transmittal 8-8-07

b. ICR Protocol A117 8-8-07

This protocol proposes a laboratory test of repellency of *Culex spp.* mosquitoes by two formulations containing picaridin

c. EPA Science & Ethics Review ICR A117 9-24-07

Charge Questions.

7. Protocol A-117 from Insect Control & Research, Inc.:

a. If the proposed research described in ICR's proposed picaridin protocol 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 of the genus *Culex*?

b. If the proposed research described in ICR's proposed picaridin protocol 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?