January 10, 2008

EPA-HSRB-07-04

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

Subject: October 24-26, 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) the EPA Office of Research and Development's document, *Scientific and Ethical Approaches for Observational Exposure Studies*; (2) a sodium azide study; (3) Carroll-Loye Biological Research Completed Field Efficacy Studies (SCI-001 and WPC-001); (4) Carroll-Loye Biological Research Proposed Insect Repellent Efficacy Protocols (SPC-001 and SPC-002); and (5) ICR Proposed Repellent Efficacy Protocol (A 117). The enclosed HSRB report provides the Board's response to EPA charge questions presented at the October 24-26, 2007 meeting.

At previous HSRB meetings, the Board raised a number of science questions related to mosquito repellent efficacy field research. At the Board's request, three consultants in the field of entomology were invited to the October 2007 HSRB meeting to discuss the frequency and duration of exposure of subjects to potential mosquito landings. Board discussion of the consultants comments are briefly provided. This HSRB report includes Board discussions on the consultants opinions presented in the consultants' responses and supplemental information shared at the meeting. Finally, the Board also appreciated the Agency highlighting progress on issues relating to the design of sampling strategies for handler research programs proposed by the Agricultural Handlers Exposure Task Force and the Antimicrobials Exposure Assessment Task Force II.

On a general note, future protocols should include a statistical analysis plan for subsequent Board review. In addition, the Board requests that revised protocols or subsequent studies submitted to the Agency should include a response to changes as specified by the Agency. Such a written response would assist the Board in its review process. Finally, the HSRB requests expert consultants at a future meeting to educate the Board and Agency on acceptable statistical approaches to insect repellent studies.

A summary of the Board's conclusions is provided below.

<u>Scientific and Ethical Approaches for Observational Exposure Studies</u>

Introduction, Purpose and Scope

- The Board concurred that the document is extremely well-written, presents information accurately and clearly, and will be extremely useful; however, the Board provided suggestions for improvements.
- Expand the discussion on how observational research is distinguished from intentional exposure research with specific illustrations, including discussion of the need for ethical review and evaluation of observational research.
- The document presents more ethical than science approaches for observational exposure studies. The Board recommends that the document be revised to present a more balanced presentation and highlight the interplay between good science and ethics.
- The Board also recommended providing examples of study questions, citing other documents to guide researchers in alternative research designs, and providing bulleted summary highlights at the end of each chapter.
- The abstract states that the document will address chemicals and other stressors, but focuses on chemicals, which gives the impression that attention is not needed except for research involving chemicals. The language and examples used in the document should reflect the importance of the document for both chemicals and other stressors.

Elements to Be Considered in Study Conceptualization and Planning

- The Board concurred that Section 2 adequately identified the major areas and issues where ethical considerations should be addressed in the study conceptualization. The Board suggested that rather than having distinct sections and even documents on ethics and science there be just one document, with the study design elements being a portion of the human subjects protocol. This would more closely parallel the information submitted to an IRB.
- Bulleted items should also include justification for sample selection and size and sampling method, discussion of alternative designs that were rejected to help justify the use of human subjects in the particular way being proposed, expanded examples of conflicts of interest, and the importance of using validated measures. Expansion of text regarding adverse events vs. unanticipated problems, scientific misconduct, subject attrition, reporting biases etc. were recommended.

Ensuring Protections of Vulnerable Populations

- The Board recommended additional discussion on justifications for including vulnerable populations in research as well as expansion on discussion of who is vulnerable outside of the federal regulations (e.g. pregnant women, prisoners, children) such as economic, educational or social vulnerabilities; noting however that in federal regulations vulnerability is defined in terms of susceptibility to coercion and undue influence.
- Expand examples of studies that might involve these populations.

- Discuss the tension between over and under sampling these populations including the importance of including vulnerable populations in research to ensure that there is safety data on compounds to which they are more likely than other populations to be exposed.
- Discuss the weighing of risks and benefits in these types of studies.

Privacy, Confidentiality, and other Concerns Related to Observational Exposure Studies

- This section of the document is sensitive to many key ethical and legal considerations relating to the safeguarding of research-subject privacy, including the need to (1) disclose the possibility of incidental reporting requirements to potential volunteers as part of the informed-consent process, (2) provide advance notification of research visits to third parties who may be residing in private environments, and (3) consider potential harms to research volunteers who display personal monitoring equipment in public settings. It would be strengthened by including specific advice on reporting and disclosure procedures when confidential information indicates a participant or another person is in jeopardy, the uses of the Certificate of Confidentiality and additional references.

Creating an Appropriate Relationship Between Participant and Researcher

- Most of the major areas and issues where ethical considerations should be addressed were included in this section, with the exception of communication/language issues. However, in many cases the section takes the tone of reporting what others have said, with and without comment; and sometimes (and more appropriately) stating "it is recommended." A document with clear recommendations will be more useful by researchers than one that raises issues without giving direction.
- OMB and other guidelines for payment/remuneration could be included.
- Provide more examples of appropriate participant-researcher relationships to observational studies.
- The role of informed consent and the IRB or other institutional representative who protects subjects' rights.

Building and Maintaining Appropriate Community and Stakeholder Relationships

- Many of the major issues requiring ethical considerations were included. However, more data to support points made and less assertion or "theory" would strengthen this section. It is also important to differentiate the terms stakeholder and community as well as their interrelationships and discussing the value of community advisory boards and community sensitive piloting of procedures.
- Successful community advisory board procedures, how the scientist-community relationship will evolve and be monitored over time, how the results of research are disseminated and the informational benefits to the community should also be discussed.

- The Board also cautioned about editing the section so that readers would not erroneously conclude that the EPA is advocating that scientists become community advocates.

Designing and Implementing Strategies for Effective Communication

- This section had a very comprehensive and informative list of reference and several suggestions for additional references have been noted. While this section is very well-written, it does not clearly focus on the communication methods most suitable for observational exposure studies. The use of side bars is a very effective tool to communicate small bits of information clearly and quickly.

- The goals of the communication should also be included. In this regard, sections on data sharing and how to address potential scientist-community disagreements (e.g., interpretation of data) would be helpful.

- The context in which communication occurs (e.g. a participant's home) should also be discussed.

- The importance of formative (process) evaluation and the importance of considering in advance how the data might be used should be included.

Science and Ethics of Sodium Azide Study

- The HSRB concluded that the Black study does not contain sufficient information to be used as a point of departure to estimate a safe level of acute and chronic exposure and is not informative as to whether human responding confirms estimates based on animal studies.

- Based on lack of documentation in the Black *et al.* study, the Board was unable to conclude that there was clear and convincing evidence that the conduct of the study was fundamentally unethical.

- The Board was also unable to assert that the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

Science Issues in Mosquito Repellent Efficacy Field Research

- The Board concluded that more research is needed to determine biases and adjustments in mosquito repellent efficacy research..
- The Board remains unclear of what the mean of the times to the first 5 bites/(landings with intent to bite is measuring.
- The Board concluded that that it would be helpful for HSRB deliberations if protocols contained rationales for sample size, outcome measures, number of treatment groups and controls, why a field study is preferable, why a specific environment was selected, how different environments differ, and how controls for environmental shifts in temperature or time of day are determined.

- The Board understands that the need for smaller sample sizes and the accompanying lack of power must be balanced with subject protection, but it is also important to understand which variables can be controlled. The expertise of control and treated subjects with respect to detecting mosquito landings must be balanced and the activity of subjects also should be controlled.

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

- While the Board concluded that the participation of several subjects on the day after they had been treated with a different test repellent was not ideal and there were errors (i.e. choice of test limb) in the study, this did not affect the validity of the results.
- However, with only 33 subjects for 80 data points (excluding the negative controls), the overlap, some of same subjects for different test materials, for Sites 1 and 2, and for different dates of experiment without proper experimental design and control, the Board concluded that it is impossible to interpret the reported data adequately thus rendering scientific validity of the results into question. In addition, the study may not have been sufficiently sound to estimate variance within the population variances.
- Thus, the Board concluded that the study was not sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes.
- The Board also concluded that the research was conducted in a manner that failed to meet the applicable requirements of §40 CFR 26, subparts K and L.

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

- The Board concluded that despite problems estimating variability and some of the same design problems found in study SCI-001, the Carroll-Loye study WPC-001 assessing the repellent efficacy of the formulation tested was sufficiently sound for the purposes for which it was intended.
- The majority of the Board concurred with the initial assessment of the Agency that the study submitted for review by the Board meets the applicable requirements of §40 CFR 26, subparts K and L.

Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Studies (SPC-001)

- The Board concluded that the protocol to study the efficacy of three formulations of picaridin for repelling mosquitoes did not provide sufficient design or a statistical analysis plan that could be evaluated for its validity or utility.
- The Board concurred with the initial assessment of the Agency that the revised protocol submitted for review by the Board meets the applicable requirements of §40 CFR 26, subparts K and L.

Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Studies (SPC-002)

- The Board concluded that the protocol assessing the efficacy of the test substances for repelling ticks (SPC-002) appears likely to generate scientifically reliable data, provided that the revisions suggested by EPA are incorporated.

- The Board underscored that the statistical analysis plan was not well-laid out and urged EPA to ensure there was a sufficient analytic plan before the study be conducted
- The Board urges EPA to consider the design of newer studies and the designs already used for existing products to make certain that labels reflect information of comparative value to consumers.
- The Board concurred with the initial assessment of the Agency that the revised protocol submitted for review by the Board meets the applicable requirements of §40 CFR 26, subparts K and L.

Proposed ICR Picaridin Insect Repellent Efficacy Study (A 117)

- The Board concluded that proposed research is generally clear and appropriately designed, with the exception of the appropriate statistics.
- The Board concurred that if the proposed research is revised consistent with EPA's recommendations and the Board's suggestions, the study should yield valid data regarding the efficacy of these products in repelling *Culex*.
- The Board concurred with the assessment of the Agency that the protocol ICR A117 submitted for review by the Board, if revised as suggested in both EPA's review and by the Board, would meet the applicable requirements of §40 CFR 26, subparts K and L.

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 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.

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Consultants to the Board

Scientific and Ethical Approaches for Observational Exposure Studies Session

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National Institute of Children & Human Development
Rockville, MD

Barry Ryan, Ph.D.
Department of Environmental and Occupational Health
Rollins School of Public Health
Emory University
Atlanta, GA

Frequency, Duration and Timing of Exposure of Subjects to Potential Mosquito Landings Session

Col. Raj. Gupta, Ph.D.
Director, Research Plans and Programs
Walter Reed Army Medical Center
Medical Research and Material Command
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Steve Schofield, Ph.D.
Department of National Defence
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* Not in attendance at October 24-26, 2007 Public Meeting

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INTRODUCTION

From October 24-26, 2007, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning:

A. Scientific and Ethical Approaches for Observational Exposure Studies

Scientists at the U.S. Environmental Protection Agency's (EPA's), Office of Research and Development's National Exposure Research Laboratory (NERL) have conducted observational exposure measurement research for several decades to understand how and why people come into contact with chemicals and other stressors in their everyday lives. These studies are performed to determine what chemicals people are exposed to, the concentrations of the chemicals, the most important sources contributing to people's exposures, the routes and pathways of exposure, and the factors that have the biggest impact on exposure.

EPA strives to follow the most up-to-date approaches in designing and performing observational exposure studies to ensure that these studies are based on sound science and meet the highest ethical standards. To meet that goal, researchers in NERL have prepared a draft document that identifies key scientific and ethical issues and provides information and resources to assist researchers as they plan and implement observational exposure studies. The document is not meant to represent an official Agency "guidance document." Moreover, it recognizes that researchers will work with others – EPA's Human Subjects Research Review Official, Institutional Review Board (IRB) members, the participants and their community, and other stakeholders – to identify and address all of the relevant issues for any specific study to ensure that all participants are respected and protected.

Review material: EPA provided the following materials to the HSRB relevant to this topic:

1. External review draft document titled *Scientific and Ethical Approaches for Observational Exposure Studies*

2. Charge Questions

3. Report on the *Workshop to Discuss State-of-the-Science Approaches for Observational Exposure Measurement Studies*, dated January 25, 2007. The report provides background on the framework for the document and topic areas recommended by an expert panel.

B. 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 (NaN_3), 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 were scientifically sound and that there was 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 was there evidence to show that the subjects included nursing or pregnant women or children.

Review materials. EPA provided the following materials to the HSRB relevant to the completed oral therapeutic study with sodium azide**:**

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

C. Science Issues in Mosquito Repellent Efficacy Field Research

Currently, EPA requires all pesticide products that claim to repel mosquitoes to provide data on the duration of efficacy under field conditions at two biologically distinct sites. These data are derived from human research with subjects who have been treated with the repellent formulations in the field. The Agency evaluates the duration of repellent efficacy for a subject by calculating the time from application of the repellent to the occurrence of an event indicating an efficacy failure. Historically, for field studies of mosquito repellency, EPA has used the "first confirmed bite" as an indication of efficacy failure on a test subject. Several recent studies have shifted to the "first confirmed landing with intent to bite;" EPA has accepted this alternative endpoint. A "confirmed landing" on a test subject is a mosquito landing followed by a second landing on the same subject within a specified period of time (usually 30 minutes) after the initial landing.

Field studies typically involve 6 – 10 subjects who have been treated with a defined amount of the test material. Each subject is then regularly and repeatedly exposed to ambient mosquito populations for a fixed interval of time until the subject experiences an efficacy failure followed by a confirmation with the specified period of time. Mosquito landing pressure (representing intent to bite) at a site is monitored by concurrently exposing untreated subjects to mosquito landings. A study is considered valid only if there are at least a specified minimum number of mosquito landings on untreated subjects during each exposure interval.

On October 25, 2007, the HSRB discussed scientific aspects of the design of field studies to assess the efficacy of mosquito repellents. Prior to the meeting, the Board requested consultants to provide specialized information or assistance to the Board. The Board was particularly interested in the frequency, duration and timing of exposure of subjects to potential mosquito landings. The Board requested each consultant to respond briefly to the series of questions below.

- What do data show about the variability of the time intervals between first and subsequent landings in mosquito repellent field trials?
- What is the current scientific understanding of how factors other than repellent efficacy could affect the likelihood that an initial event—a mosquito landing or mosquito bite—would be "confirmed" by another similar event within 30 minutes? Please address at least these factors:
  - Characteristics of mosquito populations
  - Characteristics of test sites
  - Characteristics of test subjects
  - Characteristics of test methods
- Can the impact of such factors on the likelihood or timing of an initial and confirming event be predicted? Can it be quantified?

Review materials. EPA provided the following materials to the HSRB relevant to the science issues in mosquito repellent efficacy field research:

Consultant Responses to Discussion Questions

1. Col. Raj Gupta's Responses to Discussion Questions
2. Dr. Steve Schofield's Responses to Discussion Questions
3. Dr. Daniel Strickman's Responses to Discussion Questions

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

In its January 2007 meeting, the HSRB reviewed and commented on materials related 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. (Note: 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 presented the results of this testing at the October 2007 HSRB 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 believed that the conduct of WPC-001 study may affect the results of SCI-001, and vice versa. Thus EPA conducted a single ethics review addressing both studies.

The Agency's science review raised questions about whether the data are scientifically sound. In addition, EPA's ethics review raised 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 requested 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 the Board 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.

Review materials. EPA provided the following materials to the HSRB relevant to the 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

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

In the June 2007 HSRB meeting, the Board reviewed and commented on materials relating to 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.

Following the June meeting, Dr. Carroll revised the protocols to address comments from the HSRB, conducted the study, and submitted the results.

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 questioned whether and how this fact affects the review of the separate reports.

The Agency's science review raised questions about whether the data were scientifically sound. In addition, depending on whether the study covered by WPC-001 was considered separate from the study covered by SCI-001, EPA's ethics review (discussed above under the heading of SCI-001) raised 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 requested the Board's advice on whether the research was scientifically sound and whether the available information supports a determination of "substantial compliance" with the applicable rules. If the Board 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 provided the following materials to the HSRB relevant to the completed repellent efficacy studies of oil of eucalyptus:

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

F. 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 had 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.

Review materials. EPA provided the following materials to the HSRB relevant to the proposed Carroll-Loye picaridin insect repellent efficacy studies (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

G. 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 found the protocol can meet applicable scientific and ethical standards, EPA presented this protocol for review at the October 2007 HSRB meeting.

Review materials. EPA provided the following materials to the HSRB relevant to the **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

This report transmits the HSRB's comments and recommendations from its October 24-26, 2007 meeting.

REVIEW PROCESS

From October 24-26, 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 (72 Federal Register 187, 54908). At the public meeting, following welcoming remarks from Agency officials the Board then heard presentations from the Agency on the following topics:

- EPA's draft document *Scientific and Ethical Approaches for Observational Exposure Studies*. The document, prepared by researchers in EPA's National Exposure Research Laboratory, identifies the types of issues that should be considered in planning and implementing observational human exposure studies and provides information and resources to assist EPA researchers in these studies.

- A published report of a completed clinical trial measuring the effects of single and repeated treatments with sodium azide on blood pressure in human subjects. Sodium azide is a pesticidally active ingredient being proposed as a replacement for the fumigant methyl bromide.

- An overview of the discussion questions related to the Science Issues in Mosquito Repellent Efficacy Field Research.

- A research proposal from Carroll-Loye Biological Research to evaluate the field efficacy in repelling mosquitoes of three registered products containing picaridin.

- A research proposal from Carroll-Loye Biological Research to evaluate the laboratory efficacy in repelling ticks of three registered products containing picaridin.

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

- A report of a completed field study by Carroll-Loye Biological Research of the mosquito repellent efficacy of a registered product containing Oil of Lemon Eucalyptus.

- Three closely related product-specific reports from a single completed field study by Carroll-Loye Biological Research of the mosquito repellent efficacy of four pesticides, all containing DEET.

- Design of sampling strategies for handler research programs proposed by the Agricultural Handlers Exposure Task Force and the Antimicrobials Exposure Assessment Task Force II.

The following oral comments were presented at the meeting:

(1) Judith Hauswirth, Ph.D., and Mr. Douglas Richards - representing American Pacific Corporation and addressing the *Completed Oral Therapeutic Study with Sodium Azide*.

(2) Thomas Osimitz, Ph.D., and M. Keith Kennedy, Ph.D., - representing Science Strategies and addressing the *Science Issues in Mosquito Repellent Efficacy Field Research*.
(3) Scott Carroll, Ph.D. - representing Carroll-Loye Biological Research and addressing: (1) *Science Issues in Mosquito Repellent Efficacy Field Research; (2) Completed Field Efficacy Studies by Carroll-Loye Biological Research: SCI-001 and WPC-001*; and (3) *Proposed Insect Repellent Efficacy Studies SPC-001 and SPC 002*.
(4) Mr. Niketas Spero and Robin Todd, Ph.D. - representing ICR, Inc. and addressing the *ICR Repellency Efficacy Protocol A117*.

For their deliberations, the Board considered the materials presented at the meeting, written public comments and Agency background documents (e.g., the published literature, Agency data evaluation record, weight of evidence review, ethics review, pesticide human study protocols and Agency evaluation of the protocol). For a comprehensive list of background documents visit the www.regulations.gov, Docket ID No. EPA-HQ-ORD-2007-0942, or EPA's HSRB website at http://www.epa.gov/osa/hsrb/oct-24-26-2007-public-meeting.htm.

CHARGE TO THE BOARD AND BOARD RESPONSE

A. Scientific and Ethical Approaches for Observational Exposure Studies

Charge to the Board

1. One of the goals of the document is identify the major scientific and ethical areas and issues that researchers should address in the design and implementation of observational human exposure measurement studies, with the emphasis on the areas requiring ethical considerations. Does each section identify the major areas and issues where ethical considerations should be addressed?

2. The document is intended to serve as a reference and resource of information that researchers can use in the design and implementation of observational exposure studies. For each section, are there additional sources of information that should be considered for inclusion?

3. Is the information presented accurately and clearly in each section?

Board Response

Board discussion focused on responding to the three charge questions together by section (Section 1 to 7) of the EPA draft document.

Section 1: Introduction, Purpose and Scope

Strengths

The document received nearly universal praise from the Board for the clarity of its writing and its thoughtful consideration of the many issues involved in observational studies of toxicant exposure in human subjects. The introduction set the tone for this excellent document. In particular, the Board found that it did a superb job of explaining the purpose of the document and defining its scope. It gave attention to the proper goals of such studies and the nature of the data to be collected. Most importantly, it outlined the range of ethical issues in the conduct of such studies. And finally, it accomplished exactly what an introduction must do by clearly indicating the organization and general contents of the several sections to follow in the main body of the document.

Document Enhancement

The document can be enhanced by:

- Expanding the discussion on how observational research is distinguished from intentional exposure research with specific illustrations, including discussion of the need for ethical review and evaluation of observational research.
- Revising the document to present a more balanced presentation and highlight the interplay between good science and ethics.
- Providing examples of study questions, citing other documents to guide researchers in alternative research designs, and providing bulleted summary highlights at the end of each chapter.

HSRB Consensus and Rationale

Section 1 is well written and sets the tone for ethical consideration of observational exposure studies. The document could be enhanced by examples distinguishing observational from intentional exposure studies, introducing the appropriate balance between scientific and ethical concerns, and providing study questions and bullets.

The abstract states that the document will address chemicals and other stressors, but focuses on chemicals, which gives the impression that attention is not needed except for research involving chemicals. The language and examples used in the document should reflect the importance of the document for both chemicals and other stressors. Finally, while the Agency does define and differentiate observational versus intentional exposure, such a definition should be more prominently displayed in the body of the report versus as a footnote.

Section 2: Elements to be Considered in Study Conceptualization and Planning

Strengths

Section 2 is very strong in its consideration of the overall conceptualization of study planning, especially the ethical component often insufficiently conceptualized by the scientists in their initial approach to the study. The planning and scoping of the study conceptualization

includes both the science and the ethics, as does the review process (in which each component reviews the other component as well). The strong emphasis on the ethical issues is beneficial. Recognizing some of the needs and scope of exposure sciences is noteworthy, as well. The text boxes are particularly helpful, as they summarize many of the important points from the text quite succinctly.

Document enhancements

The Board made many constructive comments with the intent of making a good document better. As with other chapters, Section 2 has a strong emphasis on ethics, to the apparent lack of emphasis on scientific aspects. In addition, a primary concern is that separating the study design document from the human subjects protocol will potentially lead to inconsistencies between the documents (Figure 2-1). The Board suggests that there be just one document, with the study design elements being a portion of the human subjects protocol. Science cannot easily be separated from ethics, so any single document should contain elements of both study design and implementation, as well as other elements that may be required for an IRB to assess whether all regulatory requirements have been met.

The major area of deficiency, given the purpose of the document, is in the paucity of information, materials, and references regarding the purpose, design and conduct of exposure studies. Even the initial paragraphs place more emphasis on the ethical issues (covered extensively elsewhere) than on the scientific ones; there should be more of a balance. In addition there are contradictions starting in Section 1.1 as to whether epidemiologic studies are included or not.

Specific Suggestions to the Document

There is little explanation or coverage of exposure study designs and methods, and their different attributes. Well-recognized study designs such as cross-sectional, case-control, and cohort (both prospective and retrospective) designs should be fully described. Sufficient examples are not provided and references to such discussions, as well as to such studies, are inadequate. There are excellent sources for such material to guide researchers, starting with EPA documents (e.g., actual examples and references for TEAM, PTEAM, NHEXAS, the pesticide studies, etc.). There are also excellent NRC/NAS & WHO documents that could be utilized. There are many lessons learned from such that could be culled to provide research guidance. Some of these sources include the NRC/NAS 1991 report on Human Exposure Assessment for Airborne Pollutants, the WHO EHC 27 (1983) report on Guidelines on Studies in Environmental Epidemiology, and the WHO/EURO & EC/EU documents on Exposure Assessment from the ECEHs & EU Lab. Additional suggestions are provided below.

1. Section 2.1.1 does not define the types of study problems and questions scientifically (or specific EPA & other references where such can be found).

2. Section 2.1.2 does not provide any basis or criteria for justification of the science component (or specific EPA & other references where such can be found), only the ethical component.

3. In Text Box 2-1 Elements to be Considered in Justifying a Study, there should be a bullet added "A discussion of alternative designs, alternative models, or alternative populations"

4. Page 21, line 4: "considers" should be changed to "considered"

5. Section 2.2 does not outline the steps in planning the study scientifically (or specific EPA & other references where such can be found). Section 2.2.1 has only one sentence about the scientific aspects, and does not really discuss "innovative" scientific aspects. Text Box 2-2, Study Elements that Could Affect People's Behavior, is the closest the section comes to delineating the components of the study that are relevant also to its planning.

6. Section 2.2 Planning and Scoping: The latter term is jargon and can be eliminated, or if not, it should at least be defined.

7. Section 2.2.1 is entitled Innovative Study Designs, but is actually about adding direct benefit (such as educational materials) for research subjects in studies for which there is not direct benefit. Innovative designs might instead include computer modeling or Bayesian designs. Either the section title or the content needs to be changed. In addition, the section's current content could be said more directly and succinctly.

8. Page 23, line 42 "…community's perspective" . Sentence should read, "…community's perspective better**, the** researcher…"

9. Section 2.2.4 states that conflicts due to project funding are "the most likely to occur." Please verify that this is the case in EPA related to observational exposure studies, or change the sentence. Unless this type of research is unique, it is likely that financial conflicts are not necessarily the most common, but rather they are the easiest to identify and manage.

10. Text Box 2-3 (Elements That May Be Included in a Study Design) and its corresponding section list elements to be included in a study design. One bullet lists items to describe technical approach and conceptual model. The Board recommended adding to the list that endpoint or outcome measures should include a description of their accuracy and precision. Survey instruments and questionnaires should include a description of whether they have been previously validated and, if not, how they will be validated prior to use within a study. A source for additional elements that might be included in a study description can be found at PLoS Medicine, http://medicine.plosjournals.org, volume 4, number 10, October 2007 in two articles concerning STROBE: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies (von Elm E et al., 2007) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration (Vandenbroucke et al., 2007)

11. Section 2.3 did not provide some of the more important specifics of the scope and technical approaches (or specific EPA and other examples and references where such can be found). Sec. 2.3.1 does not include all the important appropriate questions regarding scientific

feasibility – its one "bullet" does not even include questions about the feasibility of measurement methods. The sub-sections also did not include monitoring of observer errors and biases, participant reporting biases and reliability, inappropriate (as well as inadequate) selection criteria, representativeness (refusals and withdrawals), etc. (or specific EPA and other examples and references where such can be found). Enrollment criteria (inclusion and exclusion) need to be included, and a discussion of the ethical issues of subject selection should be added.

12. Section 2.3.1.1 Sample Size Determination: The authors are to be commended for including this section. However, the section should be written in consultation with a biostatistician. There are, in fact, many references on this topic, and to state that there is "surprisingly small amount of literature" is inaccurate. In addition, the methodology cited may not be optimal. One needs to quote and reference statistical specifics as provided in the documents previously mentioned, specific survey statistical textbook questions approaches, and also more from other statistics books), and the issue of design factors (e.g. Clickner book and other books) as well as expected refusals and expected losses that need to be taken into account. Issues of intra- and inter-participant and observer variability are not discussed.

13. A section on obtaining an appropriate sample or a representative sample in order to derive generalizable data should be written. Descriptions of sampling methods with their relevant strengths and weaknesses are critical, and would help investigators enormously.

14. Text Box 2-5, Potential Topics in a Human Subjects Research Protocol, lists potential topics for a submission to an IRB.

- Item #6 should be changed to "Affirmation of Belmont Principles…" rather than Belmont Report.
- Item #13 should be changed to "Sample size/power and statistical analysis plan."
- Item #22 should either be changed to include "unanticipated problems" or a separate item should be added.
- Item #32 should also include a comment concerning unforeseen uses, if appropriate.
- Item #42 should be changed to state "Procedures for preventing falsification of data" with the emphasis on prevention rather than on what to do if falsification occurs.

<u>HSRB Consensus and Rationale</u>

The Board concurred that Section 2 adequately identified the major areas and issues where ethical considerations should be addressed in the study conceptualization. The Board suggested that rather than having distinct sections and even documents on ethics and science there be just one document, with the study design elements being a portion of the human subjects protocol. This would more closely parallel the information submitted to an IRB. Bulleted items should also include justification for sample selection and size and sampling method, discussion of alternative designs that were rejected to help justify the use of human subjects in the particular way being proposed, expanded examples of conflicts of interest, and the importance of using validated measures. Expansion of text regarding adverse events vs. unanticipated problems, scientific misconduct, subject attrition, reporting biases etc were recommended.

Section 3: Ensuring Protection of Vulnerable Groups

Strengths

Section 3 is of high quality and does a very good job in addressing the major areas and issues related to vulnerable subjects. The section presently devotes the bulk of the discussion to issues relating to children and women. It might be helpful to present a somewhat more balanced discussion, with added material devoted to discussing issues relating to other vulnerable groups.

Specific Suggestions to the Document

1. Section 3.1, Identification of Vulnerable Groups, it might be helpful to more specifically point out the differences between the rules under which the EPA is operating with regard to identification of vulnerable groups (primarily, the Common Rule), as compared to the concepts of vulnerability that the lay public might have. In addition, a discussion of how vulnerability can be context-dependent could be helpful.

2. In Section 3.2, the current discussion puts an emphasis on the "special justification" needed for inviting vulnerable subjects to participate in research, without expanding on how that concept plays out in observational studies. In fact, many of the observational studies with regard to which this document will apply are studies that are intended to collect important health information regarding the well-being of various vulnerable groups (such as children and pregnant women). Moreover, unlike many other studies (such as interventional studies), observational studies generally do not impose more than minimal risks on subjects. Those circumstances—the possible large benefits to the vulnerable populations from gaining the information to be learned, and the minimal risk regarding including them in the studies – combine to often make a strong ethical case for including such groups in these studies. Thus, it would be appropriate for this section to also discuss the harms from *inappropriately excluding* various groups of vulnerable subjects from this category of studies, and how those harms would often be to those very groups. This point is already made in Section 3 in some of the discussions of specific subject groups (e.g., in the discussion in Section 3.4 with regard to children), but it would be helpful to highlight it as a general proposition in the analysis of the general issue of the justification for including vulnerable subjects.

3. It might be helpful to have a more expanded discussion of how to mitigate risks to vulnerable subjects in these studies. This point is particularly important given the substantial reasons (as noted in item 2 above, and already discussed in portions of Section 3) for including such vulnerable subjects in these studies. This discussion could go beyond the risks created or imposed by the inclusion of the subjects in the study (which are often minimal), and also address the extent to which it is appropriate for researchers to be standing by and observing while vulnerable groups are exposed to risks not created by the study.

4. It could be helpful to add a subsection dealing specifically with workplace-based studies. The types of vulnerabilities of workers who participate in those studies are somewhat unique, and can vary depending on the specific type of study.

5. Given the very substantial literature on the topic of vulnerable subjects, the list of references in Section 3.7 might be expanded.

HSRB Consensus and Rationale

The Board determined that Section 3 is of high quality, accurate and written clearly. The Board recommended additional discussion on justifications for including vulnerable populations in research as well as expansion on discussion of who is vulnerable outside of the federal regulations (e.g. pregnant women, prisoners, children) such as economic, educational or social vulnerabilities; noting however that in federal regulations vulnerability is defined in terms of susceptibility to coercion and undue influence.

The Board also recommended the document: (a) expand examples of studies that might involve these populations; (b) discuss the tension between over and under sampling these populations including the importance of including vulnerable populations in research to ensure that there is safety data on compounds in which they are more likely than other populations to be exposed; and (c) discuss the weighing of risks and benefits in these types of studies

Section 4: Privacy, Confidentiality, and Other Concerns Related to Observational Exposure Measurement Studies

Strengths

Section 4 provides a good discussion of several privacy concerns associated with observational studies, particularly those conducted in private or semi-private places such as homes and schools. Although research volunteers allow study staff to access these environments, others who may be residing in these environments may object or feel that their privacy is not being appropriately respected. Additionally, during the course of collecting research data, study staff may observe illegal or immoral activities that may challenge their ability to maintain the confidentiality of research volunteers or others who may be living in these environments.

Document Enhancement

Considerations relating to the protection of the vulnerable groups, where more active intervention by study staff may be appropriate should be strengthen. For example, Section 4 suggests that researchers develop a plan for responding to the incidental observation of illegal behaviors such as child or elder abuse. It does not recommend that research staff be trained with regard to the recognition of such behaviors, which is essential for avoiding both missed opportunities for intervention and inappropriate accusations of abuse. Similarly, this section provides little guidance with respect to the observation of environmental situations associated with imminent harm, such as observations of combustible materials near an open flame, a child

playing unattended by a pool, a firearm placed near young children, etc. Section 4 could be strengthened by including advice for addressing such situations or offering general guidance for determining when members of the research team should act in circumstances involving imminent harm. It would also be helpful to reinforce the point that local and state reporting requirements may vary considerably.

Section 4 does not consider the potential risks to members of the research staff who may find themselves in situations involving illegal activities such as drug use or sales, nor does it consider the potential burdens that research staff members may feel when presented with behaviors that they find morally objectionable. In contrast to several of the other sections in the document, the citations to relevant literature provided in this section are lacking (e.g., no recent review articles are cited, nor are there any references to important privacy documents such as HIPAA).

Specific Suggestions

Section 4 could be strengthened by including advice for addressing environmental situations associated with imminent harm and offering guidance for determining when members of the research team should act in circumstances involving imminent harm.

Purpose and use of the Certificate of Confidentiality should be included. Such certificates do not diminish the need to protect personally identifiable information and does not relieve the requirements for reporting illegal behaviors. While the Agency's document states that certificates should be used for "sensitive matters," it does not define sensitive matters. Finally, Federal regulations exist that clearly define populations needing certificates of confidentiality. Such regulations should be noted in the document.

HSRB Consensus and Recommendations

This section of the document is sensitive to many key ethical and legal considerations relating to the safeguarding of research-subject privacy, including the need to (1) disclose the possibility of incidental reporting requirements to potential volunteers as part of the informed-consent process, (2) provide advance notification of research visits to third parties who may be residing in private environments, and (3) consider potential harms to research volunteers who display personal monitoring equipment in public settings. It would be strengthened by including specific advice on reporting and disclosure procedures when confidential information indicates a participant or another person is in jeopardy, the uses of the Certificate of Confidentiality and additional references.

Section 5: Creating an Appropriate Relationship Between the Participant and Researcher

Strengths

The Board also commented that this section, like other sections of the document is excellent; it is readable and useful. In general, Section 5 accurately and clearly discusses the ethical considerations in the relationship between investigator and participant. A major strength of this work is its focus on researcher responsibilities and guidance for researchers. A strength is that it includes consideration of the context of the participant's community, etc. (One assumes that "community" includes all the socio-cultural aspects in which the investigators are competent and respectful.) In relation to these strengths, it would help if the document stressed the importance on researcher training in human subject protection, with emphasis on observational techniques and community-based research,

The sub-section relating to remuneration (payment) is highly appropriate and well written. Likewise, Section 5.3 on rights is well done. Section 5.4, Creating a Supportive Environment for Research and Interaction , as defined, is very useful and well stated also.

Section 5.5 provides good discussion of equitable selection and of IRB guidelines (Text Box 5-3) for selecting sub-populations for study from the ethical standpoint (see below re: scientific standpoints). Section 5.6 on retention issues and ideas, especially in longitudinal studies, is useful and generally well done.

Document Enhancements

One of the areas that is important not only to recruitment, but to the successful conduct of studies is language. The regulations require information be presented in a language that is "understandable" to the subjects/potential subjects. That has always been interpreted to mean two things; at a literacy level (oral and reading) that is appropriate for the target population and, in a language that the listener/reader speaks/reads. Because various populations to be studied in the U.S. tend to include persons who speak/read little, if any, English, it is very important that researchers address how communications will be handled. At a minimum, written documents, such as consent forms, advertising flyers, instruction sheets, etc must be developed in more than just English. Such written materials must be reviewed and approved by an IRB prior to use. Those review bodies should obtain independent back-translations to ensure that the communication accurately conveys the information in the English version(s). That is only part of the issue, however, because during the conduct of the research, investigators and the research team must be able to communicate orally with subjects, including those who may not speak English. Thus researchers must address in protocols how planned and *ad hoc* translations will be accomplished. It should be stressed in this document that untrained persons (e.g., co-workers etc.) generally do not meet the ethical requirement for facilitating full understanding and protecting subject welfare.

Too many discussions/descriptions/examples are correct, but the examples given are for/applicable to research in general. Section 5 would be more useful to researchers conducting observational studies if the discussion were more focused on the special needs/considerations in that type of research. In a related vein, Section 5 makes some global statements, such as "additional considerations arise …" or "a number of issues have been identified …," but there is no expansion/explanation; so there is no "teaching point." These generalities should be removed or used to start a description of the concern or issue; Text

Boxes 5-2, 5-3 and Appendix C are good examples of getting the key points into this section without repeating the source verbatim.

There are additional sources of information that should be considered for inclusion in the section, specifically the NRC/NAS 1991 report on Human Exposure Assessment for Airborne Pollutants and the WHO EHC 27 (1983) report on Guidelines on Studies in Environmental Epidemiology, statistical survey sampling textbooks, the Board's discussions of "purposive" sampling, EPA and NIEHS documents on environmental equity/justice, and other references contained in this document on community and Community Advisory Boards (CAB) involvement. Also, the literature on observational studies, such as the developing community based participatory research literature may be informative. With a caution about keeping the focus on observational research, there is also a wealth of "good clinical practice" (GCP) references which could be used to expand some issues (such as payment and other incentives in section 5.2.1).

Specific Suggestions to the Document

Section 5.1.1 seems to include descriptions of consent elements that are of general application, but this section would be more useful to researchers conducting observational studies if the discussion was focused on the special needs/considerations in that type of research.

Section 5.5, Recruiting Strategies, does not address the scientific necessities of sometimes including over-sampling (via stratified/cluster methods) of sub-populations, including the underrepresented and the overexposed. Thus, there should be a similar delineation of when such sampling and recruitment are necessary, similar to Text Box 5-3, which discusses those needs from an exposure science standpoint. For instance, it is not inappropriate to study minority/poor children when evaluating exposures to lead, pesticides, etc., under existing laws/rules/statutes. Some of the "environmental equity/justice" issues need to be discussed. CABs need to be involved in approving recruitment materials.

Section 5.5 should discuss consideration of the limitations, especially statistical issues (representativeness & generalizability) and non-random sampling (i.e., the scientific problems inherent in "convenience," "purposive," etc. sampling).

There should be a parallel section to Section 5.7 that discusses the benefits of longitudinal follow-up for the participants, communities, and responsible agencies and the decrease of risks that may be so obtained.

The way some references are used (e.g., Grady (page 58, lines 13-21) seems more suited to a journal article than a review document; that is, "what does this mean for the researcher" and "what is the application to observational research" is lost.

Additional Specific Suggestions

The Board had a few suggestions for possible additional information that might be included in the chapter:

1. Page 51, lines 37-39 makes the comment that the consent process must explain risks, but in order for subjects to make decisions about participation that reflect their individual concerns, it would be well to state that an accurate and realistic description of possible benefits must be included as well. See lines 41-44.

2. Page 52, lines 2-3 refers the reader to three sources for additional information. It would be more useful for readers if key points made in these publications were listed or summarized. That allows the point to be made or the issue to be raised.

3. Page 52, lines 36-39 discusses one interpretation of "language understandable to subjects" (native tongue), but it also should be pointed out that this has a readability requirement too. Page 53, lines 1-4 and Page 55 lines 1-2 seem to relate this requirement just to a description of purpose. This should be fixed.

4. Page 53, line 16 makes a reference to a court case; its relevance needs to be explained.

5. Page, line 24 uses the term "informed consent" incorrectly to imply the form, not the process of information exchange needs to be presented to parents. (Note the rest of that bullet is fairly dense and could be revised to make it more readable.)

6. Page 55, line 9 uses the term "administration procedure" when "consent procedure" would be more appropriate.

7. Page 55, line 28 uses the term "study elements" when "study characteristics" would be better.

8. Page 55, line 29 is the first use of the word "remuneration" in this section. This term clouds the reason subjects are offered payment for participation in research. It is not payment for services in the way employment is. It is an "inducement," hopefully not unduly large, that encourages participation. The word "remuneration" should be changed to "inducement" throughout the section and the document (search and replace) so that the ethical issue regarding payments is not lost.

9. Page 57, line 5 is the first use of the word "compensation" in this section. This term is a "regulatory word" and is therefore associated with "compensation for injury." It would be clearer and more accurate to use the term "payment" throughout the section and the document – for example in the Executive Summary on page 5 - (search and replace) so that the ethical issue regarding payments is not clouded.

Page 61, lines 4-5 indicates that community input can be obtained from research team members. While true, to be truly representative of community attitudes, non-research team members should be sought out as they should be free from any potential scientific biases.

HSRB Consensus and Rationale

Section 5 identifies most of the major areas and issues where ethical considerations should be addressed, with the exception of communication/language issues. However, in many cases the section takes the tone of reporting what others have said, with and without comment; and sometimes (and more appropriately) stating "it is recommended." A document with clear recommendations will be more useful by researchers than one raising issues without giving direction. The Board raised three overall questions in reviewing this section of the document. The questions were as follows:

1. Can the authors define "a strong relationship", and what is a strong scientific relationship?
2. Are there specific OMB guidelines on remuneration that could be included?
3. Should the participant grievance procedures include also any component of EPA or the IRB(s) who approved the study?

Section 6: Building and Maintaining Appropriate Community and Stakeholder Relationships

Strengths

Section 6 identifies many important areas and issues that need to be considered in addressing ethical aspects of observational exposure studies. This section addresses the rationale for and the complexity of building and maintaining trustworthy and effective relationships with communities and stakeholders who are either directly or indirectly affected by observational exposure studies. The authors are to be commended for identifying the key components of this complex and multi-faceted process.

This section identifies options for researchers with regard to community involvement including CABs, which have been shown to be quite successful in several observational epidemiologic studies in which exposures are quantified in relation to human health effects. The composition of CABs is not well defined. Such boards should be representative of the community. This section also does not clearly articulate the advantages and disadvantages of engaging a community of research, nor does it clearly describe best practices. For example, investigators should be advocates for the data, not for the community and a CAB is not a substitute for ethical decisions.

Section 6 carefully defines important concepts and operationalizes them for researchers. Definitions, by design, are relatively broad offering flexibility to meet specific study objectives tailored for particular communities.

Document Enhancements

This section identifies and provides some of the supporting documentation for key components required for building relationships; e.g., within an overall conceptual framework that builds largely upon the *diffusions of innovations* literature (Rogers, 1995a, 1995b). However, much of the presentation is in the form of assertions rather than supported by sound

science. While many of the assertions are quoted from references, there may be no hard data in the references to back up the statements. The Board recommended that the final report include evidence-based discussions and/or tables that show better compliance, retention, and data quality when community involvement is obtained compared to when it was not. Scientific rigor is essential in the exposure science field and therefore should be attended to carefully in this document.

Both moral and "best practice" considerations are included as ethical aspects of these studies. (For example, moral principles with aspirational results are listed on p. 67, lines 12-15, while Text Box 6-1 lists "best practice" considerations.) Clearer distinction of the types of ethical issues and the better use of text box listings to highlight the differences would strengthen this section [and document]. Further, clarification would make it easier for the reader to understand whether "ethical issues" in this section refers to moral principles, "best practices," or both.

Examination of the many ethical issues raised in Section 6 suggests that the section [and document] may benefit from a text box or table (i.e., a box that would be parallel to Table 1-3) summarizing the ethical principles, which are *essential* for observational exposure studies. The advantage of such a summary would be to pull out the principles that resonate throughout the document; i.e., the ones that are more than single mentions. [This summarization may be more effective on a section-by-section basis, rather than across the entire document.]

Specific Suggestions to the Document

Important points that may merit emphasis in text boxes or other mechanisms in Section 6 include the underlying principles essential for effective relationships (now spread throughout Section 6):

- Respect, fairness, beneficence, honesty, openness, trust, commitment, confidentiality, and responsiveness [Note that justice and other principles are listed on pages 2 and 5 (etc.). Perhaps a cross-reference to earlier, more complete text or supporting materials is needed in Section 6.]
- As appropriate for the contexts, early and active community involvement, meaningful community roles and responsibilities, and two-way communications
- Effective representation of the community's diverse views
- Dignity, veracity, sustainability, justice and community (p. 69)
- Establishing a relationship with the community before a study (p. 71)
- Build community capacity (p. 73)
- Researchers need to be forthright with communities (e.g., p. 73)
- Research relevant to communities (p. 74)

Introductory paragraphs

Community-based studies involve numerous ethical issues that are fundamentally different in important ways from clinical studies (p. 67, lines 19-21). Some of these issues are addressed in the earlier sections of the document, but not discussed in Section 6. The one issue

highlighted here is two-way communications (p. 67, line 30), but this emphasis is not consistently presented throughout Sections 6 and 7.

Section 6.1

This section is quite good and includes a compendium of ways to approach the community and get the community involved with a study. Such information is invaluable to the neophyte researcher attempting to gather data in a new community.

However, some of the reasoning presented in Section 6.1.1 and sub-sections borders on philosophical, is convoluted and occasionally circular: ethical action requires trust and trust is essential in ethical action. Still, the points are of interest and should be developed. Exposure researchers typically have "hard science" backgrounds, and therefore need both guidance in this area and substantial evidence supporting the points (e.g., those cited from the EPA November 2007 workshop on observational exposure studies). Perhaps the use of examples would be a better teaching tool and would serve EPA's needs better.

Sections 6.1.1.1 and 6.1.1.2

The sections are not balanced in their discussions of community and stakeholders, giving less attention to the latter. The reason for this imbalance is not apparent and may confuse researchers about who stakeholders are and what their roles are.

Who is to be involved in community-based studies and how involves a variety of ethical concerns. The distinction between "community" and "stakeholder" should be made clearer (see pp. 69-70). The "stakeholder" descriptions on p. 70 (lines14-17) and p. 74 (lines 19-20) could be improved; e.g., stakeholders can physically speak for communities but may not be seen as *legitimate* spokespersons for community interests. The key issue is whether the community has actually or officially delegated any of its representation or speaking rights to stakeholders (whether stakeholders are also members of the community or not); this seems to be the intent of p. 70, lines 21-23, 27-29, and 38-39. Perhaps minor editing of this page will clarify and strengthen the Agency's guidance, or – more likely – a major reconsideration of the definitions and differences between "community" and "stakeholder" may be needed for use throughout the document.

Section 6.1.1.4

Reading comprehension needs to be stressed more and, possibly, operationalized further. While there is at least one comment to strive for an 8th grade reading level, many IRBs require materials prepared for a 5th grade level. Also, if translation is required, many IRBs require a certified translating service and increasingly are requiring back translation when certificated services are not available. In the advisory spirit, some reference may be needed with regard to translation.

Additionally, data collection instruments can be designed so that reading comprehension is objectively measured. To this end, researchers could be advised to formally evaluate grade level reading and comprehension while capturing data relevant for exposures.

Sections 6.1.1.4 and 6.1.1.5

A new section should be included since means of communication (sometimes referred to as channels of communication) are not discussed here. Just as the level and type of language used is important, means of communication should align with communities' preferences. Understanding and using the ways in which communities want to receive and share information are essential ways of demonstrating respect for communities' interests and showing that their input makes a difference. The Board suggests that a brief section about this issue be added between Sections 6.1.1.4 and 6.1.1.5.

Section 6.1.1.5

Cultural differences should include race/ethnicity but, minimally, also religious beliefs or other unique lifestyles. Currently, the text only pertains to the former and thus is unbalanced and potentially misleading. The Board recommended that the authors consider adding language about providing study results to the communities (and stakeholders) before publication.

Section 6.1.1.7

The role of the researcher as an advocate (in addition to capacity building) for the community is alluded to in the document (e.g., p. 73, lines 73-75), but is noticeably absent here. This is an important aspect for this section but one that is strongly resisted by many researchers. The Agency needs to consider this section very carefully as it will embark on a new expected path for many EPA researchers - advocacy – in addition to researcher.

Section 6.2

This section could also provide advice about a reasonable length of time for communicating study values (including personal exposure results) to participants. Ideally, such times should be determined upfront with community input. For example, a reasonable time might be within 6-12 months upon quantification of biospecimens.

Perhaps, attention should be given to the planned inclusion for health alerts in real time. Some observational epidemiologic studies have health alerts built into web-based data management structures so that researchers and participants can be alerted to any value requiring further attention. This approach needs formalization and guidelines for implementation in the overall study protocol.

This section also should address the lessons learned from various observational epidemiologic studies that have utilized CABs or other forms of participatory research. For example, a wealth of information has been learned from the environmentally oriented studies

involving adults and children or from the Long Island Breast Cancer research (Gammon *et al.*, 2002).

Section 6.3

The use of "other stakeholders" (p. 74) is confusing to the reader; what types of stakeholders are "other?" If the definition of "stakeholder" is broad, then the concept of "other" becomes moot. The text of this section is not fully aligned with the stakeholder concepts in Section 6.1.1.1 (p. 70, lines 13-14) or the Glossary (p. 107) and therefore needs to be reconsidered.

Further, the stakeholder discussion in Section 6.3 is given short shrift when compared with the Community Involvement discussion (Sections 6.1 and 6.2). Buy-in from stakeholders is often as important as buy-in from the community even if for the reason that stakeholders often have more fiscal resources to draw upon. Without their buy-in, this would limit financial resources, potentially hampering the ability for the study to be conducted. Stakeholders may offer alternative points of view involving jobs for the community versus the views of some groups in the community that may want "no pollution and no risk" without regard to fiscal and social costs. More comprehensive information about stakeholders, particularly the needs of local government and business stakeholders, should be included.

The importance of continually attending to the dynamics of relationships is not recognized in this section. Beyond identifying stakeholders (p. 74, lines 25-29), an additional benefit of Mitchell et al's (Mitchell et al, 1997) framework is that it offers a means for ongoing assessment of the shifts in power, legitimacy and urgency that occur during studies and that affect views of who is which type of "stakeholder" (as defined in their article) and how they should be involved. Further, Michell et al (1997) describe different ways in which organizations may interact with different types of stakeholders throughout a dynamic process (such as occurs in observational studies). Recognition and guidance about anticipating and strategically managing relationships throughout observational studies would strengthen this section.

It is important to be sure the text boxes (not just in this section) are fully documented in the text in order to avoid careless use of the points without regard to the broader issue of community and/or stakeholder involvement. Ordering of bulleted items should reflect logical steps in the process or importance; nonetheless, the rationale for ordering should be stated.

Editorial Suggestions

Page	Line/s	Section	Comment
67	5	intro	The word exposure is missing "…observational exposure research…"
67	36	intro	Add c after 2003. [See reference on page 76.]
68	5	6.1	Consider revising this sentence to read "…nature of the research itself and affected (or targeted) community…"
68	12	6.1	Do you really mean all qualified members? Possibly add text

			to say how to select among qualified members if the number is high (e.g., randomly select, established rotations, etc…)
68 to 69	47 to 30	6.1	The section gets a bit far a field in its discussion of new forms for Institutional Review Boards. Perhaps a new section or sub-section is warranted at this point.
69	7-8	6.1	Ensure that these lines reflect the author's intent. As now written they could be misinterpreted. "CAB members • …have to be educated" sounds directive and could be read as condescending; is that what the author said? [The point made on p. 69, lines 24-26 is related.] • …should represent their communities honestly…" sounds judgmental, as if the presumption is that CABs will not do so. Is that what the author said? • …need to be willing to interact…" involves the same issues as the bullet immediately preceding this one.
69	28-30	6.1	What is the evidence base for the conclusion made here? If none, consider rephrasing this point.
70	13-14	6.1.1.1	This definition of stakeholder could overlap with the definition of community found on p. 69, lines 39-41. Inserting a well-accepted definition for "stakeholder" here and in the Glossary is recommended.
70	29-32	6.1.1.2	Delete this sentence. It doesn't add to the document.
70	46-47	6.1.1.2	Is this a "should" or "must" issue? The latter implies that it is a critical issue, while the former does not. If the agency believes that reaching out to multiple organizations is essential, this sentence would benefit from rephrasing. There are other should/must issues in the document; these also may benefit from similar reconsideration by Agency authors.
71	4-6	6.1.1.3	Delete this sentence. It doesn't add to the document.
71	20-21	6.1.1.3	This sentence could be misinterpreted as being directive to communities, rather than advisory to researchers. Rephrasing is recommended.
72	10	6.1.1.4	"Materials distributed" implies written and/or visual tools only. This suggests that oral/aural and interactive forms of communication are excluded; the Board doubts that the authors intended to exclude such forms of communication here and suggest rephrasing.
72	19	6.1.1.4	"Explanation" is a limited concept in light of the document's earlier discussion of the importance of two-way communications. Listening to communities' feedback about the research should be coupled here to complement the explanation function noted.
72	30-32	6.1.1.5	The key points from this reference should be included here. Without them, this sentence is of little use to the reader and does not provide a level of information about ethical issues

			comparable to the rest of the paragraph.
72	35-39	6.1.1.6	This sentence uses the terms "relational paradigm" and "societal context." These terms stand in sharp contrast to the urgings earlier to present information in a manner understandable to subjects in a study. These words are jargon and are not clear; this sentence should be re-worked.
73	6-7	6.1.1.5	An important ethical issue not mentioned here is the need to attend to the dynamics of relationships; these may change whether one or more parties judge pre-established roles and responsibilities as acceptable. An ongoing process of assuring mutual understanding and acceptability is often needed because community research environments are inherently complex and dynamic.
73	17-19	6.1.1.7	Same issue as on p. 71, lines 20-21.

HSRB Consensus and Rationale

In large part, the information is presented accurately and clearly in each section; however, suggestions for improvements are noted. Section 6 addresses many of the major issues requiring ethical considerations but lacks the level of scientific rigor needed by exposure scientists. Major suggestions by the Board included:

- More data to support points made and less assertion or "theory" would strengthen this section.
- It is important to differentiate the terms stakeholder and community as well as their interrelationships and discussing the value of community advisory boards and community sensitive piloting of procedures.
- Successful community advisory board procedures, how the scientist-community relationship will evolve and be monitored over time, how the results of research are disseminated and the informational benefits to the community should be discussed.
- The Board cautioned about editing the section so that readers would not erroneously conclude that the EPA is advocating that scientists become community advocates.

Section 7: Designing and Implementing Strategies for Effective Communication

Strength

Section 7 discusses principles for designing and implementing effective communication strategies between all affected stakeholders in an observational exposure study. One of the important messages coming from this section is that an effective communication strategy should be a structured, formal plan and should be given extensive forethought prior to beginning the study. Additionally the communication strategy plan should be a living document that is constantly reexamined and updated as the study progresses. It should be stressed that this involves a two-way communication strategy and an intentional process. It is as (or more) important for the researchers to listen to the stakeholders as it is for them to give information to the stakeholders.

Document Enhancements

However, Section 7 emphasizes one-way, media-directed, and crisis communications, which conflicts with the rest of the document. These aspects of communications may be part of a comprehensive, strategic communication program but often are not appropriate as the major emphasis for community-based, observational exposure studies. Instead, community concerns about potentially being stigmatized by research participation and/or results are often important issues.

In Section 7.1, the importance of formative evaluation should be noted. Ongoing evaluation is a means to identify community needs and issues, thereby permitting researchers the opportunity not only to improve conduct of the study but also to actively demonstrate respect to participants, showing that their input makes a difference.

Section 7.2 states it is essential to engage all stakeholders early and often in the process. One area that has been commented on for previous sections is the definition of "stakeholder". On page 74 of the document (Section 6.3) it states "stakeholders may include business, industry, and local or state governments or agencies with jurisdiction over the community." In contrast, Section 7 includes the community as one of the stakeholders. It is important upfront to define the term "stakeholder" and what groups it encompasses and to use that definition consistently throughout the document. The community from which the subjects are to be drawn has traditionally been considered as one of the stakeholders.

While it is critical to identify all pertinent stakeholders, there is a danger that the group would become so large that it becomes unmanageable. In a group such as this there is the potential for having strong divergent interests. This could generate enough conflict that it could impede the research from moving forward in a timely manner. It is therefore advisable to add as references some articles on managing conflict with a diverse population. A sidebar with some salient points on managing conflict might help.

Specific Suggestions to the Document

Section 7.3 discusses communication timetables. It encourages researchers to begin the dialogue with the community as soon as possible, learn from the participants and the community, and continue exchanges of data and information through the reporting of the study results and beyond. It suggests using press releases as an important tool to engage the community. Section 7 states that observational studies should also be announced to stakeholders and the public via media, community interactions, or other means well in advance of study implementation. It is strongly recommended that there be some "buy-in" by the community before any public announcement.

Section 7.4 talks about the importance of developing communication materials at different levels of science literacy. It stresses that all materials be written in "plain language." However, there are no follow-up references on available "plain language" strategies and tools. Below is the link to the Department of Health and Human Services Plain Language webpage.

Other empirically-based references could also be included in the document along with a sidebar on "plain language" tips.

http://www.health.gov/communication/literacy/plainlanguage/PlainLanguage.htm

While comprehension is correctly identified as an issue, testing of tools is under-emphasized here and at the end of Section 7.5.. Empirical testing of communication methods and content is known to be essential and demonstrates respect for communities (cf. Health Canada's strategic risk communication handbook available at http://www.hc-sc.gc.ca/ahc-asc/activit/ris-comm/index_e.html).

Section 7.5 discusses the development of communication materials. An example of a pediatric assent document is given. The point that should be stressed with this example is that it must be written at the level of understanding of the reader. The use of generic communication materials for several different stakeholders would not be appropriate, contrary to what the document might suggest, because each stakeholder will be unique in its understanding, level of involvement, and connection to the research. Researchers should be strongly encouraged to gather data about individual stakeholder needs and priorities prior to developing communication materials geared towards that population. Again two way communication is essential because stakeholders can best define their strengths and limitations in understanding.

Another communication tool emphasized in this section is the use of the internet to communicate with study subjects and with interested stakeholders. One important point that should be stressed here is that a communication tool is only useful if it is readily available and readily understood by the target stakeholder population. For example, if the researcher chooses to communicate by internet, he/she should be certain that everyone in the stakeholder population has ready access to the internet and has the requisite computer skills to navigate the research site. Researchers will have to be even more creative in developing communication strategies with stakeholder groups that include populations of illiterate members or those which do not speak English.

The real emphasis should be on listening carefully to and the learning from the stakeholders and looking carefully at the communication needs and limitations of all the pertinent stakeholders before beginning the development of communication materials.

The end of this section brings up the important issue of conflicting ethical values and study elements. However, the final lines only address remuneration and communication materials (see comments above); two elements of a study that are not tools for addressing conflicting values and elements. The text should segue into comments about methods appropriate for addressing conflicting values and study disputes.

Section 7.6 states that researchers need to make a commitment to communicating with and educating the study participants and the community on the purpose of the study. Some discussion should be included about the issue of whether behavior will be adversely changed as

a result of educating the participants. If too much education results in a behavior change, the goals of the research will be compromised.

Section 7.7 discusses that approaches for reporting results to the participants but does not note that these approaches should be developed with community input. In communicating the results, it is vital to make sure the study participants clearly understand the meaning of the results. Additionally the study participants and the community should be directed to sources of additional information, resources, and counselors where they can turn to for additional information or follow-up information in case of additional questions or concerns.

Participants should also be given the option of not receiving any results. Their options about receiving results should be clearly laid out and discussed prior to initiation of the study. The community and stakeholders should be notified prior to the publication of any study results or any press releases relating to the publications. These interested parties have a right to know when data are going to be made public but do not have the right to change the science or the researcher's interpretation of the science in the publication. They can, however, dispute the interpretations in public.

It is unclear why part of this Section focuses on crisis communications and "responding." There is no rationale to help researchers understand why this discussion is included, or how this advice for a specific type of communication would fit in a comprehensive risk communication strategy for observational exposure studies. However, judging people's perceptions as "accurate" is not appropriate; perceptions are what they are whether someone else agrees with them or not. Perceptions may differ among individuals and groups; perhaps the intent here is that lay people may have perceptions that differ from that of experts (see Morgan et al. 2002. Risk communication: a mental models approach.) . Section 7.9 deals with communicating with the interested stakeholders when a dispute in interpretation of data results occurs. This is an important area to stress so that researchers discuss strategies to deal with this as they develop their implementation plan. An additional section on how to deal with litigation, should it occur, might be helpful to researchers should they find themselves in this situation.

HSRB Consensus and Rationale

Section 7 covered most of the important issues. This section had a very comprehensive and informative list of reference and several suggestions for additional references have been noted. While this section is very well-written, it does not clearly focus on the risk communication methods most suitable for observational exposure studies. The use of side bars is a very effective tool to communicate small bits of information clearly and quickly. Other areas that need additional discussion include: (a) the goals of communication; (b) data sharing and how to address potential scientist community disagreements; (c) the context in which communication occurs; and (d) the importance of formative evaluation.

B. Completed Oral Therapeutic Study with Sodium Azide

Charge to the Board

1. 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.

Board Response to the Charge

The Black et al. (1954) study was not designed adequately to estimate a NOAEL rather it focused on evaluating the therapeutic nature of sodium azide. Accordingly, the study did not investigate the critical effect and it also did not report the administered dose precisely. Further, the study lacked clarity on baseline data and overlap of subjects in the various treatment groups. The Board felt that the study did not meet the prevailing standard in scientific conduct and reporting in clinical trials. Sir A. Bradford Hill's randomized, placebo-controlled trial of streptomycin for treatment of tuberculosis reported in the British Medical Journal in 1948 had better experimental design, conduct, analysis and reporting of results from a clinical trial. The Black et al. (1954) study, however, suggested increased sensitivity in several subjects with chronicity, even though the basis of that sensitivity is undefined. Whether that was due to additional blood pressure-lowering effect or another adverse effect is really not clear. In its discussions, the Board noted that it may also not be relevant to make direct comparisons of these human data with animal data, without body surface correction or appropriateness of the endpoint measured. The specific concerns of the Board are summarized below:

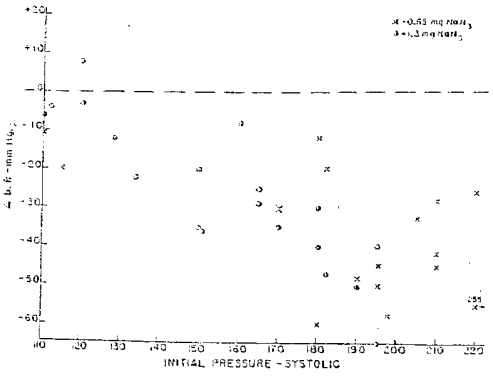
- **Dose**: The information provided by Black et al. (1954) suggested that doses of 0.65 and 1.3 mg were given three to five times to individuals with no known body weight gender, race, and age. In the case of chronic study, the doses were given during 5 days to more than 2 years. In page 15 of the report, the authors refer to decreasing the dose from 0.5 to 0.25 mg in 20 patients. However in Table I which lists 30 out of the 39 patients, only 2 patients received 0.5 mg dose. This kind of reporting does not facilitate confident determination of the point of departure for establishing a safe level of acute and chronic exposure to sodium azide.

- **Toxicity**: The study looked for some side effects (liver, kidney) and clinical measures (no description of methodology or control values) at the therapeutic doses given to people. There was no focus on the critical organ or critical toxicological effect. Further, toxicity was evaluated only in 3 individuals and it did not involve any time course analysis. The rationale regarding why, when and what was evaluated – is missing. One out of three subjects reported pounding of the head after taking sodium azide, and this level of information is not adequate to determine a scientifically-defensible NOAEL or LOAEL for acute and chronic exposures to sodium azide.

- **Subjects:** There was no baseline/pre-treatment information about the patients, other than pre-treatment blood pressure, limiting the value of the results presented in Black *et*

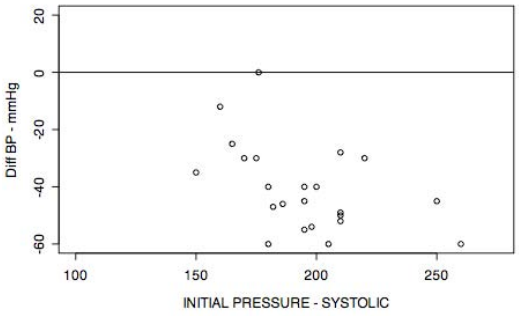
al. (1954). It is also unclear whether there was an overlap of patients for the acute and chronic effects of sodium azide.

The blood pressure data for the 30 hypertensive patients given in Table I appeared to be included in the data presented in Figures 2 and 3 for the acute blood pressure change for 35 patients, but only partially. In Table I, there are 19 patients with pre-treatment systolic blood pressure (SBP) of > 190 mmHg and 11 patients with pre-treatment SBP of $\geq$ 140 but $\leq$ 190 mmHg among 30 hypertensive patients. However, in Figure 2, there are only 13 patients with pre-treatment SBP of > 190 mmHg, 13 patients with pre-treatment SBP of $\geq$ 140 but $\leq$ 190 mmHg, and 9 normotensive patients with pre-treatment SBP of < 140 mmHg. The gap in the data cannot be accounted for, and as a result, the veracity of the data is being called into question. As shown in the figure below, the plots of the acute systolic and diastolic blood pressure changes based on the data presented in Table I for 30 hypertensive patients in contrast to Figures 2 and 3 from Black *et al*. (1954).

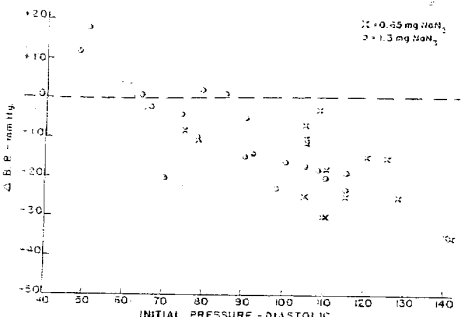


n=35

FIG. 2

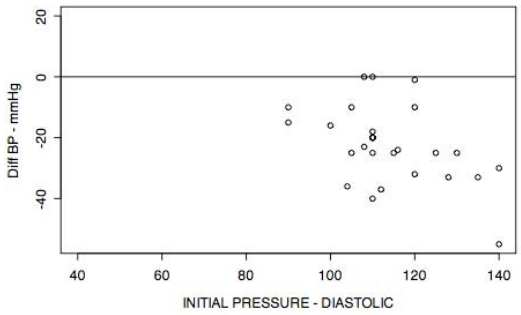


n=30



n=35

FIG. 3



n=29

HSRB Consensus and Rationale

Based on the inadequacies in the design, methodology and reporting, the Board concluded that the Black et al study was not sufficiently sound, from a scientific perspective, to be used as a point of departure to estimate a safe level of acute and chronic exposure to sodium azide. In addition, it was not informative as to whether human responding confirms estimates based on animal studies.

Charge to the Board

2. Please comment on the following:

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

Board Response

The Board noted the lack of documentation pertaining to the ethical conduct of the research reported by Black and colleagues (Black, et al., 1954). It was not unusual for clinical reports of this era to be vague with respect to matters related to subject recruitment and informed consent. The publication by Black and colleagues does not provide many details with regard to the protection of human volunteers but does hint at the following: (1) the public-health rationale for the study was supported by prior research, (2) medical monitoring was in place to minimize potential risks to research volunteers, and (3) initial dosing schedules were set at levels believed to be substantially below acutely toxic levels. A full assessment of these issues is not possible, however, due to the limited information available. Even if more information were available, the Board's analysis is complicated by the absence of widely agreed upon standards for the ethical conduct of research during the time this study was conducted.

The report makes just a single statement that is related directly to the adequacy of the process used to obtain informed consent from research volunteers. That statement is that the study drug "was administered without informing the patient of either the nature of the drug, or the change to be expected." Contemporary standards of informed consent would suggest that this was ethically worrisome because key facts affecting the assessment of the study's risk-to-benefit ratio were withheld from volunteers. Without a more detailed description of the set of procedures used to present the study, however, it is difficult to conclude that the researchers deliberately sought to deceive research subjects about the nature of the research—which might be seen as a reason for regarding the study as significantly deficient with regard to the prevailing ethical standards of the mid 1950s. For example, subjects might have been informed that, to avoid a possible placebo-like effect, they would be "blinded" to the nature of the study drug or the clinical features being studied. If subjects were informed about other pertinent aspects of the study, and agreed to participate, then that might be viewed as consistent with prevailing ethical standards of the time. Alternatively, the researchers conducting the study may have conceptualized this experimental intervention as "innovative care" and not felt it appropriate to present the intervention as a research study.

In summary, two factors combine to limit the ability to assert that the study was "significantly deficient relative to the ethical standards prevailing at the time the research was conducted": (1) lack of additional detail regarding the procedures used to recruit research subjects and obtain their consent to participate in the Black study, and (2) lack of unambiguous ethical standards for determining what information must be disclosed to potential research volunteers.

HSRB Consensus and Rationale

Based on lack of documentation in the Black *et al.* study, the Board was unable to conclude that there was clear and convincing evidence that the conduct of the study was fundamentally unethical. The Board was also unable to assert that the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

C. Science Issues in Mosquito Repellent Efficacy Field Research

Appendix A provides background and discussion questions for Board member and consultant consideration concerning mosquito repellent studies. Board responses to the questions are provided below.

Board Response

Issue 1: Factors Affecting Repellent Efficacy

Presentations by EPA and consultants indicated that factors which may affect the variability of initial and confirmed landings include biotic factors such as characteristics of the mosquito population (genus and species distribution, level of ambient mosquito pressure) or

abiotic factors, which are related to characteristics of the test site such as season, time of day/brightness, or the microclimate (including temperature, humidity, and wind speed and direction). Other factors that may affect landings include characteristics of the test subjects (such as differences in mosquito attractiveness; use of alcohol, tobacco, or scented products; or behavior). Characteristics of the test methods used that may affect variability include the pattern and duration of exposure, area of skin treated, method used to determine the amount of test material applied, and number of concurrent treatments per subject.

Variable factors that affect first or second landing or bite include characteristics of the subjects' skin, temperature, age, hair on the skin surface, and the density of the mosquito population at the test site. Usually, mosquitoes will bite within 5 to 15 minutes after the subject enters the area; after that, the mosquitoes have acclimated to the subject's presence and bite much less frequently. Temperature plays a major role in landing or biting activity; an increase in skin temperature is associated with a decrease in repellency. Skin color or type does not have a major effect on landing or biting, and hair on the skin surface has a small effect. The density of the insect population has a major effect on landing or biting activity.

Factors affecting landing or biting activity also include characteristics of the mosquito population and the test sites. There is significant disagreement among researchers concerning the most appropriate mosquito population to use for testing. Density of the population can affect landing or biting activity. The age of the mosquito population also plays a role, with mosquitoes between 5 to 15 days of age being the most avid biters. Susceptibility of the test subjects to mosquito bites also can affect landing and biting, although most people are susceptible to bites. Selection of test sites critically affects landing and biting. Weather, particularly temperature, can significantly affect biting behavior; repellency decreases by 8 minutes for every 1 degree Celsius ($^{\circ}$C) increase in ambient temperature. Human skin temperature (30-32°C) is considered to be constant. Wind can significantly affect the efficacy of vapor repellents because the wind will quickly remove the vapors; increased wind speed is associated with decreased repellency. Humidity interferes with evaporation and repellency. Light does not appear to have a significant impact because different mosquito populations exist that are active either during the day or at night. The local fauna or flora can impact repellency, especially if the local fauna are the mosquitoes' preferred hosts.

Test subject attraction for mosquitoes is variable. Skin chemistry may have an impact, but the delivery mechanism used to apply the repellent to the skin has a larger effect. Skin temperature is constant and thus has no impact. Skin permeability affects repellency, but it is dependent on the formulation of the repellent.

HSRB Consensus and Rationale

Based on the thorough and highly informative presentations by the consultants the Board concluded that in general a protocol needs to elucidate environmental, insect, and subject factors that would create variability and then provide a rational for the design, sampling method, number of subjects based on those factors. Efficacy relevant information that might be included: a description and rationale for the activity level of the subject population, the proximity of subjects to one another (or to a partner), the expected density of the insect

population, comparison of insect density and other environmental factors (e.g. temperature, wind) across sites. The Board also concluded that while replication is important it is difficult to define across different studies.

Issue 2: Designing for length based sampling

The rationales for different designs should be available by reference and the effects of different designs should be noted. It is unknown what, if any temporal protocol for exposure is standard (classical). That is, how were the designs derived and who accepted them as standard. Each design has different length based sampling. One rationale for using first confirmed intent to bite (LIBe) rather that first confirmed bite (FCB), as stated by Dr. Carroll, is that using LIBe minimizes the probability that a subject is actually bitten by a foraging mosquito [that might contain a pathogen or produce an irritant or allergic reaction, etc.].

Exposures in one study were during one-minute periods of exposure in 15-minute intervals, and in another study 5 minutes every 30-minutes. The time between first and second (or subsequent) landings is likely to be very variable. Thirty minutes is usually suggested as a long enough interval to allow for any mosquitoes in the area to land.

The Board raised the following general questions. Were these periods at the beginning, the middle, or the end of the interval, or were their timing randomly determined, and what impact did these choices have? What impact is there of using 1 or 5 minute periods, and/or of 15 or 30-minute intervals, compared to other period intervals?

Investigators have calculated Complete Protection Time (CPT) as the interval between application and the first confirmed LIBe or first confirmed bite (FCB). However, investigators state that the first confirmed criterion has to be followed by another within a period of time (e.g., "one-half hour, i.e., in either of the subsequent two exposure periods" for the LIBe). Dr. Carroll has indicated but not confirmed that LIBe is identical to that of 'First Confirmed Bite', which was classically used in measures of repellency to biting insects.

Dr. Carroll has indicated that it is most likely that a second LIBe (or bite - FCB) would occur within that 30-minute period. However, from an analytic perspective, caution is warranted where FCB is calculated on the basis of non-continuous field exposure because it reduces biting pressure by a factor equivalent to: 1/(1-proportional decrease in exposure). The upshot (where RP < 100%) is a decrease in the probability of receiving a first and confirmatory bite in any 30 min period.

Dr. Carroll's modeling of continuous versus. two intermittent exposure scenarios indicates that the intermittent exposures can substantially reduce the probability of seeing a FCB at a given RP", though this has not been validated experimentally.

Intermittent exposure of treated subjects to establish FCB has not been used widely in field studies. This implies that continuous exposure approaches have been used widely in field studies. To make intermittent exposure protocols standard should require comparison testing for experimental validation. Board consultants acknowledge that a 30-minute or one-hour

design is more common in the literature, but does not state whether such designs are continuous or intermittent exposure designs but imply (from other statements) that is continuous exposure. It is never really accurate to do a repellent trial continuously for more than about an hour or two because the avidity of the mosquito population will start to change significantly. The best designs treat people the appropriate number of hours before the peak biting time and then expose all subjects simultaneously.

The military, USDA and ICR do various types of continuous periods of measurements. The military may do numbers of landings in 20-minute exposures (challenges) with a criterion of 1 mosquito per minute (and compare treated versus untreated leg), with exposures (challenges) at 2, 4, 6, 8, 10 and 12 hours post-application. Or they can have a protocol with staggered treatment times during the day (e.g., 800, 1200 or 1600) with specified continuous exposures at two times during the day (e.g., 1800, 2000). USDA may do 6-hour duration testing starting at 0730 and 1345.

There are further concerns regarding such protocols and their effects on CPT. A set of concerns has to do with situational factors within the field setting. What differential effect is there within such studies from light intensity, such as obtained during days in which dusk was included? Dr. Schofield states there is an [unspecified] effect, as there are effects due to variations in temperature (partially related to the mosquito species in that area as well), and the impact of subject-activity patterns. One Board member believed that there must be also effects of field variations in relative humidity, barometric pressure, wind speed, and smoke pollution, etc., on mosquito behavior. Such variations probably affect species-specific and general mosquito behavior and may be relevant to CPT calculations.

The Board consultants added that it might be possible to adjust for wind and temperature, if the studies have been done for that particular area and those species of mosquitoes. A much more serious problem is that the biting activity of mosquitoes varies systematically with time of day. Variability is due to subjects, location, date and time, and one would not obtain a normally-distributed (Gaussian) result. Lab variability has been related to biotic factors (in subjects and mosquitoes) and abiotic factors (temperature, relative humidity, light, dose and exposure time). These are likely to be variability factors in the field.

The impact on the factors listed described for Issue 1 on the likelihood and timing of a first and confirming bite can be predicted and quantified. For example, we can reasonably predict that moderate-level exercise will attenuate product performance thereby resulting in a (probabilistic) systematic decrease in the time of the first and subsequent bites. Similarly, we can design a set of protocols to evaluate the phenomena and to quantify (a posteriori) the effect for that specific suite of experimental circumstances. However, given the lack of standardization between studies, the paucity of research specifically directed towards evaluation of the above-mentioned factors and the complexity of the test system, elaboration of anything more than a very basic general model is not possible.

HSRB Consensus and Rationale

The Board noted that the choice of intermittent vs. continuous exposure designs depends upon the goal of the study (e.g. relative or complete protection) as well as other factors. The Board concluded that more research is needed to determine the relative benefits of these designs and concurred with EPA that future guidance on this matter would be helpful.

Issue 3: Complete Protection Time

Dr. Matt Kramer, a USDA statistician, has suggested that the precision of CPT estimates in repellent testing could be significantly increased by defining failure of efficacy as the mean time from treatment to a series of several [e.g., five] landings or bites. The Board consultants were asked to determine whether this approach would markedly increase the precision of CPT estimates without requiring additional subjects and, if so, whether the increased precision would justify the incremental risk to the subjects resulting from their exposure to mosquitoes. The consultants also were asked to consider the practicalities involved in testing long-lasting repellents to the point of five landings.

The complete protection time for a subject is clearly defined as the time of repellent application to the first bites/LIBe's with or without the confirmation of a second bites/LIBe's. It is unclear what the mean of the times to the first 5 bites/LIBe's is measuring. A discussion on the precision seems irrelevant when one is not so sure what is being measured. Besides, these 5 times are all correlated within each subject, and so the efficiency gain is not so obvious due to lack of independence among measurements. With the censoring of efficacy failure seen in a number of mosquito repellency studies, it is unrealistic to be able to observe, say first 5 bites or LIBe's, and probably impractical to test to the point of 5 bites/LIBe's.

Perhaps more critical is the artifact of taking average of times to the first five bites/LIBe's, which is to overestimate the time to efficacy failure. This seems to make sense if one is interested in understanding the average mosquito biting/LIBing behavior. However, it seems unsuitable if one is interested in characterizing the "efficacy" of repellent products.

The rationale for this idea of measuring times to five bites/LIBe's became very clear during the consultant's presentation. If the population for statistical inference is the population of mosquitoes and the statistical inference is on the mosquito biting behavior, it makes sense. However, that is not the case in these mosquito repellency efficacy studies. The population for statistical inference is the population of repellent users, not mosquitoes, and the statistical inference is on the time from application of repellent to failure of its efficacy.

Currently there is no consensus on whether continuous or intermittent methods are most desirable. Prior to the new regulations, continuous and intermittent methods were used. A preference for the intermittent method became dominant after the new regulations were in place because it is more protective of individual subjects since they are exposed to less bites. However the use of continuous methods might also call for less subjects.

HSRB Consensus and Rationale

Based upon information provided by the consultants, the Board remains unclear of what the mean of the times to the first 5 bites/(landings with intent to bite) would measure of relevance to EPA determinations of efficacy. Therefore The Board concluded that precision of CPT estimates in repellent testing would not be significantly increased by defining failure of efficacy as the mean time from treatment to a series of several [e.g., five] landings or bites.

The Board concluded it would be helpful to their deliberations if protocols submitted to the HSRB included rationales for sample size, outcome measures, number of treatment groups and controls, why a field study is preferable, why a specific environment was selected, how different environments differ, and how controls for environmental shifts in temperature or time of day are determined.

The Board understands that the need for smaller sample sizes and the accompanying lack of power must be balanced with subject protection, but it is also important to understand which variables can be controlled. The expertise of control and treated subjects with respect to detecting mosquito landings must be balanced and the activity of subjects also should be controlled.

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

Charge to the Board

1. 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:

    a. 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.

Board Response

The active ingredient DEET formulated in three forms was tested for its ability to repel mosquitoes from the 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 the HSRB. The results were reported in SCI.001.1, LipoDEET 302; SCI.001.2, LipoDEET 3434; and SCI.001.3 Coulston's Duranon, all compared to Ultrathon (approved by the military). All experiments were conducted using Good Laboratory Practices.

The dosimetry for the three products was done in the laboratory on July 3-5, 2007. The field tests were conducted at Site 1 in Butte County, a grassland habitat, on July 7, 8 and 15, and at Site 2 in Glenn County, a forest habitat, on July 12, 13 and 14. Different mosquito species composition occurred at the two sites. Ten subjects were used for the dosimetry tests. Ten subjects were used for each of the three products. Some of the subjects participated for all three of these test articles as well as for the Ultrathon. The subjects were required to be above

18 years of age and no more than 55 years of age, active in rural outdoor settings, and having used no repellent on the day before the test. Only legs were tested in this study because of greater biting pressure on legs than arms. There were two experienced persons serving as negative controls (i.e., without any repellent 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 at Site 1 and the second site selected to be Site 2). Experimental subjects, in pairs, monitored LIBe's during a one minute interval each 15 minutes, until the First Confirmed LIBe (FCLIBe) could be determined. Stopping rules were employed. No evidence of West Nile Virus (WNV) was present in either test site. Mosquitoes landing were taken to the laboratory for later identification, and for screening for WNV, Western Equine Encephalitis, and St. Louis Encephalitis Virus, and all mosquitoes were negative. All subjects wore Tyvek coverall, head nets and surgical gloves, and they worked in pairs. There was a one minute observation period during each 15 minute interval, starting 150-210 minutes post application. Toward the end of the day, controls were reduced from 2 to 1 subject to limit exposure to mosquitoes. Complete protection time (CPT) was measured, defined as the time to the First Confirmed Landing with Intent to Bite (FCLIBe). Adequate LIBing pressure was maintained throughout the test period.

LipoDEET 302 is 30% DEET on lipid spheres designed to improve the durability and to improve the cosmetic properties. Six females and four males were tested for dosimetry, 7 females and 3 males at Site 1, 3 females and 7 males at Site 2. The MOE was 522. It yielded a CPT of 10.3 ± 1.3 hr in Site 1 and 9.5 ± 1.8 hr in Site 2.

LipoDEET 3434 is DEET at 34.34%; this protocol SCI.001.2 was amended to test a different test article than the original protocol described Five females and five males were tested at Site 1, 4 females and 6 males at Site 2. The MOE was 492. It yielded a CPT of 10.6 ± 1.3 hr in Site 1 and 10.4 ± 1.9 hr in Site 2.

Coulson's Duranon is 20% DEET in microscopic protein spheres to reduced skin absorption of DEET, improve cosmetic properties and inhibit evaporation. Five females and five males were tested at Site 1, 3 females and 7 males at Site 2. The MOE was 856. It yielded a CPT of 8.4 ± 1.9 hr in Site 1 and 9.5 ± 1.3 hr in Site 2.

Data were presented for the comparison article, Ultrathon, CPT of 10.1 ± 2.3 hr for Site 1 and 10.0 ± 2.2 hr for Site 2. While this comparison may have been of interest to the sponsor, it is unclear why this information was provided in this report.

The report was clearly written and a greater attention to statistical analysis was provided than has been provided in the past by Carroll-Loye Biological Research. The study was justified in that additional insect repellents that are more efficacious and/or more acceptable cosmetically to the public would be an advantage from both the standpoint of health (to reduce the chances of contracting a mosquito-borne disease) and of comfort. The information should be generalizable to the public, although the exclusions, which were highly appropriate, excluded some subpopulations that would likely use insect repellents. The experiment was necessary to determine the field efficacy of these test formulations, and the

experiments were set up to meet the study objective. Measurements taken were appropriate for the objective and quality assurance considerations were in place.

The experiment was conducted according to the approved protocol with some deviations. One of the most serious deviations, which was not acknowledged in the description, was the fact that some of the subjects were tested on the day following a test with another product, despite the fact that the protocol stated "Use of insect repellent within one day of preceding the study" was an exclusion criterion. Additionally, the tests on any given repellent (including the repellent used in study WPC-001) were not conducted on a single day and the statistical treatment of the data did not account for different days of testing.

The deviation of not allowing a day of non-repellent use before testing was of concern to the Board because of potential persistence of the repellent of one day's test into the test of the following day. However, information provided by the Carroll-Loye Biological Research via public comments indicated that the repellent was carefully washed off at the end of the experiment both with soap and water and with alcohol. The public comments also indicated that the reason for the one day wait in the protocol was not related to concerns about the persistence of the repellent. Therefore this deviation did not affect the validity of the results obtained. In addition, the public comments indicated that the reason for the compression of the tests on these several test materials into a short span of time was because of the reports that West Nile virus-contaminated mosquitoes were moving close to the test area and that this test region would have been unsafe in a matter of just a few more days. This explanation was adequate to explain why the testing days were set up as they were. It would have been advisable to have had this deviation and the rationale for it presented in the report.

Charge to Board

b. 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.

Board Response

Strengths

One of the strengths of the study is the inclusion of the positive control treatment with 3M's Ultrathon.

Weaknesses

SCI-001 studies are very troubling from a statistical design point of view. There is some indication that there was no desire to compare the various repellents to one another, and yet each of reports compared a repellent to a positive control, the Ultrathon repellent. The statistical analysis assumes that there are 20 different subjects on each repellent over two sites, but many of the subjects wore both repellents and a few subjects were used in both sites. Subjects that were used at both sites were subjects: 8, 13, 14, 15, 37, 40, 46, 52, 53, 60, 61, 62,

63, 67, 71, 72, and two control subjects. Almost all subjects wore more than one repellent. This is not an inherent flaw in the design, although if subjects are going to be used more than once, there should have been some counterbalancing of the repellents to the subjects. The major flaw is in the statistical analysis, particularly when repellents are being compared to one another as is done in the reports by comparing each repellent to Ultrathon. The analysis assumes that there are 20 different subjects involved in each of the three write-ups. That is, the analysis assumes that the experimental design is a parallel subjects design and it is clearly not.

In the combined experiments, there were only 33 unique subjects, representing 80 data points, excluding the negative controls. Subjects do not appear to have been randomly allocated to four test materials, between Sites 1 and 2, and over five days. This lack of statistical independence of data between different test materials, Sites 1 and 2, and different dates of experiment renders the analysis incorrect. For example, due to overlap of subjects between Sites 1 and 2, one cannot pool the results by site for statistical analysis. Also there is substantial overlap of subjects among and between test materials, the comparison among and between test materials cannot be made. This renders the analysis scientifically invalid.

In SCI-001, there is 0% censoring. This differs to previous studies conducted and reported by Carroll-Loye Biological Research, Inc and reviewed by the Board. As an example, there was 40% censoring in EMD-004.1, 10-30% censoring in EMD-004.2, and 90-100% censoring in EMD-004.3. The Board supports the EPA's evaluation that "Further clarification is needed to verify the accuracy of the data generated."

The data analysis (pairwise comparison between three test materials and the positive control Ultrathon) is inadequate and is inconsistent with the experimental design and conduct of the study in which subjects were allocated to four treatment groups. As was suggested by the HSRB in its January 2007 meeting, the appropriate analysis would have been an analysis of variance type. Wilcoxon rank sum test in the presence of censored data is known as Gehan's test, and is known to be inefficient for comparison of Kaplan-Meier estimates. A more appropriate test comparison of censored time to event data is the log rank test or better yet a regression analysis for censored time to event data based on Cox proportional hazards regression models. The analysis of the number of LIBe's is inappropriate as it ignores the duration of follow-up during which LIBe's are recorded. An appropriate analysis would have been Poisson analysis.

Having ten subjects spread over five days and combining the results into the current analysis has a potential to confound the effect of repellent with the different mosquito pressures on different days. This would have been better if it were planned in advance. The whole idea is that the experimenter has control over the experiment by using random mechanism for subject selection and for allocation of subjects to repellents, days and sites. One solution would be to perform the analysis of variance as was done when the results for two sites were pooled, i.e., by including the day as the main effect and the two-way repellent by day interaction (repellent effect modification by day effect) in the analysis of variance, in Table 5, on page 17 of 217, of the report for SCI-001.3. Of course, this requires making the assumption that the experimenter had adequate control of the experiment as described above and that observations are statistically independent, which is not the case. With the proper

experimental design using site and day of experiment as blocking factors, the analysis of variance would allow evaluation of the three main effects of repellent, day and site, along with the two-way and three-way interactions. There is no inherent problem with pooling across studies. Study site can be considered as a blocking factor, and as such it would generally be appropriate to pool across the two blocks. This assumes independence of data from sites, namely, no overlap in subjects between the sites. This was not the case for these experiments, and as a consequence the data cannot be pooled across the two sites.

Pooling of results by site for statistical analysis is generally preferable if the other experimental design aspects are the same, which appears to be the case with the reported studies. The main advantage of a pooled analysis versus marginal analyses for each site is two-fold: 1) by doubling the sample size for the analysis, you increase the statistical efficiency by a factor of 1.41 in the point estimation of the CPT exactly or in the analysis of variance approximately (as you lose one degree of freedom for site effect) and 2) you can assess the effect of repellent more accurately by accounting for the potential effect of site difference in mosquito pressure. However, this assumes that the data from two sites are independent, which is again obviously not the case. There are three subjects (40, 18 and 62) used in both sites with LipoDEET 302, two subjects (53 and 46) used in both sites with Ultrathon, and three subjects (40, 8 and 63) used in both sites with Duranon.

HSRB Consensus and Rationale

While the Board concluded that the participation of several subjects on the day after they had been treated with a different test repellant was not ideal and there were errors (i.e. choice of test limb) in the study, this did not affect the validity of the results.

However with only 33 subjects for 80 data points (excluding the negative controls), the overlap of some of the same subjects for different test materials, for Sites 1 and 2, and for different dates of the experiment without proper experimental design and control, the Board concluded that it is impossible to interpret the reported data adequately thus rendering scientific validity of the results into question. In addition, the study may not have been sufficiently sound to estimate within population variances.

Thus, the Board concluded that the study was not sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes.

Charge to Board

2. 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:

    a. 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.

b. 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?

Board Response

Brief Overview of the Study

The basic protocol for these studies (SCI-001) was initially reviewed at the January 2007 meeting of the HSRB, at which time the Board concluded that the study would meet the requirements established in the Environmental Protection Agency's final human studies rule (40 CFR Part 26) pending minor revision. In particular, the Board was concerned about several matters relevant to subject recruitment and the overall conduct of the study. For example, the protocol did not describe how untreated controls would be recruited, but instead implied 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. The Board recommended that the protocol clarify how untreated controls will be recruited, and that the IRB of record (Independent Investigational Review Board [IIRB], Inc. of Plantation, FL) review any materials used for recruiting purposes, including any telephone scripts fliers, emails, letters, or local ads. The Board also felt that the risks associated with DEET exposure during the course of the study are mischaracterized, and that the informed-consent document was also structured in a manner that did not apply to unexposed control subjects. In light of these deficiencies, the Board recommended that the informed-consent document be redesigned and re-reviewed by IIRB (EPA HSRB 2007a).

Subsequent to the aforementioned meeting of the HSRB, the informed consent documents were revised in accordance with Board and EPA recommendations, submitted to IIRB for re-review, and approved (Carley, 2007). It is unclear, however, whether the protocol was also revised in accordance with the Board and EPA recommendations, and submitted to the IIRB for review.

The documents provided by Carroll-Loye (Carroll, 2007a; Carroll, 2007b; Carroll, 2007c) specifically state that each study was conducted in compliance with the requirements of the U.S. EPA Good Laboratory Practice Regulations for Pesticide Programs (40 CFR 160); 40 CFR 26 subparts K and L; FIFRA § 12(a)(2)(P); and the California State EPA Department of Pesticide Regulations for study monitoring (California Code of Regulations Title 3, Section 6710). Each study was also reviewed and approved by a commercial human subjects review committee, IIRB. Documentation provided to the EPA by IIRB indicated 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 Agency, each completed study consists of two interdependent analyses: 1) a dosimetry study designed to determine the amount of an insect-repelling compound (30% or 34% DEET in liposomal capsules, or 20% DEET in protein capsules) that typical users would typically apply when provided with a lotion formulations; and 2) an efficacy study designed to measure the effectiveness of each compound as a mosquito repellent. For each dosimetry and efficacy studies, commercially available and obtained 3M Ultrathon (34.34% polymerized DEET) was used as a comparator. Ultrathon is the principal insect repellent used by American military forces and is considered to be one of the most effective insect repellents available.

Dosimetry and efficacy studies for personal insect repellents containing LipoDEET 302 and 3434 (30% and 34% DEET in liposomal capsules, respectively) and Duranon (20% DEET in protein capsules) were conducted from July 3 through August 2, 2007 (Carroll 2007a; Carroll 2007b; Carroll 2007c). All studies (one using each test compound) were performed simultaneously at a laboratory site in Davis, California, and at field sites in Butte and Glenn Counties, California, by researchers at Carroll-Loye Biological Research. The study sponsor was Scientific Coordination, Inc., of Rockville, Maryland. The studies were conducted using products from two manufacturers: LipoDEET 302 and 3434 was manufactured and supplied by DermAegis, Inc. of Rockford, Illinois; Duranon was manufactured and supplied by Sawyer Products of Safety Harbor, Florida. It is important to note, however, that the protocol originally reviewed and approved at the January 2007 HSRB meeting listed a different set of test compounds; at the sponsor's request Carroll-Loye Biological Research changed one of the test compounds from Insect Guard II (EPA Reg. No. 54287-8) to LipoDEET 3434 (an unregistered compound) at the sponsor's request.

Dosimetry was determined by direct measurement of compound application. The efficacy of each as a mosquito repellent was determined by measuring the ability of the 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 will be 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, participants 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 dosimetry study enrolled a total of 10 individuals, each of who tested all four formulations (the three test compounds and the comparator). Each efficacy study enrolled 10 subjects for each formulation at each of the two field sites. Many volunteers participated in multiple analytic phases. For example, six of the 10 participants in the dosimetry study also participated in one or more of the field tests. In total, 39 volunteers participated in at least one analytic phase of SCI-001.1, SCI-001.2 or SCI-001.3. Fifteen of these volunteers also participated in the dosimetry and/or efficacy phase of Carroll-Loye study WPC-001 described below. In addition to these 41 volunteers, two controls (described as "experienced personnel" and who were untreated with repellent) also participated to determine ambient LIBe pressure at field site. On any given day at a field site, the same pair of participants served as controls for

SCI-001.1, SCI-001.2, SCI-001.3 and the concurrently run WPC-001 study. Five individuals served (repeatedly) as controls during each of the six field tests; two also participated in the repellent efficacy tests, to give a cumulative total of 45 volunteers. In addition, three alternate participants were enrolled to: 1) replace any individual who withdrew; and 2) protect the confidentiality of any participant excluded from the study as a result of pregnancy or other potentially stigmatizing condition, as described below.

Critique

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, 2007). The risks to study participants, in general, were minimal and were justified by the likely societal benefits, including data on the efficacy of these new formulations (30% or 34% DEET in liposomal capsules, or 20% DEET in protein capsules) as personal insect repellents. Higher concentrations of DEET are commercially available and have been used as repellents for years; the subjects enrolled in this study were thus 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 individuals who have a history of such severe skin reactions to further minimize the risk of a participant 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 participants will be exposed to illnesses 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. Mosquitoes collected during the field studies also were subjected to serologic or molecular analyses to confirm that they were free of known pathogens. Finally, the study protocol also included several mechanisms designed to minimize coercive 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" participants, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

Regrettably, several serious protocol deviations occurred during the conduct of these studies. Most notably, due to the study investigator's failure to obtain IRB approval for fundamental changes to one of the study protocols, the research described in SCI-001.1, SCI-001.2 and SCI-001.3 does not comport with the applicable requirements of 40 CFR Part 26, subparts K and L.

First, as mentioned previously, many study volunteers participated in multiple analytic phases of SCI-001.1, SCI-001.2 and SCI-001.3, testing the field efficacy of different insect repellents on different days. Many volunteers participated in field trials conducted on consecutive days, and were re-randomized to receive the same or a different test compound

each time. The approved protocol, however, includes clear criteria excluding any participant who "[used an] insect repellent within one day preceding the study" (c.f., Carroll, 2007a; Carroll, 2007b; Carroll, 2007c). This change is unlikely to have increased the risks to study participants, but several Board members nevertheless raised the concern that compromising these exclusion criteria may adversely affect the scientific validity of the study data (as described above). The decision to disregard previously established exclusion criteria was also made without submitting the protocol for approval or informing study participants of this change, and may represent a departure from accepted review and approval practices. There was some disagreement among Board members, however, as to whether the phrase "one day preceding the study" specifically excluded participants who had used or been exposed to an insect repellent on the day preceding a field trial, or simply prior to consent and enrollment in the study overall. Dr. Carroll submitted a response to the EPA that implied the former (Carroll, 2007d), but the Board nevertheless recognized the uncertainty surrounding this issue.

Second, to minimize the risk that study participants will be exposed to arthropod-borne illnesses like WNV, for example, during its review of another Carroll-Loye protocol at the April 2007 HSRB meeting (EPA HSRB, 2007b) the Board recommended conducting serologic or molecular analyses to confirm that mosquitoes collected during the field studies were free of known pathogens. Study investigators did conduct such analyses in the context of these studies, but did so without submitting the protocol for approval or informing study participants of these analyses in the informed consent document. Although this change is likely to have actually reduced the risks faced by study participants, it is nevertheless a substantial departure from accepted review and approval practices.

Finally, and most seriously, at the sponsor's request Carroll-Loye Biological Research changed one of the test compounds from Insect Guard II (EPA Reg. No. 54287-8) to LipoDEET 3434 (an unregistered compound) without IRB or HSRB review or approval. Dr. Carroll has justified the decision to substitute a test material by stating that, in conversations that he has previously had with the IRB and the California EPA, that IRB review and approval is needed only for "proposed changes … that are likely to increase risk to participants" (Carroll 2007d, 3). Because the substituted material (LipoDEET 3434) was nearly identical to another compound approved for testing (LipoDEET 302), and contained a concentration of DEET considerably less than that in already approved and marketed personal insect repellents, Dr. Carroll felt that the substitution posed no increase in risk to study participants and fell within the "latitude" given to study investigators with respect to minor protocol changes. The Board disagreed, feeling that a change of test materials was not simply a minor protocol change; although it is unlikely that study participants were subjected to greater risk, the substitution of LipoDEET 3434 for Insect Guard II was a protocol change of sufficient magnitude to warrant IRB notification and review. More importantly, the failure to seek IRB review and approval is a significant and serious departure from accepted review and approval practices, as well as a violation of the letter and intent of the Agency's Final Human Studies Rule.

Federal guidelines from the Office of Human Research Protections (OHRP) clearly state that all proposed protocol changes must be reviewed by the IRB of record at convened meetings, in accordance with HHS regulations at 45 CFR 46.108(b), although institutions may adopt policies describing the types of minor changes in previously approved research that can

be approved under an expedited review procedure in accordance with HHS regulations at 45 CFR 46.110(b)(2). Except in cases when necessary to prevent imminent harm to study participants, an investigator should never institute a protocol change without IRB review. Federal regulations regarding review and approval of human subjects research, for example, explicitly prohibit investigators from implementing any protocol changes without prior IRB approval unless such changes are necessary to prevent immediate, serious harm to study participants. It is never an investigator's prerogative to determine which protocol changes warrant IRB review and which do not; only the IRB (or some authority other than the investigator) has that authority.

The failure of Carroll-Loye Biological Research to 1) obtain IRB approval of the revised protocol; and 2) report these protocol deviations to the Independent Investigational Review Board in a timely manner are serious regulatory breaches. The failure of Dr. Carroll to notify the EPA and the HSRB of protocol deviations such as the substitution of LipoDEET 3434 for Insect Guard II in submitted study documents for studies SCI-001.1 and SCI-001.3 is also troubling. The Board recommended the 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.

Because of the serious nature of these deviations, the research described in SCI-001.2 using the unapproved pesticide formulation failed to comport with the applicable requirements of 40 CFR Part 26, subparts K and L, and the Board recommended that the Agency not accept for regulatory decision-making purposes any of the data obtained during the conduct of that particular study. Furthermore, this particular ethical deficiency also affects the acceptability of the results from testing the other two formulations. SCI-001.1, SCI-001.2 and SCI-001.3 were run concurrently, and study participants enrolled in all three studies ran the risk of being randomized to receive treatment with the unapproved investigational compound, LipoDEET 3434. It is thus impossible to separate the data collected in SCI-001.1 and SCI-001.3 from that collected in SCI-001.2, and the Board recommended that the Agency not utilize any the data obtained during the conduct of these three studies.

HSRB Consensus and Rationale

Based on a careful review of the study documents provided, the Board concluded that the research was conducted in a manner that failed to meet the applicable requirements of §40 CFR 26, subparts K and L. The study investigator failed to obtain IRB approval for fundamental changes to one of the study protocols and, as a result, the data collected from these three concurrently run studies cannot be used by the Agency for regulatory decision-making purposes.

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

Charge to the Board

1. 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.

Board Response

The active ingredient Oil of Lemon Eucalyptus (OLE) formulated as a pump spray was tested for its ability to repel mosquitoes from the legs of volunteers by a study presented by Carroll-Loye. All experiments were conducted using GLP. This study was conducted similarly to and in conjunction with the DEET efficacy studies of SCI-001, and the descriptions of the experimental conditions and design of SCI-001, above, are appropriate for this study and will not be repeated here.

The test product had 30% OLE in a pump spray. Seven females and three males were tested at Site 1, 3 females and 7 males at Site 2. It yielded a CPT of 6.1 ± 1.5 hr in Site 1 and 4.2 ± 0.8 hr in Site 2.

As was discussed for the SCI-001 study, the experiment was conducted according to the approved protocol with some deviations, with the most serious being the lack of at least a one day wait for some of the subjects before they were tested with another product. The Board's analysis of this deviation and design of this experiment was discussed above for SCI-001, and is pertinent to this experiment also and will not be repeated here.

The science assessment of WPC-001 was the same as that for SCI-001. However, unlike SCI-001 the residual effects of successive days of testing were unlikely to have had an effect (CPTs were shorter) and the data therefore are useable. Treatment of subjects on successive days is not intellectually satisfying, but it was unlikely to have a significant effect.

HSRB Consensus and Rationale

The Board concluded that despite problems estimating variability and some of the same design problems found in study SCI-001, the Carroll-Loye study WPC-001 assessing the repellent efficacy of the formulation tested was sufficiently sound for the purposes for which it was intended.

Charge to Board

2. 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.

Brief Overview of the Study

The protocol for this study was initially reviewed at the April 2007 meeting of the Human Studies Review Board, at which time the Board concluded that the study would meet the requirements established in the Environmental Protection Agency's final human studies rule (40 CFR Part 26) pending minor revision. In particular, the Board was concerned about several matters relevant to subject recruitment and the overall conduct of the study. To minimize the risk that study participants would be exposed to arthropod-borne illness, for example, the Board recommended that investigators trap landing mosquitoes or other vectors for pooled serologic or nucleic acid-based testing and alert research participants if they had been inadvertently exposed to vector-borne pathogens. Secondly, the Board expressed concerns about plans to recruit research subjects in Florida, as these recruitment procedures were not described adequately in the protocol and supporting materials. Finally, the Board raised questions about the informed consent procedures for control subjects, suggesting that the informed consent procedures should be modified to more clearly explain the risks to control (untreated) research subjects. In light of these deficiencies, the Board recommended that the protocol and informed-consent document be revised and submitted to re-review by IIRB (EPA HSRB, 2007b). The protocol and informed consent documents subsequently were revised in accordance with Board and EPA recommendations, submitted to IIRB for re-review, and approved (Carley, 2007).

The documents provided by Carroll-Loye (Carroll, 2007e) specifically state that each study was conducted in compliance with the requirements of the U.S. EPA Good Laboratory Practice Regulations for Pesticide Programs (40 CFR 160); 40 CFR 26 subparts K and L; FIFRA § 12(a)(2)(P); and the California State EPA Department of Pesticide Regulations for study monitoring (California Code of Regulations Title 3, Section 6710). Each study was also reviewed and approved by a commercial human subjects review committee, IIRB. Documentation provided to the EPA by IIRB indicated that it reviewed these studies pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A) and determined them to be in compliance with that Rule.

As submitted to the EPA, the completed study consists of two interdependent analyses: 1) a dosimetry study designed to determine the amount of oil of lemon eucalyptus-based personal insect repellent that typical users would typically apply when provided with a pump spray formulation; and 2) an efficacy study designed to measure the effectiveness of the pump spray formulation as a mosquito repellent. The dosimetry and efficacy studies were conducted from July 10 through August 1, 2007 (Carroll, 2007e). The studies were performed simultaneously at a laboratory site in Davis, California, and at field sites in Butte and Glenn Counties, California, by researchers at Carroll-Loye Biological Research. The study sponsor was WPC Brands, Inc. of Bridgeton, Missouri. The studies were conducted using product manufactured and supplied by ChemRite CoPac, Inc. of Lannon, Wisconsin.

Dosimetry was determined by direct measurement of compound application. The efficacy of each as a mosquito repellent was determined by measuring the ability of the 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, participants 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 dosimetry study enrolled a total of 10 individuals. Each efficacy study enrolled 10 subjects at each of the two field sites. Many volunteers participated in multiple analytic phases. For example, six of the 10 participants in the dosimetry study also participated in one of the field tests. In total, 23 volunteers participated in at least one analytic phase of WPC-001. Fifteen of these volunteers also participated in the dosimetry and/or efficacy phase of Carroll-Loye studies SCI-001.1, SCI-001.2 or SCI-001.3 described previously (Carroll, 2007a; Carroll, 2007b; Carroll, 2007c). In addition to these 23 volunteers, four controls (described as "experienced personnel" and who were untreated with repellent) also participated to determine ambient LIBe pressure at field sites. On any given day at a field site, the same pair of participants served as controls for WPC-001 and the concurrently-run SCI-001.1, SCI-001.2, and SCI-001.3 studies. Three individuals served (repeatedly) as controls during each of the three field tests; all three also participated in the repellent efficacy tests, giving a cumulative total of 27 volunteers. In addition, three alternate participants were enrolled to: 1) replace any individual who withdrew; and 2) protect the confidentiality of any participant excluded from the study as a result of pregnancy or other potentially stigmatizing condition, as described below.

Critique

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, 2007). In general, the research described in WPC-001 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 this formulation as a personal insect repellent. Based on toxicological data currently available, 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 individuals who have a history of such severe skin reactions to further minimize the risk of a participant experiencing a severe physical reaction to a mosquito bite. In addition, the study protocol was designed specifically to minimize the likelihood that a mosquito would 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 participants will be exposed to illnesses 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. Mosquitoes collected during the field studies also were subjected to serologic or molecular analyses to confirm that they were free of known pathogens. Finally, the study protocol also included several mechanisms designed to

minimize coercive 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" participants, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

Although a majority of the Board concluded that research described in WCP-001 comports with the applicable requirements of 40 CFR Part 26, subparts K and L, and that there was no clear and convincing evidence that the conduct of the research was fundamentally unethical, further comments are warranted on certain events that took place during the conduct of the study. In particular, as noted in the EPA's review of these studies, several significant protocol deviations occurred.

As discussed in greater detail in the Board's review of Carroll-Loye studies SCI-001.1, SCI-001.2 and SCI-001.3, for example, some members were concerned that the study investigator failed to obtain IRB approval for significant changes to the study protocol. Many of the study volunteers participated in multiple analytic phases of WPC-001 (as well as phases of SCI-001.1, SCI-001.2 and SCI-001.3), participating in field trials conducted on consecutive days and being re-randomized to receive the same or a different test compound each time. The approved protocol, however, includes clear criteria excluding any participant who "[used an] insect repellent within one day preceding the study" (c.f., Carroll, 2007e). As mentioned previously, however, there was substantial disagreement among Board members as to whether this constitutes a deviation 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; and 2) report these protocol deviations to IIRB in a timely manner are serious regulatory breaches. The Board recommends the 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.

Although the research conducted under WPC-001 was conducted at the same times and at the same places as the research covered under protocol SCI-001, there is no evidence that study participants enrolled in this study ran the same risk of being randomized to receive treatment with an unapproved investigational compound as participants in SCI-001.1, SCI-001.2 and SCI-001.3. A majority of the Board thus concluded that there was no clear and convincing evidence that the conduct of study WPC-001 was fundamentally unethical, and concluded that the research described therein meets the applicable requirements of §40 CFR 26, subparts K and L. A significant minority of the Board, however, argued that the Agency should not utilize any data obtained during the conduct of this study; these Board members concluded that the study investigator's repeated failure in this and other studies to obtain IRB approval for significant protocol changes or to report study changes and protocol deviations to the IRB, created an unprecedented pattern of departure from accepted review and approval practices that could have study participants at increased risk or significantly impaired the informed consent process.

HSRB Consensus and Rationale

The Board agreed that the investigator's failure to report changes to the IIRB were ethical violations. However while a majority of the Board agreed that these violations did not rise to the level of substantial noncompliance, some Board members believed it did meet that level. Thus a majority of the Board concurred with the initial assessment of the Agency that the study submitted for review by the Board meets the applicable requirements of §40 CFR 26, subparts K and L.

F(1). Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Studies (SPC-001)

Charge to the Board

1. 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?

Board Response

The active ingredient Picaridin in three formulations will be tested in the field for its ability to repel mosquitoes by the Carroll-Loye company. The active ingredient will be formulated into 1) a 7% pump spray that will also be used for a 10% pump spray, an aerosol and a 5.75% towelette; 2) a 15% pump spray that will also be used for a 15% aerosol and a 12% towelette; and 3) a 15% lotion that will also contain a sunscreen. All experiments will be conducted using GLP. A dosimetry experiment with 10 individuals will be performed to determine the amount of product that would be utilized by people using the product as directed. The experiment will be a field study. Two locations in California would be used.

Legs and/or arms will be tested. There will be two experienced persons serving as negative controls (i.e., without any repellent product) to confirm mosquito biting/landing pressure. Experimental subjects, in pairs, will monitor LIBe's during a one minute interval each 15 minute, until the First Confirmed LIBe (FCLIBe) can be determined. Stopping rules will be employed. The Complete Protection Time (CPT) will be determined.

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

- The scientific question was stated (i.e., to test the efficacy of Picaridin in several formulations to repel mosquitoes).
- 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 are 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.
- The risks are minimal because the active ingredient is of very low toxicity, the other formulation ingredients are of very low toxicity, the mosquitoes will be aspirated before they have an opportunity to bite, and the regions selected will not have evidence of West Nile or encephalitis viruses.
- Deficiencies related to information about the lotion formulation have been addressed.

Study Design Criteria

- The purpose of the study is clearly defined (i.e., efficacy testing).
- There are specific objectives (i.e., to determine the CPT that Picaridin in three formulations displays as a mosquito repellent).
- The sample size will be 10 individuals per product along with 2 experienced individuals to confirm mosquito biting pressure. A dosimetry experiment prior to the field experiment will quantify the amount of repellent being used.
- The Board had some concern that with respect to data interpretation, a stronger solution would be used to estimate CPT for the lower concentration towelettes. However, it was explained during the meeting that the concentration quoted for the towelette also included the weight of the fabric, and the picaridin solution was identical to the spray.
- There was also insufficient information regarding relevant environmental, mosquito and subject factors that might contribute to variability.

Participation Criteria:

- The participants will be representative of a subset 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.

Measurement Criteria

- There was concern about using data from the tested products to extrapolate for other products. Extrapolating information from the 7-percent pump spray to a 10-percent pump spray formulation is acceptable, however there are problems with extrapolating from the 7-percent pump spray to the 5.75-percent towelette because the towelette may not administer the same dose. On the other hand, if the dosimetry phase demonstrates the towelette administers approximately the same dose, extrapolation would be acceptable. Quality assurance will be a part of the experimental plan. If the products will not be compared, randomization is less of an issue if the experiments can be performed on separate days, however randomization and allocation of subjects to treatments needs to be fully specified.
- There were also statistical concerns that data generated would not be appropriately analyzed, especially as it related to the assignment of subjects to conditions.

- The measurements will be accurate and reliable.
- The measurements will be appropriate to the question being asked.
- Quality assurance will be a part of the experimental plan.

Laboratory and Field Conditions

- Laboratory experiments are not proposed, except for the dosimetry
- Field experiments will be appropriate.
- The study will include a stop rule plan, medical management plan, and a safety monitor.

HSRB Consensus and Rationale

While the Board agreed that the study rationale, formulations to be tested and data collection procedures were scientifically sound, the protocol did not adequately explain the relationship between the study design and analytic plan nor did it include an appropriate statistical analysis plan (including estimation of variability) that could be evaluated for its validity or utility. There was also insufficient information regarding relevant environmental, mosquito and subject factors that might contribute to variability. Thus, the Board concluded that the proposed research does not appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substance for repelling mosquitoes.

Charge to the Board

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?

Board Response

Brief Overview of the Study

The research is to be conducted by Carroll-Loye Biological Research, a private laboratory in Davis, California by using healthy volunteers and a controlled environment. The study sponsor is Spectrum Brands, Inc. of Bridgeton, Missouri, a division of United Industries Corporation. The study protocol was reviewed and approved by a commercial human subjects review committee, IIRB of Plantation, Florida. Minutes of IIRB meetings were provided to the EPA as a separate document, and documentation previously provided to the EPA by IIRB indicates that it reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

The research protocol submitted consisted of two interdependent studies: 1) a dosimetry study designed to determine the amount of an insect-repelling compound, known as picaridin, that normal subjects would typically apply when provided with one of three compound formulations (7% Picardin Pump Spray [data will be bridged to 10% Pump Spray and Aerosol and 5.75% Towelette],15% Picaridin Pump Spray [data will be bridged to 15% Aerosol and 12% Towelette], and 15% Picaridin Lotion formulated with sunscreen); and 2) an efficacy

study designed to measure the effectiveness of picaridin as a mosquito repellent. Dosimetry will be determined either by passive patch dosimetry (spray formulations) or by direct measurement of compound application (lotion formulation). The efficacy of each formulation as a mosquito repellent will be determined by measuring the ability of the formulations to prevent mosquito landings (defined as "Lite with Intent to Bite"; LIBe) under field conditions. Mosquitoes will be aspirated mechanically prior to biting; prior to initiation of the efficacy study, all volunteers will be 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, participants will work 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 dosimetry study will enroll a total of 10 subjects, each of whom will test all three formulations. The efficacy study will enroll 10 subjects per test formulation per field site, for a total of 30 subjects. Efficacy will be tested independently at two different sites, representing two different environments. Two controls (described as "experienced personnel" and who were untreated with repellent) also participated to determine ambient LIBe pressure at each field site, giving a cumulative total of 28 volunteers. Subjects may participate in either or both studies, making the total number of volunteers enrolled no less than 32 but no greater than 74. In addition, three alternate subjects will be enrolled to: 1) replace any subject who withdraws from participating; 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.

Critique

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley and Sweeney, 2007a). The proposed research described in Protocol SPC-001 comports with the applicable requirements of 40 CFR Part 26, subparts K and L.

The risks to study participants are minimal and justified by the likely societal benefits, including data on the efficacy of picaridin as a mosquito repellent. The risks to study participants are three-fold: 1) reaction to test materials themselves; 2) exposure to biting arthropods; and 3) possible exposure to arthropod-borne diseases.

The active ingredient of these three repellent formulations is commercially available and is present at similar concentrations in other EPA-registered products; specifically, picaridin is registered and marketed as an insect repellent in the United States under the registered trade name Bayrepel^{TM} and the brand name Autan. As volunteers with known allergic reactions to insect repellents and common cosmetics are excluded from participating in this study, enrolled participants are unlikely to be at increased risk of experiencing adverse side effects upon exposure. Clear stopping rules also have been developed, as have plans for the medical management of any side effects or adverse events associated with product exposure.

Reactions to mosquito bites are usually mild and easily treated with over-the-counter steroidal creams. The study also excluded individuals who have a history of such severe skin

reactions to further minimize the risk of a participant 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. All volunteers will be trained both to recognize LIBe's and to remove such mosquitoes with an aspirator prior to biting. Risk of bites is further minimized through the use of clear stopping rules, limited exposure periods, and paired observation.

To minimize the risk that study participants will be exposed to illnesses like WNV, the study protocol calls 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. Mosquitoes will be collected during the field studies and subjected to serologic or molecular analyses to confirm that they were free of known pathogens.

Finally, the study protocol also includes several mechanisms designed to minimize coercive recruitment and enrollment, compensation does not appear to be so high as to unduly influence participation, and minors and pregnant or lactating women are 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). In reviewing similar protocols submitted by Carroll-Loye Biological Research at previous HSRB meetings, for example, the Board has expressed concern about the potentially coercive nature of study subject recruitment. Although the study is to be conducted by Carroll-Loye Biological Research, a private research laboratory in Davis, California, the Principal Investigator of the study and Co-Owner of the research laboratory, Dr. Scott P. Carroll, also is an adjunct faculty member of the Department of Entomology at the University of California, Davis. As the majority of research participants will be recruited from the University's student population, including from Dr. Carroll's own department, the Board previously recommended that the protocol and consent documents be altered to define clearly the mechanisms in place to prevent coercion. The current protocol includes several mechanisms, including the exclusion of any student or employee the Study Director, a substantial waiting period between recruitment and study enrollment, and an interview by Dr. Carroll, designed to minimize coercive subject recruitment and enrollment.

In accordance with the EPA's final human studies rule, 40 CFR §§ 26.1701-1704, minors and pregnant women are explicitly excluded from participation, the latter being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study. In reviewing previous protocols, the Board has previously raised concerns about the potentially stigmatizing nature of a positive test, and recommended that investigators develop additional protections to ensure that the results of over-the-counter pregnancy tests would be kept private. The use of so-called "alternate" subjects is one such safeguard; that study participants may be designated as alternate subjects and automatically excluded from participation allows for potentially pregnant volunteers to withdraw without compromising their confidentiality.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that the revised protocol submitted for review by the Board meets the applicable requirements of §40 CFR 26, subparts K and L.

F(2). Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Studies (SPC-002)

Charge to Board

1. 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 ticks?

Board Response

The active ingredient Picaridin in three formulations will be tested in the laboratory for its ability to repel ticks by the Carroll-Loye company. The active ingredient will be formulated into 1) a 7% pump spray that will also be used for a 10% pump spray, an aerosol and a 5.75% towelette; 2) a 15% pump spray that will also be used for a 15% aerosol and a 12% towelette; and 3) a 15% lotion that will also contain a sunscreen. These are the same formulations as would be tested in protocol SPC-001 (to test repellency against mosquitoes). All experiments will be conducted using GLP.. A dosimetry experiment with 10 individuals will be performed to determine the amount of product that would be utilized by people using the product as directed; this amount will be applied by technicians to the subjects in the experiment. Subjects will be trained in the procedures. One of each subject's arms will serve as a negative control to validate each experimental tick for its questing behavior.

Ticks will be laboratory reared American dog ticks (*Dermacentor variabilis*) and deer ticks (*Ixodes scapularis).* Because these are laboratory reared, the ticks are anticipated to be disease-free.

This protocol is very similar to protocols on tick repellency submitted by this investigator in the past, using the metric of repellency from the treated area on the arms of the subjects during a 3 minute observation period during each 15 minutes of the test. The Complete Protection Time from the First Confirmed Crossing will be calculated.

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

- The scientific question was stated (i.e., to test the efficacy of Picaridin in several formulations to repel ticks).
- 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 are 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 will be determined in carefully designed laboratory experiments.
- The risks are minimal because the active ingredient is of very low toxicity, the other formulation ingredients are of very low toxicity, the ticks should be removed before they have an opportunity to bite, and the laboratory reared ticks will not possess any diseases.

Study Design Criteria

- The purpose of the study is clearly defined (i.e., efficacy testing for tick repellency).
- There are specific objectives (i.e., to determine the Complete Protection Time that Picaridin in three formulations displays as a tick repellent).
- The sample size will be 10 individuals per product. A dosimetry experiment prior to the field experiment will quantify the amount of repellent being used.
- It is anticipated that the findings from this study can be generalized beyond the study sample.

Participation Criteria

- The participants will be representative of some of the population of concern, but are not representative of the entire population, as acknowledged by the Investigator; however, since it would either be unethical to test them or would be less appropriate to test them, the participating population is considered appropriate and reasonable.

Measurement Criteria

- The measurements of tick crossing will be accurate and reliable.
- The measurements will be appropriate to the question being asked.
- Quality assurance will be a part of the experimental plan.

Laboratory and Field Conditions

- Laboratory experiments are proposed.
- Field experiments are not proposed.

The EPA science review did not identify any questions or concerns that needed to be addressed by the HSRB. As was true for protocol SPC-001, the Board had some concern that, with respect to data interpretation, a more concentrated product appeared to be proposed to estimate CPT for the lower concentration towelettes. However, it was explained during the meeting that the concentration quoted for the towelette also included the weight of the fabric, and the Picaridin solution was identical to the spray.

There were a number of concerns from a statistical perspective. The protocol states in section 8.3.1 that "[s]ubjects will be assigned to the treatment groups on the basis of a randomly assigned subject number," 1-10 to Lotion, 11-20 to 7% Pump, and 21-30 15% Pump. However, it also states in section 8.3.2 that "individual subjects may test more than one repellent, on separate days." These two statements are inconsistent as the former statement implies 30 distinct and unique subjects, whereas the latter implies an overlap, which may render the statistical interpretation of the data very difficult, depending on how the experiment is carried out. If there is going to an overlap of subjects among test groups, an appropriate

experimental design needs be employed to allow proper statistical inference. It is also unclear what is meant by the sentence "The experiment will be partially randomized by subjects" in section 8.2 on experimental design.

As for the method of analysis, the statement that "Kaplan-Meier analyses provide median estimates with substantially reduced error estimates" is incorrect as it can go either way. One cannot make a direct comparison between the median and its 95% confidence interval based on the Kaplan-Meier estimate of survival function and the mean and the 95% confidence interval based on the normal theory. Also the statement that the median based on Kaplan-Meier method is "less sensitive to data censoring" is incorrect.

Complete Protection Time defined as the mean time across all treated subjects from application of the repellent to the First Confirmed Crossing cannot be estimated due to censoring; neither can the standard deviation or the confidence interval be accurately calculated. The more appropriate statistic in the presence of censoring is the median and the confidence interval based on the Kaplan-Meier estimate of the survival distribution for the time to efficacy failure.

The Board disagreed with the EPA's assessment on compliance with applicable scientific standards on the following items:

- Quantification of efficacy of the test materials is inappropriate as the normality assumption is inadequate and due to potential censoring.
- Discussion of the statistical power is irrelevant as there is no statistical test of hypotheses is involved.
- Justification of the sample size for the repellency phase is not scientific and thus inadequate.

The Carroll-Loye Protocol SPC-002 7/10/07 document contained the Site Questionnaire (pp 63-66 of 70) and the Study Specific Instructions (p 67 of 70) for SPC-001, which must be in error, as they refer to mosquitoes, instead of ticks. There appears to be discrepancies in the Material Safety Data Sheets (MSDS) in the above document: On pp 59 and 61 the EPA Registration Number is identical (121-92), but Product Item Numbers are different (53667 on p 59 and 53661 on p 61) for the identical formulation. There did not seem to be a MSDS included for the formulation with sunscreen.

The IRB is universally understood as an acronym for "Institutional Review Board." Therefore, reference to "Independent Investigational Review Board" as "Independent IRB" is inappropriate and misleading.

HSRB Consensus and Rationale

The Board concluded that the research appears likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling ticks, provided that the revisions suggested by EPA are incorporated and that the experimental design is made more specific to the allocation of the test substances into three groups of subjects and that there is no

overlap of subjects from one test group to the other, if the data are intended to be compared among test substances.

The Board urges EPA to consider the design of newer studies and the designs already used for existing products to make certain that labels reflect information of comparative value to consumers. If there are currently inconsistencies in the information used to authorize label information on efficacy, the Board urges EPA to develop new guidelines or revisions to the current guidelines that will balance accuracy of data collected, safety to human subjects and consistency in the ultimate labels produced.

Charge to Board

2. 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?

Board Response

Brief Overview of the Study

The research is to be conducted by Carroll-Loye Biological Research, a private laboratory in Davis, California by using healthy volunteers and a controlled environment. The study sponsor is Spectrum Brands, Inc. of Bridgeton, Missouri, a division of United Industries Corporation. The study protocol was reviewed and approved by a commercial human subjects review committee, Independent Investigational Review Board, Inc. (IIRB) of Plantation, Florida. Minutes of IIRB meetings were provided to the EPA as a separate document, and documentation previously provided to the EPA by IIRB indicates that it reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

The research protocol submitted consists of two interdependent studies: 1) a dosimetry study designed to determine the amount of an insect-repelling compound, known as picaridin, that normal subjects would typically apply when provided with one of three compound formulations (7% Picardin Pump Spray [data will be bridged to 10% Pump Spray and Aerosol and 5.75% Towelette],15% Picaridin Pump Spray [data will be bridged to 15% Aerosol and 12% Towelette], and 15% Picaridin Lotion formulated with sunscreen); and 2) an efficacy study designed to measure the effectiveness of IR3535 as a tick repellent. Dosimetry will be determined either by passive patch dosimetry (spray formulations) or by direct measurement of compound application (lotion formulation). The efficacy of IR3535 as a tick repellent will be determined by placing Western black-legged ticks (*Ixodes pacificus)* on picaridin-treated and untreated forearms and measuring the speed and distance that moving insects would migrate into the treated area. The strengths and weaknesses of each study design are described above.

The dosimetry study will enroll a total of 10 subjects, each of whom will test all three formulations. The efficacy study will enroll 10 subjects per test formulation. Each subject will serve as his/her own control. Participants in the dosimetry study may or may not participate in the efficacy study, and participants in the efficacy study may also test different formulations on

different days; this makes the total number of volunteers enrolled in both the dosimetry and efficacy studies no less than 10 but no greater than 40. In addition, three alternate subjects will be enrolled to: 1) replace any subject who withdraws from participating; 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.

Critique

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley and Sweeney, 2007b). Once the recommended changes outlined therein are incorporated into the protocol, the proposed research described in Protocol SPC-002 should comport with the applicable requirements of 40 CFR Part 26, subparts K and L.

The risks to study participants are minimal and justified by the likely societal benefits, including data on the efficacy of these picaridin-based formulations as a tick repellent. The risks to study participants are three-fold: 1) reaction to test materials themselves; 2) exposure to biting arthropods; and 3) possible exposure to arthropod-borne diseases.

The active ingredient of these three repellent formulations is commercially available and is present at similar concentrations in other EPA-registered products; specifically, picaridin is registered and marketed as an insect repellent in the United States under the registered trade name Bayrepel^{TM} and the brand name Autan. As volunteers with known allergic reactions to insect repellents and common cosmetics are excluded from participating in this study, enrolled participants are unlikely to be at increased risk of experiencing adverse side effects upon exposure. Clear stopping rules also have been developed, as have plans for the medical management of any side effects or adverse events associated with product exposure.

The risks of bites are negligible and minimized by the study design; tick questing and biting behavior is slow, and study participants are trained to remove ticks from their forearms prior to biting.

The ticks used for the study are bred and raised in a laboratory environment and are considered to be pathogen-free, minimizing the risk of vector-borne disease. The Agency noted in their review (2007b) that the tick-borne rickettsial illness Rocky Mountain Spotted Fever (RMSF) has been passed within tick colonies through a transovarian transmission mechanism, so the laboratory colonies in question should either be tested for RMSF prior to initiation of SPC-002, or the consent form and protocol altered accordingly to reflect the low but not negligible risk posed to trial participants.

The study protocol also includes several mechanisms, similar to those described above in the Board's review of Study Protocol SPC-001, designed to minimize coercive recruitment and enrollment, compensation does not appear to be so high as to unduly influence participation, minors and pregnant or lactating women are 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), and the use of so-called

"alternate" subjects allows for volunteers to withdraw or be excluded without compromising their confidentiality. The Board's only concern about subject recruitment was the unjustified exclusion of study participants older than 55 years of age; most Board members felt that a clear rationale for excluding older volunteers should be provided, or the exclusion criteria changed.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that the revised protocol submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

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

Charge to the Board

1. 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?

Board Response

This protocol presented by ICR was designed to determine in laboratory studies whether two Picaridin-containing products will repel mosquitoes of the genus *Culex*. This product is already registered and the study, if showing efficacy of the product in repelling *Culex*, would allow repellency of this genus to be added to the label. This is important because *Culex* is one of the major carriers of West Nile virus, and efficacy against this genus would be of interest to consumers. The particular products to be tested are Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent and Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent spray. The hypothesis was that 8 hours of protection against *Culex quinquefasciatus*, a species known to be a vector for West Nile virus, would be demonstrated by the two products.

The protocol was clearly written. Laboratory reared insects that were disease free would be used. The protocol proposed the use of the guideline amount of repellent, not an amount determined by a dosimetry study, and would monitor bites, not landings, in order to be consistent with the methods used to obtain the label currently borne by these products. The negative control would use only landings, avoiding bites as much as possible, and would be used to guarantee that a landing rate of at least 5 in 60 seconds was maintained; if the landing rate dropped below this, more mosquitoes would be added to the cages.

This protocol appeared to follow guideline procedures, and data from a study such as this would be necessary to modify label claims to include efficacy against *Culex*, particularly if *Culex* was not represented or was not represented well in the original field studies, which presumably was the case. The procedures seem to be straightforward. Pre-testing the subjects

for attractiveness to *Culex* should yield more consistent results than if such pretesting was not done.

There were a few points of confusion. The reference to dose range finding (pg. 27) was not clear, particularly when the standard guideline dose level was proposed. It is unclear whether confounding from the subject's other arm containing a different product, or the presence of the arms of the second subject in the cage would occur. However both subjects would use the same two products and both products would contain the same active ingredient, i.e., Picaridin, so there is probably little, if any, confounding likely. There was a question as to whether the laboratory temperature and humidity would be similar to that occurring in the field. There was also a question of how, with an 8 hour limit to the test, an average of 8 hours efficacy with a 2 hour deviation might be obtained. It was suggested that a Q test was not the most appropriate statistical method, and that the Kaplan Meier test might be the better approach.

Two of the aspects of this protocol are at variance with what the Board had previously concluded regarding other insect repellency protocols, and these deserve specific discussion. One is the use of the standard guideline dosage instead of a dosimetry test to determine the dosage to be used. While in a totally new study, the dosimetry test would yield a dosage more representative of the amount of product that the consumer would use, in this situation, this study is supposed to match a previously conducted field study with the same products. It is therefore appropriate to use the same dosage as was used in the earlier field study. Likewise, the previous field study used bites. While the Board has been impressed with the added safety to participants imparted by the landing endpoint over the bite endpoint, these data would need to match the data obtained in the previous field study, which used bites as the endpoint. In addition, the consultants indicated that landings did not necessarily predict bites, leading to even more support for the use of bites in order to match the earlier study with bites.

HSRB Consensus and Rationale

The Board concluded that this study would be appropriate to confirm efficacy against *Culex*, was designed to meet the current EPA guidelines, and was generally clear and adequately designed, with the exception of the appropriate statistics. If revised consistent with EPA's recommendations and the Board's suggestions, the study should yield valid data regarding the efficacy of these products in repelling *Culex*.

Charge to Board

2. 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?

Board Response

Brief Overview of the Study

The proposed study (Spero, 2007) would evaluate the efficacy of two different skin-applied lotion formulations of picaridin-based insect repellents under laboratory conditions; these two formulations are Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent (EPA Reg. No. 806-29) and Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent Spray (EPA Reg. No. 806-31.

The research is to be conducted by ICR, a commercial organization based in Baltimore, Maryland; ICR provides testing and regulatory consulting services for companies developing and marketing pesticides and insecticides in the United States and Canada. The study is managed by toXcel, LLC of Gainesville, Virginia. The sponsor of this study is Avon Products, Inc. of New York, New York. The submitted documents assert that the study will be conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements of FIFRA §12(a)(2)(P), and the U.S. EPA's GLP Standards described at 40 CFR 160. The protocol was reviewed and approved by an independent human subjects review committee, Essex Investigational Review Board (EIRB), Inc., of Lebanon, New Jersey prior to submission to the Agency.

Efficacy of the two picaridin-based formulations will be evaluated by using healthy volunteers. The study will be performed at ICR's laboratory in Baltimore, Maryland, and test the effectiveness of the two compounds as mosquito repellents by measuring the ability of each formulation to prevent mosquito bites under laboratory conditions. The strengths and weaknesses of the study design are described above.

The effectiveness study will enroll a total of 13 subjects. Of the 13 participants, twelve will be treated and test the effectiveness of the two picaridin-based repellent formulations. The compounds will be applied to 250 cm^2 patches of skin on the forearms of each study participant; one compound will be applied to the right forearm and one to the left forearm, with the effectiveness of each formulation simultaneously evaluated. Treated skin will be exposed to mosquitoes for five minutes at half-hour intervals by having study participants insert their forearms into 8 $ft.^3$ test "cages" containing 100 laboratory-reared, pathogen-free female *C. quinquefasciatus*. The efficacy of each repellent formulation will be ascertained by measuring the time from application to "breakdown" of repellency, with "breakdown" defined in the protocol as either two confirmed bites in a single five-minute exposure period, or one bite in each of two consecutive exposure periods. Treated study participants will work in pairs, observing mosquito landings and alerting attendant ICR staff of potential bites; ICR staff will determine whether or not these are confirmed bites. Probes (i.e., "bites" where the mosquito punctures the skin but does not collect blood) and bites from mosquitoes that do not fully alight (i.e., all six legs on the surface of the exposed skin) will not be considered as confirmed bites. Once breakdown has occurred for a particular repellent formulation, no further exposure of the subject's treated skin will occur. The study protocol justifies the enrollment of twelve treated participants by stating that ten volunteers are needed to obtain statistical validity; an additional two participants will be enrolled as alternates to "allow for drop outs" (Spero and Gaynor, 2007).

One study participant, chosen by lottery (a "coin toss"), will remain untreated and will be monitored to determine mosquito-biting pressure under laboratory conditions. A 250-cm^2

patch of untreated skin will be exposed for five minutes at half-hour intervals, with the ambient biting pressure determined by measuring the number of mosquitoes landing on the skin. A minimum rate of 5 landings per minute is necessary for the laboratory trial to be conducted or continued. Landing mosquitoes will be "shaken" away by the study participant while ICR staff counts the number of landings.

Critique

The supporting documentation provided by the study investigators, sponsor and EIRB, as submitted to the Agency, appear to meet the regulatory requirements of 40 CFR 26.1115a and 40 CFR 26.1125. A description of EIRB procedures was provided to the EPA with a claim of confidentiality, so were not available for review by the HSRB. Agency staff, however, reviewed the documentation provided by EIRB and determined these procedures and policies to be in compliance with the applicable standards of the Common Rule (45 CFR 46, Subpart A). The protocol as submitted to the Agency thus is substantially compliant with the regulatory requirements of review and documentation, minor deficiencies not withstanding.

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley and Sweeney, 2007c). Specifically, the Board agreed with the Agency's recommendations that ICR: 1) revise the current protocol discussion of risks and benefits; 2) provide more information about ICR's subject recruitment and enrollment processes; and, 3) alter the data collection form to remove all identifiable information. Most Board members disagreed, however, with the EPA's recommendation that study investigators provide a clearer justification for relying on time to FCB as a measure of repellent efficacy. Previous field studies using time to FCB as an endpoint for these particular repellents efficacy have already be submitted to and approved by the Agency. These additional laboratory studies are to be conducted solely for the purpose of justifying additional label claims as per Agency requirements. For consistency, use of time to FCB, using pathogen-free colonies of mosquitoes under controlled conditions, is justified.

Once these changes are incorporated into the protocol, the proposed research described in ICR A117 should comport with the applicable requirements of 40 CFR 26, subparts K and L. In brief, the risks to study participants are minimal and justified by the likely societal benefits, including data on the efficacy of these picaridin-based formulations as a repellent for one of the key mosquito genera known to transmit WNV in the United States. At first glance, the potential risks to study participants are three-fold: 1) reaction to test materials themselves; 2) exposure to biting arthropods; and, 3) exposure to arthropod-borne diseases.

These two picaridin-based repellent formulations are commercially available in the United States, and have been used widely as cosmetic and personal care products with little evidence of toxic effects. Volunteers with known allergic reactions to insect repellents and common cosmetics are excluded from participating in this study, and the amount of skin treated with picaridin is limited, so enrolled participants are unlikely to be at increased risk of experiencing adverse side effects upon exposure to the test materials. Clear stopping rules also have been developed, as have plans for the medical management of any side effects or adverse events associated with product exposure. The Board did recommend, however, that the

informed consent documents be modified to more accurately represent the known toxic risks associated with acute picaridin exposure, particularly via ocular, oral and respiratory routes of exposure.

The endpoints of the study protocol require two confirmed mosquito bites to document breakdown of repellent effectiveness. Reactions to mosquito bites are usually mild and easily treated with over-the-counter steroidal creams; such a cream, in addition to Calomine™ and rubbing alcohol, will be provided to study participants to alleviate minor symptoms associated mosquito bites. The study excludes individuals who have a history of such severe skin reactions to further minimize the risk of a participant experiencing a severe physical reaction to a mosquito bite.

The mosquitoes used for the study are bred and raised in a laboratory environment and are considered to be pathogen-free, minimizing the risk of vector-borne disease. In the Agency's Scientific and Ethics review of the protocol (Carley and Sweeney, 2007b), a concern was raised that the risk of arthropod-borne illnesses is not adequately discussed in the informed consent document; the Agency recommended that a discussion of these risks be added. The Board agreed.

The differential risks to untreated control subjects (chosen by lottery rather than via separate enrollment of more experienced study participants) are listed in both the protocol and the informed consent document. The Board did note, however, a misleading statement in the consent document, in which mosquitoes will be "brushed [off] by ICR staff" from untreated control subjects arms prior to biting. The protocol stated that untreated controls will "shake" landing mosquitoes off. This inconsistency must be corrected.

Furthermore, it is clear from the protocol that all study volunteers, be they untreated controls or treated volunteers, will be asked to expose an untreated arm to the mosquito colony before the efficacy study begins, in order to test "attractiveness." The attractiveness component of the study is not listed in the informed consent document, and must be added. The informed consent document also lists one of the societal benefits of the study as bringing a "new repellent to market." The study as described, however, is designed to simply allow labeling change. The repellent formulations under evaluation are already on the market.

A more detailed explanation of study recruitment is also needed; the exact procedures for recruiting study participants are unclear. As currently written, however, compensation for study participation is not so high as to unduly influence enrollment, and employees and contractors of ICR, toXcel and the sponsor (as well as family members) are excluded from participation. In accordance with the newly promulgated provisions in the EPA's final human studies rule (40 CFR §§ 26.1701-1704), minors and pregnant women are explicitly excluded from participation, the latter being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the field study. The use of two potential "alternate" subjects allows for volunteers to withdraw or be excluded without compromising their confidentiality.

Finally, the Board was concerned that an overlooked risk of study participation might be the strain associated with the physical requirements imposed upon volunteers. Each study participant will be asked to spend a full day in a warm, humidified laboratory environment. Although the likelihood of an adverse event precipitated by the physical strains of study participation is small, these risks nevertheless should be incorporated into the informed consent document, and a clear plan for medical monitoring and treatment be articulated.

HSRB Consensus and Rationale

The Board concurred with the assessment of the Agency that the protocol ICR A117 submitted for review by the Board, if revised as suggested in both EPA's review and by the Board, would meet the applicable requirements of 40 CFR 26, subparts K and L.

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APPENDIX A: DISCUSSION QUESTIONS FOR MOSQUITO REPELLENT STUDIES

The Human Studies Review Board (HSRB or Board) has discussed and provided advice to EPA on scientific and ethical issues related to the conduct of field studies to evaluate the efficacy of mosquito repellent products. The HSRB has reviewed both proposals for new field studies and the results of completed studies. The HSRB has noted that, although there are many similarities across studies, not all studies employ the same study design. The HSRB has identified several methodological issues for which additional background information would assist the Board in its evaluation of such studies.

BACKGROUND

Currently, EPA requires all pesticide products that claim to repel mosquitoes to provide data on the duration of efficacy under field conditions at two biologically distinct sites. These data are derived from human research with subjects who have been treated with the repellent formulations in the field. The Agency evaluates the duration of repellent efficacy for a subject by calculating the time from application of the repellent to the occurrence of an event indicating an efficacy failure. Historically, for field studies of mosquito repellency, EPA has used the "first confirmed bite" as an indication of efficacy failure on a test subject. Several recent studies have shifted to the "first confirmed landing with intent to bite;" EPA has accepted this alternative endpoint. A "confirmed landing" on a test subject is a mosquito landing followed by a second landing on the same subject within a specified period of time (usually 30 minutes) after the initial landing.

Field studies typically involve 6 – 10 subjects who have been treated with a defined amount of the test material. Each subject is then regularly and repeatedly exposed to ambient mosquito populations for a fixed interval of time until the subject experiences an efficacy failure followed by a confirmation with the specified period of time. Mosquito landing pressure (representing intent to bite) at a site is monitored by concurrently exposing untreated subjects to mosquito landings. A study is considered valid only if there are at least a specified minimum number of mosquito landings on untreated subjects during each exposure interval.

On October 25, 2007, the HSRB will discuss scientific aspects of the design of field studies to assess the efficacy of mosquito repellents. For this meeting the Board has requested consultants to provide specialized information or assistance to the Board. The Board is particularly interested in the frequency, duration and timing of exposure of subjects to potential mosquito landings. The Board requests each consultant to respond briefly to the series of questions below. Please send the responses to the HSRB Chair and Designated Federal Official (DFO) at least one week before the meeting—i.e., by no later than October 18. All responses will subsequently be provided to the other consultants, the HSRB members, and EPA staff for their review, and will be posted on www.regulations.gov under docket ID number, EPA-HQ-ORD-2007-0942. HSRB consultants will be available at the

meeting to discuss their responses and address questions from the Board. The questions for Board consultant consideration are provided below:

DISCUSSION QUESTIONS

- What do data show about the variability of the time intervals between first and subsequent landings in mosquito repellent field trials?

- What is the current scientific understanding of how factors other than repellent efficacy could affect the likelihood that an initial event—a mosquito landing or mosquito bite—would be "confirmed" by another similar event within 30 minutes? Please address at least these factors:

    - Characteristics of mosquito populations
    - Characteristics of test sites
    - Characteristics of test subjects
    - Characteristics of test methods

- Can the impact of such factors on the likelihood or timing of an initial and confirming event be predicted? Can it be quantified?

At its June 27 - 29, 2007 meeting the Board learned that different designs with different "length-biased" sampling for mosquito repellent field studies are in use. One design exposes subjects to potential mosquito landings for one minute of every 15 minutes; another design exposes subjects to potential mosquito landings for five minutes of every 30 minutes. The DFO is separately providing a CD containing the background materials for the June 27 – 29, 2007 HSRB meeting. The protocols are loaded on the CD. These designs have different "length-biased" sampling.

- What is the methodological rationale for the two different designs?

- Which design is used more widely in the field? Why?

- Can potential effects of variation in the pattern of intermittent exposure on the results of efficacy testing be isolated from the effects of other variables? If so, can the direction or magnitude of the effects be predicted? How might these influences be analyzed and accounted for in collecting, reporting and analyzing repellent efficacy data?

Dr. Matt Kramer, a USDA statistician who has served as a consultant, has suggested that the precision of estimates of Complete Protection Time (CPT) in repellent testing could be significantly increased by defining a failure of efficacy as the mean time from treatment to a series of several landings or bites. He has stated:

> The precision of CPT increases when it is estimated beyond time to [First Confirmed Bite] FCB or FCLanding. How well CPT can be estimated depends on the distribution of

so many bites beyond FCB. The number of mosquitoes that will bite (*n*) will determine results of the test. Each person in the field should be his/her own control; that way it is possible to know *n* per person, and reduce person-to-person variability.

If using the mean time to the first 5 bites, the SE will decrease proportionally as *n* increases ($n = 5$ in this case). That is equivalent to an increase in the power of the test of 5 times. This method allows for detecting formulation differences near the CPT.

- Does this approach, indeed, increase the precision of estimates of CPT markedly without requiring additional subjects?

- If so, would this increased precision justify the incremental risk to the subjects resulting from their exposure to a great?

- Is it practical to test long-lasting repellents to the point of five landings?