EPA-HSRB-07-01

George Gray, Ph.D.
Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: January 24, 2007 EPA Human Studies Review Board Meeting Report

Dear Dr. Gray:

The United States Environmental Protection Agency (EPA or Agency) requested the Human Studies Review Board (HSRB) to review scientific and ethical issues addressing: (1) two completed human studies (EMD 003 and EMD 004) evaluating repellent efficacy of formulations containing the active ingredient IR3535; and (2) a research proposal to evaluate the efficacy in the field of multiple formulations of the repellent DEET against mosquitoes.

The enclosed HSRB report addresses the Board's response to EPA charge questions at its January 24, 2007 meeting. A summary of the Board's conclusions is provided below.

**Completed IR3535 Insect Repellent Efficacy Studies**

**Studies EMD-003.1 and EMD 003.2**

Scientific Considerations

- The reported studies on the efficacy of lotion and pump spray formulations of IR3535 (studies EMD-003.1 and EMD-003.2) on repelling ticks are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the two formulations against ticks.

- The Board also recognized that recent advances in statistical analyses means that there are probably ways of measuring efficacy of individual products that would be an improvement over traditional techniques. The Board encourages the Agency to proceed in its efforts to examine how a transition to more accurate methods of calculating efficacy can be introduced so that consumers can not only compare relative efficacy of products based on traditional methods but also have better information on the degree of protection individual products provide.

- The Board commended Dr. Carroll for conducting the preliminary dosimetry phase of the study. Since the Agency noted that this was the first repellency study to have a specific dosimetry phase. the HSRB suggested the Agency might wish to provide guidance concerning whether the method employed in this study was the most valid way to determine dose.

Ethical Considerations

- The Board concurred with the initial assessment of the Agency that the studies EMD–003.1 and EMD-003.2 submitted for review by the Board met the applicable requirements of §40CFR26, subparts K and L.

- The Board also noted that there were a series of deviations from Subpart K that while not adversely affecting the rights and welfare of human subjects of the study, reflected a lack of familiarity with IRB procedures and protocol requirements described in Subpart K. The HSRB advised the Agency that it recommend investigators perform human research protection training and include completion of such training as part of their submission of protocols or completed studies to the Agency. Examples of such training could include the on-line training program offering by NIH/NCI or development of such a program by EPA.

**Studies EMD-004.1 and EMD-004.2**

Scientific Considerations

- The reported studies on the efficacy of lotion and pump spray formulations of studies EMD-004.1 and EMD-004.2 on repelling mosquitoes are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the two formulations against mosquitoes.

- The Board also recognized that recent advances in statistical analyses means that there are probably ways of measuring efficacy of individual products that would be an improvement over traditional techniques. The Board encouraged the Agency to proceed in its efforts to examine how a transition to more accurate methods of calculating efficacy can be introduced so that consumers can not only compare relative efficacy of products based on traditional methods but also have better information on the degree of protection individual products provide.

- The Board recommended inclusion of a description of the sampling frame and definition of eligible subjects to help justify subject generalizability.

Ethical Considerations

- The Board concurred with the initial assessment of the Agency that studies EMD 004.1 and EMD 004.2 submitted for review by the Board met the applicable requirements of §40CFR26, subparts K and L.

- The Board also noted that there were a series of deviations from Subpart K that while not adversely affecting the rights and welfare of human subjects of the study, reflected a lack

of familiarity with IRB procedures and protocol requirements described in Subpart K. The HSRB advised the Agency that it recommend investigators perform human research projection training and include completion of such training as part of their submission of protocols or completion studies to the Agency. Examples of such training could include the on-line training program offering by NIH/NCI or development of such a program by EPA.

**Insect Repellent Efficacy Protocol SCI-001**

Scientific Considerations

- While the Board raised several comments in terms of the statistical design of SCI-001 (applicable to the conduct of future related studies), such recommendations should be compared to Agency guideline requirements for conducting such studies.

- If the recommendations provided by EPA and those suggested by the Board are followed, protocol SCI-001 appears likely to generate scientifically valid data to assess the efficacy of the test products against mosquitoes.

- In addition, the protocol would satisfy the scientific criteria recommended by the HSRB, namely, producing important information that cannot be obtained except by research with human subjects, and having a clear scientific objective and a study design that should produce adequate data to test the hypothesis.

Ethical Considerations

- The Board concluded that the protocol should meet the applicable requirements of §40CFR26, subparts K and L if the points raised in the EPA review and in this report are adequately addressed.

In conclusion, the EPA HSRB appreciated the opportunity to advise the Agency on the scientific and ethical aspects of human studies research and looks forward to future opportunities to continue advising the Agency in this endeavor.

Sincerely,

Celia B. Fisher, Ph.D. Chair
EPA Human Studies Review Board

## NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use. Further information about the EPA Human Studies Review Board can be obtained from its website at http://www.epa.gov/osa/hsrb/. Interested persons are invited to contact Paul Lewis, Designated Federal Officer, via e-mail at lewis.paul@epa.gov.

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

**United States Environmental Protection Agency Human Studies Review Board**

Chair

Celia B. Fisher, Ph.D., Marie Ward Doty Professor of Psychology, Director, Center for Ethics Education, Fordham University, Department of Psychology, Bronx, NY

Vice Chair

William S. Brimijoin, Ph.D., Chair and Professor, Molecular Pharmacology and Experimental Therapeutics, Mayo Foundation, Rochester, MN *

Members

David C. Bellinger, Ph.D., Professor of Neurology, Harvard Medical School
Professor in the Department of Environmental Health, Harvard School of Public Health
Children's Hospital, Boston, MA

Alicia Carriquiry, Ph.D., Professor, Department of Statistics, Iowa State University, Ames, IA

Gary L. Chadwick, PharmD, MPH, CIP, Associate Provost, Director, Office for Human Subjects Protection, University of Rochester, Rochester, NY

Janice Chambers, Ph.D., D.A.B.T., William L. Giles Distinguished Professor, Director, Center for Environmental Health Sciences, College of Veterinary Medicine, Mississippi State University, Mississippi State, MS

Richard Fenske, Ph.D., MPH, Professor, Department of Environmental and Occupational Health Sciences, University of Washington, Seattle WA *

Susan S. Fish, PharmD, MPH, Professor, Biostatistics & Epidemiology, Boston University School of Public Health, Co-Director, MA in Clinical Investigation, Boston University School of Medicine, Boston, MA

Suzanne C. Fitzpatrick, Ph.D., DABT, Senior Science Policy Analyst, Office of the Commissioner, Office of Science and Health Coordination, U.S. Food and Drug Administration, Rockville, MD

Kannan Krishnan, Ph.D., Professor, Département de santé environnementale et santé au travail, Faculté de medicine, Université de Montréal, Montréal, Canada

KyungMann Kim, Ph.D., CCRP, Professor & Associate Chair, Department of Biostatistics & Medical Informatics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI

Michael D. Lebowitz, Ph.D., FCCP, Professor of Public Health & Medicine. University of Arizona, Tucson, AZ

Lois D. Lehman-Mckeeman, Ph.D., Distinguished Research Fellow, Discovery Toxicology, Bristol-Myers Squibb Company, Princeton, NJ *

Jerry A. Menikoff, M.D., Associate Professor of Law, Ethics & Medicine, Director of the Institute for Bioethics, Law and Public Policy, University of Kansas Medical Center, Kansas City, KS *

Sean Philpott, PhD., MS Bioethics, Policy and Ethics Officer, Global Campaign for Microbicides, Program for Appropriate Technology in Health, Washington D.C.

Richard Sharp, PhD., Assistant Professor of Medicine, Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, TX

Human Studies Review Board Staff

Paul I. Lewis, Ph.D., Designated Federal Officer, United States Environmental Protection Agency, Washington, DC

* Not in attendance at the January 24, 2007 Meeting

1 **TABLE OF CONTENTS**
2
3

## INTRODUCTION

On January 24, 2007, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning two categories of research:

(1) two completed human studies (EMD 003 and EMD 004) evaluating repellent efficacy of formulations containing the active ingredient IR3535.

In its last two meetings (June 27-30, 2006 and October 18-19, 2006) the HSRB reviewed and commented on materials relating to two insect repellent efficacy protocols from Carroll-Loye Biological Research. These two protocols described proposed research to evaluate the efficacy of 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.

Following the June 2006 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 had submitted the results to EPA for review.

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 were 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 sought 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 presented these studies for review at the Board's January 2007 meeting.

(2) research proposal to evaluate the efficacy in the field of multiple formulations of the repellent DEET against mosquitoes.

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. If such a study is to be initiated after April 7, 2006, 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 submitted a description of proposed research to be performed by Carroll-Loye Biological Research. The proposal, identified as SCI-001, described a study to evaluate the efficacy of four formulations of repellent products containing the active ingredient DEET (one formulation includes two other active ingredients as well). The study would measure the efficacy of three test formulations and one "comparison article"—the US military standard repellent—against mosquitoes under field conditions. The proposal bears many similarities to the protocol EMD-004 that the HSRB had previously reviewed. EPA had reviewed Dr. Carroll's protocol and concluded that, with some required refinements, it 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.

In its initial review, EPA 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 found the protocol generally meeting applicable scientific and ethical standards, EPA presented this protocol for review at the Board's January 2007 meeting.

This report transmits the HSRB's comments and recommendations from its January 24, 2007 meeting.

**REVIEW PROCESS**

On January 24, 2007 the Board had a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the Federal Register "Human Studies Review Board: Notice of Public Meeting (71 Federal Register 249). At the public meeting, following welcoming remarks from Agency officials, Celia B. Fisher, HRSB Chair, summarized the

Board's process for its review. The Board then heard presentations from the Agency on the following topics: (1) Insect Repellent Completed Efficacy Studies EMD-003 and EMD-004; and (2) Insect Repellent Efficacy Protocol SCI-001.

The Board received written public comments from Dr. Scott Carroll representing Carroll-Loye Biological Research. In addition, Dr. Carroll, representing Carroll-Loye Biological Research, provided oral comments at the meeting.

For their deliberations, the Board considered the materials presented at the meeting, written public comments and Agency background documents (e.g. pesticide human study, Agency data evaluation record (DER) of the pesticide human study, weight of evidence review, ethics review, pesticide human study protocols and Agency evaluation of the protocol).

## CHARGE TO THE BOARD AND BOARD RESPONSE

### Completed IR3535 Insect Repellent Efficacy Studies

Background

Protocol EMD-003 proposed testing 3 formulations of repellent (lotion, pump spray, and aerosol) containing the active ingredient IR-3535 for efficacy in repelling ticks under laboratory conditions. Protocol EMD-004 proposed testing of the same 3 formulations for efficacy in repelling mosquitoes under field conditions in two habitats (dense forest and moist pasture or marshland). EPA guidelines recommend testing in two habitats to assess efficacy in the presence of different mosquito species with different behaviors. Both protocols had a dosimetry phase to establish a "typical consumer dose" that would be used in the efficacy phases of the trials. Twelve subjects participated in dosimetry testing of the 3 formulations whose results were used for both protocols. An error in formulation of the aerosol test material caused a delay in testing this formulation, and the reports considered during this meeting addressed testing of only the lotion and pump spray formulations. Separate reports for each formulation (lotion and pump spray) were submitted for each protocol, and then a subsequent report including both formulations was re-submitted.

### Studies EMD-003.1 and EMD 003.2

### Charge to the Board

Scientific Considerations

Are these studies sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against ticks?

### Board Response to the Charge

The active ingredient IR 3535 was tested for its ability to repel ticks on the forearms of volunteers by the protocol presented and modified by Carroll-Loye. The protocol had been

modified based on the suggestions and input of EPA and HSRB. The results were reported in EMD-003.1 and EMD-003.2

The active ingredient was formulated into two products, a pump spray and a lotion, but data on the originally proposed aerosol was not provided because of an error in the formulation. The products were produced using Good Manufacturing Practices. All experiments were conducted using Good Laboratory Practices. A passive dosimetry experiment was done, as suggested previously by the HSRB both at its June and October 2006 meeting reviewing this protocol, to determine the amount of product that would be utilized by people using the product as directed. This passive dosimetry experiment was used to determine a grand mean of the 12 individuals tested (3 subsamples each) per product that was then used for all 10 individuals per product participating in the subsequent tick repellency tests for each product. (It should be noted that the dosimetry experiment was in common for both this study and the mosquito repellency study, EMD-004, since the same formulated products were used for both.)

The experiment was a laboratory study and was conducted according to the approved protocol with only very minor deviations, and none of these deviations would have affected the quality of the data or the safety of the subjects. The number of 10 subjects was justified in the text as leading to sufficient statistical power while exposing only a small number of people to the potential risks. Each subject had one limb treated. Each of the subjects served as a negative control in that each tick was tested first on the untreated limb to guarantee that the ticks demonstrated typical questing behavior (all did) prior to being tested on the treated limb. All ticks were laboratory reared with no history of tick-borne pathogens. Each tick was used only once. Repellency was tested during a 3-min interval each 15 minutes, starting 15 minutes after product application, using the criterion of First Confirmed Crossing (FCC) for each individual (replicate) to calculate Complete Protection Time (CPT) for the study. Stopping rules were employed. The study identified a range of 5-12 hr with a mean CPT of 9.1 hr for the lotion and a range of 6.5 to 12 hr with a mean CPT of 12.1 hr for the pump spray. The CPT is probably conservative as a number of the subjects reported no crossings at all, and the experiment was terminated before a FCC.

With respect to the science criteria established earlier by the HSRB for completed studies:

<u>General HSRB Scientific Criteria</u>

- The scientific question was stated (i.e., to test the efficacy of IR3535 in repelling ticks).
- Existing data were not adequate to answer the question of efficacy of these new formulations.
- Because existing data were not adequate to answer the question of efficacy, new studies involving human subjects are necessary.
- The potential benefits of the study were clear, i.e., that an effective repellent would be available that would have either greater efficacy and/or fewer drawbacks than what was currently approved.
- It is likely that the benefits would be realized because repellent efficacy was determined in controlled experiments.

- The risks are minimal because the formulation products are of very low toxicity and ticks are laboratory-reared with no evidence of pathogens.
- The most likely relevant risk would be irritation from tick bites, but participants were instructed to remove ticks before they were bitten.

Study Design Criteria

- The purpose of the study was clearly defined (i.e., efficacy testing).
- There were specific objectives/hypotheses (i.e., that IR3535 in the proposed formulations is an effective repellent).
- The study as described tested this hypothesis.
- The sample size was 10 individuals per product with each individual serving as his/her own negative control to test for tick questing behavior. A dosimetry experiment prior to the field experiment determined the amount of repellent to be tested.
- There was a plan allocating individuals to treatments.
- It is anticipated that the findings from this study can be generalized beyond the study sample.

Participation Criteria

- There was justification for the selection of the target population.
- The participants were representative of some of the population of concern; however, there are others in the population unlike these participants who are likely to use these products, but it would either be unethical to test them or would be less appropriate to test them. The participating population is considered appropriate and reasonable.
- The inclusion/exclusion criteria were appropriate.
- The sample was not a vulnerable group.

Measurement Criteria

- The measurements were accurate and reliable.
- The measurements were appropriate to the question being asked.
- Quality assurance was addressed; however, some of the quality assurance was not as precise as it should have been.

Statistical Analysis Criteria

- The data can be analyzed to calculate CPT with a range of variability.
- The statistical method will be commented upon in more detail in the Board's response to protocol SCI-001 below. It should be noted that although there are probably better methods than have been traditionally used to calculate the repellent efficacy, new products will likely need to be compared to existing products and it is imperative that potential users of the products be informed accurately of the relative protection among products. Therefore EPA is urged to make certain that any calculations of efficacy be of a nature that allows products to be compared with some common metrics or values. The Agency is also urged to initiate discussion on how a transition to more accurate methods of calculating efficacy can be introduced so that consumers can not only compare relative efficacy of products but also have better information on the degree of protection individual products provide.

- Measures of uncertainty were addressed.

Laboratory and Field Conditions

- Laboratory experiments were appropriate.
- Field experiments were not conducted.
- The study included a stop rule plan, medical management plan, and a safety monitor.

HSRB Consensus and Rationale

In conclusion, the reported studies on the efficacy of lotion and pump spray formulations of IR3535 (studies EMD-003.1 and EMD-003.2) on repelling ticks are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the two formulations against ticks.

The Board also recognized that recent advances in statistical analyses means that there are probably ways of measuring efficacy of individual products that would be an improvement over traditional techniques. The Board encouraged the Agency to proceed in its efforts to examine how a transition to more accurate methods of calculating efficacy can be introduced so that consumers can not only compare relative efficacy of products based on traditional methods but also have better information on the degree of protection individual products provide.

The Board commended Dr. Carroll for conducting the preliminary dosimetry phase of the study. Since the Agency noted that this was the first repellency study to have a specific dosimetry phase, the HSRB suggested EPA might wish to provide guidance concerning whether the method employed in this study was the most valid way to determine dose.

**Charge to the Board**

Ethical Considerations

Does available information support a determination that these studies were conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

Brief Overview of the Study

The protocol for these two studies was initially reviewed at the June 2006 meeting of the HSRB, at which time the Board concluded that the study failed to meet the requirements established in the Environmental Protection Agency's final human studies rule (40 CFR Part 26). At that time, the protocol failed to comport with the applicable requirements of 40 CFR Part 26, subpart K. The Board also raised questions about: 1) equitable study subject selection and recruitment; and 2) whether or not the documentation and process of study subject enrollment was sufficient to meet prevailing standards of voluntary informed consent. A revised, Institutional Review Board (IRB)-approved protocol was submitted and reviewed at the October 2006 meeting of the HSRB, at which the Board concluded that the revised research protocol, as submitted to the EPA, was compliant with the applicable ethical requirements of 40 CFR Part 26, subparts K and L.

Subsequent to the aforementioned October meeting of the HSRB, two dosimetry and efficacy studies for tick repellents containing IR-3535 were conducted from October 23 through November 8, 2006 (Carroll 2006a; Carroll 2006b). The studies were performed in Davis, California by researchers at Carroll-Loye Biological Research. The studies were sponsored by EMD Chemicals, Inc., Gibbstown, New Jersey; EMD Chemicals is the North American subsidiary of Merck KGaA, Darmstadt, Germany. The documents provided by Carroll-Loye specifically state that each study was conducted in compliance with the requirements of the U.S. EPA Good Laboratory Practice Regulations for Pesticide Programs, as promulgated at 40 CFR Part 160 (Carroll 2006a, 3; Carroll 2006b, 3). Each study was also reviewed and approved by a commercial human subjects review committee, Independent Investigational Review Board (IIRB), Inc., Plantation, FL. Documentation provided to the EPA by IIRB indicates that it reviewed these studies pursuant to the standards of the Common Rule (45 C.F.R. Part 46, Subpart A) and determined them to be in compliance with that Rule.

As submitted to the EPA, each completed study consisted of two interdependent analyses: 1) a dosimetry study designed to determine the amount of an insect-repelling compound, known as IR-3535, that typical users would typically apply when provided with one of two compound formulations (lotion or pump spray); and 2) an efficacy study designed to measure the efficacy of IR-3535 as a tick repellent for each compound formulation. Dosimetry was determined either by passive dosimetry using self-adhesive roll-gauze (pump spray formulation) or by direct measurement of compound application (lotion formulation). The efficacy of IR-3535 as a tick repellent was determined by placing Western black-legged ticks (*Ixodes pacificus)* on IR-3535-treated and untreated forearms and measuring the speed and distance that moving insects would penetrate into the treated area; thus, each subject served as his/her own control. The scientific strengths and weaknesses of each study design were described above.

The dosimetry study enrolled a total of 12 individuals, seven women and five men, each of whom tested both the lotion and pump spray formulations. The efficacy study for each formulation enrolled 10 subjects: seven women and three men tested the lotion formulation, and four women and six men tested the pump spray formulation. Two subjects enrolled in the dosimetry study participated in both the lotion and pump spray efficacy studies. All remaining subjects participated in only one of the three analytic phases of EMD-003.1 and EMD-003.2, giving a total of 28 subjects enrolled. In addition, three alternate subjects were enrolled to: 1) replace any subject who withdrew; and 2) protect the confidentiality of any subject excluded from the study as a result of pregnancy or other potentially stigmatizing condition, as described below. Study documents, however, also include limb measurement information for an additional nine subjects who were not enrolled in either the dosimetry or the efficacy studies. These subjects appear to be enrolled in two additional studies also submitted to the EPA by Carroll-Loye Biological Research, EMD-004.1 (Completed Efficacy Studies for Mosquito Repellents Containing IR-3535 – Lotion) and EMD-004.2 (Completed Efficacy Studies for Mosquito Repellents Containing IR-3535 – Pump Spray) (Carroll 2006c; Carroll 2006d).

Critique of Study

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley 2006a). In general, the research described in EMD-003.1 and EMD-003.2 comports with the applicable requirements of 40 CFR Part 26, subparts K and L. The risks to study participants were minimal and were justified by the likely societal benefits, including data on the efficacy of IR-3535 as a tick repellent. As IR-3535 is commercially available and has been used as a repellent in Europe for years with no evidence of toxic effects, the subjects enrolled in this study were unlikely to be at increased risk of experiencing adverse side effects upon exposure. The ticks used for the study were reared in a laboratory environment and are considered to be pathogen-free, minimizing the risk of vector-borne disease. Clear stopping rules also were developed, as were plans for the medical management of any side effects or adverse events; no side effects or adverse events were reported. The study protocol also included several mechanisms designed to minimize coercive subject recruitment and enrollment, compensation was not considered to be so high as to unduly influence participation, and minors and pregnant or lactating women were explicitly excluded from volunteering (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study). The potential stigmatization resulting from study exclusion was minimized by the use of so-called "alternate" subjects, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

The revised protocol and informed consent documents were reviewed and approved by IIRB, Inc., on November 1, 2006, nine days after study subject enrollment began. In email correspondence between Dr. Scott Carroll of Carroll-Loye Biological Research and Mr. John Carley of the EPA's Office of Pesticide Protections, dated December 18-19, 2006, Dr. Carroll reported that subjects were enrolled using a previously approved protocol and consent form, dated September 12, 2006; these were modified to reflect protocol and consent form changes under review but not yet approved by the IIRB. For example, Dr. Carroll reported that, "to each of the 12 September consent forms used for subject enrollment … corrections were made by hand, and acknowledged by initialing by the subject and Study Director (Carley and Carroll 2006).

Although it is unlikely that these changes knowingly and/or seriously impaired the informed consent process, enrollment of subjects using unapproved protocols and consent forms represents a significant and serious departure from accepted review and approval practices. EPA regulations regarding review and approval of human subjects research, for example, prohibit investigators from implementing any protocol changes without prior IRB approval unless such changes are necessary to prevent immediate, serious harm to study participants. The regulations also require investigators to only obtain consent using IRB-approved forms. Furthermore, it is the policy of the IIRB, available online at http://iirb.com, that all "significant protocol deviations [be] reported to the Independent Investigational Review Board, Inc. in a timely manner." Protocol violations or deviations occur when there is a variance in a research study between what is described in the protocol approved by the IRB and the actual activities performed by the research team. The failure of Carroll-Loye Biological Research to 1) obtain IRB approval of the revised protocol and consent forms prior to enrollment of study subjects, and 2) report these

deviations to the Independent Investigational Review Board, are serious regulatory breaches. The Board thus recommended that Carroll-Loye Biological Research report these deviations to the IIRB as soon as possible and work with that organization to develop and implement a corrective course of action.

HSRB Consensus and Rationale

The Board concurs with the initial assessment of the Agency that the studies EMD–003.1 and EMD-003.2 submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

The Board also noted that there were a series of deviations from Subpart K that while not adversely affecting the right and welfare of human subjects of the study, reflected a lack of familiarity with IRB procedures and protocol requirements described in Subpart K. The HSRB advised the Agency that it recommend investigators perform human research protection training and include completion of such training as part of their submission of protocols or completed studies to the Agency. Examples of such training could include the on-line training program offering by NIH/NCI or development of such a program by the Agency.

**Completed IR3535 Insect Repellent Efficacy Studies**

**Studies EMD-004.1 and EMD 004.2**

**Charge to the Board**

Scientific Considerations

The active ingredient IR 3535 was tested for its ability to repel mosquitoes from the forearms or legs of volunteers by the protocol presented and modified by Carroll-Loye. The protocol had been modified based on the suggestions and input of EPA and HSRB. The results were reported in EMD-004.1 and EMD-004.2

The active ingredient was formulated into two products, a pump spray and a lotion, but data on the originally proposed aerosol was not provided because of an error in the formulation. The products were produced using Good Manufacturing Practices. All experiments were conducted using Good Laboratory Practices. A passive dosimetry experiment was done, as suggested by the HSRB, to determine the amount of product that would be utilized by people using the product as directed. This passive dosimetry experiment was used to determine a grand mean of the 12 individuals tested (3 subsamples each) per product that was then used for all 10 individuals per product participating in the subsequent mosquito repellency tests for each product. (It should be noted that the dosimetry experiment was in common for both this study and the tick repellency study, EMD-003, since the same formulated products were used for both.)

The experiment was a field study and was conducted according to the approved protocol with only very minor deviations, and none of these deviations would have affected the quality of the data or the safety of the subjects. Two locations in California were used, one a dense forest and the other a moist pasture marshland; the two locations had differences in the composition and relative abundance of mosquito species. Neither location showed evidence of the presence of West Nile Virus (WNV). The number of 10 subjects per product was justified in the text as leading to sufficient statistical power while exposing only a small number of people to the potential risks.

Each subject had one limb treated, and the remainder of the body was covered with material impervious to mosquitoes. There were two experienced persons serving as negative controls (i.e., without any repellant product) to confirm mosquito biting pressure (and biting pressure was maintained throughout the period of the study, defined as at least one Landing with Intent to Bite, LIBe, per min). Experimental subjects, in pairs, monitored LIBe's during a one min interval each 15 min, until the First Confirmed LIBe (FCLIBe) was determined. Stopping rules were employed. The Complete Protection Time (CPT) was calculated as the mean for all participants for each product. For the lotion the study identified a range of 6-8.5 hr with a mean CPT of 7.3 hr for the forest, and a range of 7.75 to 10 hr with a mean CPT of 8.5 hr for the marsh. For the pump spray the study identified a range of 5 to 8 hr with a mean CPT of 7.1 hr for the forest and a range of 7.7 to 10 hr with a CPT of 8.4 hr for the marsh. The CPT is probably conservative as a number of the subjects reported no LIBe's at all, and the experiment was terminated before a FCLIBe was observed.

With respect to the science criteria established earlier by the HSRB for completed studies:

<u>General HSRB Scientific Criteria</u>

- The scientific question was stated (i.e., to test the efficacy of IR3535 in repelling mosquitoes).
- Existing data were not adequate to answer the question of efficacy of these new formulations.
- Because existing data were not adequate to answer the question of efficacy, new studies involving human subjects are necessary.
- The potential benefits of the study were clear, i.e., that an effective repellent would be available that would have either greater efficacy and/or fewer drawbacks than what was currently approved.
- It is likely that the benefits would be realized because repellent efficacy was determined in carefully designed field experiments.
- The risks are minimal because the formulation products are of very low toxicity, the mosquitoes were aspirated before they had an opportunity to bite, and the regions selected did not have evidence of WNV.
- The most likely relevant risk would be irritation from mosquito bites, but participants were instructed to remove mosquitoes before they were bitten, or the possibility of infection with WNV, but the regions selected had no evidence of the virus.

<u>Study Design Criteria</u>

- The purpose of the study was clearly defined (i.e., efficacy testing).
- There were specific objectives/hypotheses (i.e., that IR3535 in the proposed formulations is an effective repellent).
- The study as described tested this hypothesis.
- The sample size was 10 individuals per product along with 2 experienced individuals to confirm mosquito biting pressure. A dosimetry experiment prior to the field experiment determined the amount of repellent to be tested.
- There was a plan allocating individuals to treatments.
- It is anticipated that the findings from this study can be generalized beyond the study sample.

Participation Criteria

- There was justification for the selection of the target population.
- The participants were representative of some of the population of concern; however, there are others in the population unlike these participants who are likely to use these products, but it would either be unethical to test them or would be less appropriate to test them. The participating population is considered appropriate and reasonable.
- The inclusion/exclusion criteria were appropriate.
- The sample was not a vulnerable group.

Measurement Criteria

- The measurements were accurate and reliable.
- The measurements were appropriate to the question being asked.
- Quality assurance was addressed; however, some of the quality assurance was not as precise as it should have been.

Statistical Analysis Criteria

- The data can be analyzed to calculate CPT with a range of variability.
- The statistical method will be commented upon in more detail by the Board in its response to protocol SCI-001 below. It should be noted that although there are probably better methods than have been traditionally used to calculate the repellent efficacy, new products will likely need to be compared to existing products and it is imperative that potential users of the products be informed accurately of the relative protection among products. Therefore EPA is urged to make certain that any calculations of efficacy be of a nature that allows products to be compared with some common metrics or values.
- Measures of uncertainty were addressed.

Laboratory and Field Conditions

- Laboratory experiments were not conducted.
- Field experiments were appropriate.
- The study included a stop rule plan, medical management plan, and a safety monitor.

HSRB Consensus and Rationale

In conclusion, the reported studies on the efficacy of lotion and pump spray formulations of IR3535 (studies EMD-004.1 and EMD-004.2) on repelling mosquitoes are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the two formulations against mosquitoes.

The Board also recognized that recent advances in statistical analyses means that there are probably ways of measuring efficacy of individual products that would be an improvement over traditional techniques. The Board encouraged EPA to proceed in its efforts to examine how a transition to more accurate methods of calculating efficacy can be introduced so that consumers can not only compare relative efficacy of products based on traditional methods but also have better information on the degree of protection individual products provide. The Board recommended inclusion of a description of the sampling frame and definition of eligible subjects to help justify subject generalizability.

**Charge to the Board**

Ethical Considerations

Does available information support a determination that these studies were conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

Brief Overview of the Study

This protocol for these two studies was initially reviewed at the June 2006 meeting of the Human Studies Review Board, at which time the Board concluded that the study failed to meet the requirements established in the Environmental Protection Agency's final human studies rule (40 CFR Part 26). At that time, the study failed to comport with the applicable requirements of 40 CFR Part 26, subpart K. The Board also raised questions about: 1) equitable study subject selection and recruitment; 2) description and minimization of risks to study participants; and 3) whether or not the documentation and process of study subject enrollment was sufficient to meet prevailing standards of voluntary informed consent. A revised, Institutional Review Board (IRB)-approved protocol was submitted and reviewed at the October 2006 meeting of the Human Studies Review Board, at which the Board concluded that revised research protocol, as submitted to the EPA, was compliant with the applicable ethical requirements of 40 CFR Part 26, subparts K and L.

Subsequent to the aforementioned October meeting of the HSRB, two dosimetry and efficacy studies for mosquito repellents containing IR-3535 were conducted from October 23 through November 8, 2006 (Carroll 2006c; Carroll 2006d). The studies were performed at a laboratory site in Davis, California, and at two field sites in Butte and Glenn Counties, California, by researchers at Carroll-Loye Biological Research. The studies were sponsored by EMD Chemicals, Inc., Gibbstown, New Jersey; EMD Chemicals is the North American subsidiary of Merck KGaA, Darmstadt, Germany. The documents provided by Carroll-Loye specifically state that each study was conducted in compliance with the requirements of the U.S. EPA Good Laboratory Practice Regulations for Pesticide Programs, as promulgated at 40 CFR Part 160 (Carroll 2006c, 3; Carroll 2006d, 3). Each study was also reviewed and approved by a

commercial human subjects review committee, Independent Investigational Review Board (IIRB), Inc., Plantation, FL. Documentation provided to the EPA by IIRB indicates that it reviewed these studies pursuant to the standards of the Common Rule (45 C.F.R. Part 46, Subpart A) and determined them to be in compliance with that Rule.

As submitted to the EPA, each completed study consists of two interdependent analyses: 1) a dosimetry study designed to determine the amount of a formualation (lotion or pump spray) containing an insect-repelling compound, known as IR-3535, that users would typically apply when provided with one of two compound formulations (lotion or pump spray); and 2) efficacy studies designed to measure the efficacy of IR-3535 as a mosquito repellent for each formulation. Dosimetry was determined either by passive dosimetry using self-adhesive roll-gauze (pump spray formulation) or by direct measurement of compound application (lotion formulation). The efficacy of IR-3535 as a mosquito repellent was determined by measuring the ability of the three formulations to prevent mosquito landings (defined as "Lite with Intent to Bite"; LIBe) under field conditions. Mosquitoes were aspirated mechanically prior to biting; prior to initiation of the efficacy study, all volunteers were trained both to recognize a mosquito landing with the intent to bite and to remove such mosquitoes with an aspirator using laboratory-raised, pathogen-free mosquitoes in a controlled laboratory setting. During the field studies, subjects worked in pairs to facilitate identification and aspiration of LIBing mosquitoes during brief exposure periods. The strengths and weaknesses of each study design are described above. The scientific strengths and weaknesses of each study design are described above.

The dosimetry study enrolled a total of 12 individuals, seven women and five men, each of whom tested both the lotion and pump spray formulations. The field-based efficacy study for each formulation enrolled 10 subjects: seven women and three men tested both the lotion and pump spray formulation over two days at a "forest" site in Butte County, and four women and six men tested the pump spray formulation both the lotion and pump spray formulation over two days at a "marsh/pasture" site in Glenn County. One subject enrolled in the dosimetry study participated in "forest" efficacy study, three additional subjects participated in both the "forest" and "marsh/pasture" studies, and a fifth subject participated in the dosimetry, "forest", and "marsh/pasture" studies. All remaining subjects participated in only one of the analytic phases of EMD-004.1 and EMD-004.2. Two control subjects, described as "experienced personnel" (Carroll 2006c, 9; Carroll 2006d, 9) and who were untreated with either repellent formulation, also participated to determine ambient LIBe pressure, giving a total of 26 subjects enrolled. In addition, three alternate subjects were enrolled to: 1) replace any subject who withdrew; and 2) protect the confidentiality of any subject excluded from the study as a result of pregnancy or other potentially stigmatizing condition, as described below. Study documents, however, also include limb measurement information for additional subjects who were not enrolled in either the dosimetry or the efficacy studies. These subjects appear to be enrolled in two additional studies submitted to the EPA by Carroll-Loye Biological Research, EMD-003.1 (Completed Efficacy Studies for Tick Repellents Containing IR-3535 – Lotion) and EMD-003.2 (Completed Efficacy Studies for Tick Repellents Containing IR-3535 – Pump Spray) (Carroll 2006a; Carroll 2006b).

Critique of Study

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley 2006b). In general, the research described in EMD-004.1 and EMD-004.2 comports with the applicable requirements of 40 CFR Part 26, subparts K and L. The risks to study participants were minimal and were justified by the likely societal benefits, including data on the efficacy of IR3535 as a mosquito repellent. IR3535 is commercially available and has been used as a repellent in Europe for years with no evidence of toxic effects, so the subjects enrolled in this study were unlikely to be at increased risk of experiencing adverse side effects upon exposure. Reactions to mosquito bites are usually mild and easily treated with over-the-counter steroidal creams. The study also excluded subjects who have a history of such severe skin reactions to further minimize the risk of a subject experiencing a severe physical reaction to a mosquito bite. In addition, the study protocol was designed specifically to minimize the likelihood that a mosquito will bite, through the use of clear stopping rules, limited exposure periods, and paired observation; no side effects or adverse events were reported. To minimize the risk that study subjects would be exposed to disease causal agents like WNV, the study protocol called for field tests of repellent efficacy to be conducted only in areas where known vector-borne diseases have not been detected by county and state health or vector/mosquito control agencies for at least one month. Although it would have been ideal if the mosquitoes collected during the field studies were subjected to serologic or molecular analyses to confirm that they were free of known pathogens, it is unlikely that failure to do so compromised participant safety in any significant way. Finally, the study protocol also included several mechanisms designed to minimize coercive subject recruitment and enrollment, compensation was not considered to be so high as to unduly influence participation, and minors and pregnant or lactating women were explicitly excluded from volunteering (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study). The potential stigmatization resulting from study exclusion was minimized by the use of so-called "alternate" subjects, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

As with the two tick repellent studies (EMD-003.1 and EMD-003.2), the revised protocol and informed consent documents used for these mosquito repellent studies were reviewed and approved by IIRB, several days after study subject enrollment began; some subject participating in these studies were re-consented using IIRB-approved documents, but not all were. Although it is unlikely that these changes knowingly and/or seriously impaired the informed consent process, enrollment of subjects using unapproved protocols and consent forms represents a significant and serious departure from accepted review and approval practices. The failure of Carroll-Loye Biological Research to 1) obtain IRB approval of the revised protocol and consent forms prior to enrollment of study subjects, and 2) report these deviations to IIRB, are serious regulatory breaches. The Board thus recommended Carroll-Loye Biological Research report these deviations to the IIRB as soon as possible and work with that organization to develop and implement a corrective course of action.

Second, the IIRB-approved protocol and consent documents specifically stated that they are to be conducted only in areas where known vector-borne diseases have not been detected by county and state health or vector/mosquito control agencies for at least one month (see, for example, Carroll 2006c, 75). One sentinel poultry flock in the area, however, did test positive for WNV during the month prior to conduct of the field studies (Carroll 2006c, 7). Sentinel flocks

closer to the two study sites did not test positive for arboviruses during this period, and a leading vector control ecologist consulted by Carroll-Loye reported that "WNV activity in Northern Calfornia [was] effectively concluded for 2006" (Carroll 2006c, 7), so it is unlikely that participant safety was compromised in any significant way. Nevertheless, initiation of field studies following the detection of WNV in a sentinel chicken flock represents a deviation from the approved protocol and should be reported to the IIRB as soon as possible.

Finally, even though two IR-3535-untreated control subjects were enrolled in the study, the IIRB-approved consent documents provided for review do not list the unique risks that these two volunteers faced. These control subjects were "experienced" personnel who were likely aware of these risks, but nonetheless should have been consented using documents that listed these dangers.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that studies EMD 004.1 and EMD 004.2 submitted for review by the Board met the applicable requirements of §40CFR26, subparts K and L.

The Board also noted that there were a series of deviations from Subpart K that while not adversely affecting the rights and welfare of human subjects of the study, reflected a lack of familiarity with IRB procedures and protocol requirements described in Subpart K. The HSRB advised the Agency that it recommend investigators perform human research projection training and include completion of such training as part of their submission of protocols or completion studies to the Agency. Examples of such training could include the on-line training program offering by NIH/NCI or development of such a program by EPA.

**Insect Repellent Efficacy Protocol SCI-001**

Background

The objectives of this study will be to test the mosquito repellent efficacy characteristics of three test materials, to compare them to one another, reinforce measurements of time for which they are effective, and to contrast them with the U.S. military issue topical insect repellent. Test Material #1 is LipoDEET, which contained 30% DEET that had lipid spheres and inhibits evaporation, improved field, and reduced plasticizing and odor. Test Material # 2, Coulston's Duranon, is 20% DEET in a controlled-release, low-odor formulation. Test Material #3 is Insect Guard II, which contained as active ingredients 17.5% DEET, 5% N-octyl bicycloheptane dicarboximide (synergist), and 2.5% Di-n-propyl isocinchomerate (fly repellent). Test Material # 4, 3M Ultrathon (military issue repellent), contained 34.34% DEET in a polymer-based lotion to extend efficacy and reduce plasticizing.

This study will be similar to EMD-004 in terms of the dosimetry phase, efficacy measurements (time to "first confirmed landing with intent to bite"), and training of subjects in aspirating mosquitoes before they bite. The field conditions and timing of exposure also will be similar (subjects work in pairs with 2 assistants to aspirate mosquitoes, and both treated and

untreated subjects are exposed to the mosquitoes for 1 minute every 15 minutes). The field testing sites will be the California Central Valley or Florida Keys, with expected wild mosquito populations of *Aedes vexans, Ochlerotatus melanimon, O. taeniorhynchus, and Culex pipens*. The test results would be analyzed using unspecified statistics. Measurements would be reported with 95% confidence intervals of the mean and associated standard deviations. The efficacy of each treatment would be compared to that of Ultrathon. The sample size reflects a compromise between financial and ethical concerns, although it was difficult to pre-determine sample size without knowing the distribution of outcome values. EPA guidelines recommend 6 replicates, which is considered sufficient to show statistical significance at $P<0.05$. EPA recommended changes to the protocol to include developing a full description of the statistical analysis plan to compare means and to assess within-treatment variability, and to define a testable hypothesis.

**Charge to the Board**

Scientific Considerations

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

**Board Response to the Charge**

The proposal intends to test the efficacy of three novel formulations of N,N-diethyl m-toluamide (DEET). Three topical formulations containing DEET will be tested against positive control, Ultrathon (35% DEET). The objectives, design and methods are adequately described. The plans for statistical analyses of the data, however, require significant revision as detailed below.

Specific suggestions for revision or clarification:

- *Experimental design*: While this is not identified as a limitation of the study, nowhere is it justified the randomization to left and right limbs. Thus is there any reason to believe that products will be more or less effective on the two limbs? In addition the Board questioned why use right/left as a blocking variable (that is subsequently ignored in the analysis) in the design?
- *Statistical analysis*: The investigator proposed computing the means and confidence intervals around those means for CPT in each treatment group (three test products plus the positive control). But this simple analysis makes comparisons across products more difficult. Instead, consider the following approach:
    - Let $CPT_{ij}$ denote the CPT measured on the *ith* subject in the *jth* treatment, where $i=1,\ldots,10$ and $j=1,\ldots,4$.
    - Fit a linear model to the 40 measurements, with a fixed effect for treatment. Other fixed effects can also be included if they happen to be of interest.

This approach permits direct comparisons among products. In particular, it is possible to obtain a point estimate and a confidence interval for the difference in CPT in a test product and in the comparison product, one of the objectives of the study.
If the entire study is replicated in two locations *using different subjects*, then an even better approach is to fit a model to the entire set of 80 measurements, but adding an effect for location (and perhaps an interaction between location and treatment) to the model.
The investigator can easily fit the model using JMP. Just use the Fit X by Y option in the Analyze menu and then choose ANOVA.

- *Interpretation of results*: Results from this study need to be interpreted judiciously. The sample is not representative of the population of individuals who might eventually be users of these products. While the long list of exclusions is justifiable, one consequence is that the population represented in the sample is different from the population of potential users. Further, "friends, neighbors and academic associates" of Dr. Carroll do not constitute a randomly selected sample from a well-constructed sampling frame.
- *Sample size*: Including 10 subjects per treatment is probably sufficient, but the justification provided by investigators is not convincing. First, in order to estimate power an estimate of the within-treatment variance in the response variable is needed. The investigator does not provide such an estimate in the discussion. Thus it is unclear how they can argue that "from the standpoint of statistical power, six treated and one untreated subject are sufficient to demonstrate a significant effect at $P<0.05$". Second, the argument used to justify no more than 10 subjects per treatment states that "adding subjects beyond six increases the precision of the means estimate only slowly". This argument relies on the assumption that the between-person variance in CPT does not change as sample size increases, which in general is not true. The information on interindividual variability drawn from studies completed by these investigators may be used to guide and justify sample size.
- *Inclusion/Exclusion criteria.* In previous studies, subjects dropped out at different points potentially confounding the quantification of the CPT. Criteria needs to be established for how long subjects must remain in the study in order for their data to be used. Criteria for when a new subject must be run as a substitute to meet the sample size requirements must also be determined.
- *Assumption of normality of CPT measurements*: Again, the assumption of normality is probably justifiable and in any case can be easily tested and corrected for. There seems to be some confusion) regarding the *exponential family of distributions* and the *exponential distribution*. The latter is a standard probability model for variables such as time which are strictly positive and tend to exhibit a rounded L shape when plotted. The former has nothing to do with the study at hand. If CPTs can all be expected to be noticeably larger than 0, then approximating the exponential model with a normal model may be justifiable.
- *Measurement variables*: Although it is clear from the rest of the protocol discussion, the investigator might consider adding CPT to the list of variables given in Section 10.1.
- *Dose*: Even though it is suggested that the typical consumer exposure should be far below the dermal toxicity benchmarks, there is no indication of such toxicological data in the MSDS included with this submission. Typical consumer dose and known toxicity benchmarks should be clearly identified.
- *Comparison with Ultrathon:* It is unclear as to why such comparisons (and how) will be made given that EPA does not allow statements of comparative efficacy.
- *Typo*: active ….should read active ingredient (in several places)

HSRB Consensus and Rationale

While the Board raised several comments in terms of the statistical design of SCI-001 (applicable to the conduct of future related studies), such recommendations should be compared to Agency guideline requirements for conducting such studies. If the recommendations provided by EPA and those suggested by the Board are followed, protocol SCI-001 appears likely to generate scientifically valid data to assess the efficacy of the test products against mosquitoes. In addition, the protocol would satisfy the scientific criteria recommended by the HSRB, namely, producing important information that cannot be obtained except by research with human subjects, and having a clear scientific objective and a study design that should produce adequate data to test the hypothesis.

**Charge to the Board**

Ethical Considerations

If the proposed research described in Protocol SCI-001 from Carroll-Loye Biological Research is revised as suggested by EPA, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

**Board Response to the Charge**

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley 2006c). In general, the research described in Protocol SCI-001comports with the applicable requirements of 40 CFR Part 26, subparts K and L. The risks to study participants are limited and appropriate steps have been taken to minimize these risks. The risks to participants are justified by the likely societal benefits, including data on the efficacy of new topical formulations containing DEET as a mosquito repellent. DEET is commercially available and has been used as a repellent for years with no evidence of substantial toxic effects, so the subjects enrolled in this study are unlikely to be at increased risk of experiencing adverse side effects upon exposure. Reactions to mosquito bites are usually mild and easily treated with over-the-counter steroidal creams. In addition, the study protocol is designed to minimize the likelihood that a mosquito will bite, through the use of clear stopping rules, limited exposure periods, and paired observation. To minimize the risk that study subjects will be exposed to illnesses resulting from WNV, the study protocol calls for field tests of repellent formulations to be conducted only in areas where known vector-borne diseases have not been detected by county and state health or vector/mosquito control agencies.

The Board recommended that the investigator collect mosquitoes during the field studies and that they be subject to serologic or molecular analyses to confirm absence of known pathogens. Finally, the study protocol included several mechanisms designed to minimize coercive subject recruitment and enrollment, compensation was not considered to be so high as to unduly influence participation, and minors and pregnant or lactating women were explicitly excluded from volunteering (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study). The

potential stigmatization resulting from study exclusion was minimized by the use of so-called "alternate" subjects, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

The Board concluded that research described in Protocol SCI-001 minimizes risks to subjects and has appropriate stopping rules in place. The safety monitoring proposed seems reasonable and appropriate in light of the level of risk to subjects. Despite this generally favorable assessment, the Board considered several additional matters relevant to subject recruitment and the overall conduct of the study.

First, as noted in the Agency's review of Protocol SCI-001, the protocol does not describe how untreated controls would be recruited. The protocol implies that controls will be recruited in the same manner as subjects in the "exposure" arm—via "word-of-mouth" and a Volunteer Data Base maintained by the Principal Investigator. Any possible confusion could be easily corrected, though. The Board also found it a bit unusual that the IRB did not ask to review a script of the proposed recruitment phone call as most IRBs regard recruitment as the first step in the IC process and require that all recruitment activities be reviewed. This would include any fliers, emails, letters, or local ads as well, which should be submitted to IIRB for review.

Second, the Board discussed several issues related to subject recruitment and consent. First, the description of risks associated with DEET exposure during the course of the study are mischaracterized in the submitted informed-consent document, which refers to sprayed applications containing alcohol. Since the study involved the application of lotions to the skin, these risks should be redescribed. In addition, the informed-consent document is structured in a manner that does not apply to unexposed control subjects. Also, the submitted informed-consent document indicates that up to 40 subjects may participate in the study when the correct number should be 48 (10 exposed and 2 controls per arm of the study).

Third, the Board discussed the fact that the proposed sample size is slightly larger than what EPA has historically required (10 exposed subjects vs. the historical norm of 6 exposed subjects). The protocol provides a rationale for this approach (pp. 13-15), which is meant to reduce the probability that the sample over-represents individuals who are "inherently unattractive" to mosquitoes. In light of the limited risks to subjects, this departure from the historical norm was viewed as acceptable by the Board.

Fourth, the Board found it difficult to assess the qualifications of the IIRB based on the materials that were supplied. Although the Board did not have significant concerns about the overall quality of the IRB's review of the protocol, it would be reassuring to the Board if some type of documentation of the IRB's qualifications were provided to the Agency for review (e.g., evidence of member training, accreditation by an external professional body, etc.).

HSRB Consensus and Rationale

The Board concluded that the protocol should meet the applicable requirements of §40CFR26, subparts K and L if the points raised in the EPA review and in this report are adequately addressed.

## REFERENCES

Carley, J.M. 2006a. Ethics Review of EMD-003 Reports of Completed Efficacy Studies for Tick Repellents Containing IR-3535. Dated December 19, 2006. Unpublished document prepared by Office of Pesticide Programs, United States Environmental Protection Agency.

Carley, J.M. 2006b. Ethics Review of EMD-004 Reports of Completed Efficacy Studies for Mosquito Repellents Containing IR-3535. Dated December 19, 2006. Unpublished document prepared by Office of Pesticide Programs, United States Environmental Protection Agency.

Carley, J.M. 2006c. Ethics Review of SCI-001. Unpublished document prepared by Office of Pesticide Programs, United States Environmental Protection Agency.

Carley, J.M., and S. Carroll. 2006. E-mail Exchange Between Scott P. Carroll of Carroll-Loye Biological Research and John M. Carley of EPA Concerning Repellent Studies EMD-003 and EMD-004 on December 18-19, 2006. Unpublished document prepared by Office of Pesticide Programs, United States Environmental Protection Agency.

Carroll, S. 2006a. Test of Personal Insect Repellents: Study EMD-003.1 (Lotion) – Revised. Dated December 15, 2006. Unpublished document prepared by Carroll-Loye Biological Research.

Carroll, S. 2006b. Test of Personal Insect Repellents: Study EMD-003.2 (Pump Spray) – Revised. Dated December 15, 2006. Unpublished document prepared by Carroll-Loye Biological Research.

Carroll, S. 2006c. Test of Personal Insect Repellents: Study EMD-004.1 (Lotion) – Revised. Dated December 15, 2006. Unpublished document prepared by Carroll-Loye Biological Research.

Carroll, S. 2006d. Test of Personal Insect Repellents: Study EMD-004.2 (Pump Spray) – Revised. Dated December 15, 2006. Unpublished document prepared by Carroll-Loye Biological Research.