June 25, 2008

EPA-HSRB-08-02

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

Subject: April 9-10, 2008 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) EPA Review of Antimicrobial Exposure Assessment Task Force Mop and Wipe scenario protocols; (2) ICR Protocol: A382 and (3) Carroll-Loye Biological Research Completed Studies: SCI 001.4 and SCI 001.5. The enclosed HSRB report provides the Board's response to EPA charge questions presented at the April 9-10, 2008 meeting. The Board also appreciates the Agency providing an update of the EPA/ORD document "Scientific and Ethical Approaches for Observational Exposure Studies." The Board agrees with the Agency that the document will serve as a valuable resource for EPA and other researchers to rely on as they develop and conduct observational human exposure studies. In addition to the recommendations for specific protocols and completed studies summarized below, the Board provided comments on review and format of AEATF and AHETF protocols.

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

EPA Review of AEATF-II Mop and Wipe Scenarios (due to similarities of the mop and wipe scenarios, both exposure scenarios were reviewed together)

Science

The Board considered the AEATF-II study protocols to successfully address many design challenges. The Board appreciated particularly the clarity of the protocols, the attention to detail, and the thorough description of quality assurance and quality control procedures. The Board concurred with the Agency that existing data on handler exposures to antimicrobials are inadequate and that the development of more accurate information is an appropriate goal. The Board also concurred with the Agency that there are only minimal risks associated with the application of a dilute solution of didecyl dimethyl ammonium chloride as described in the study protocols.

While the Board concluded that the research could produce scientifically reliable data, the Board identified several contextual factors that may limit the generalizability of the findings. The Board therefore recommended that the Agency reconsider the design of the

study, or develop an explicit statement of the limitations on the use of data that will be collected under the proposed design. Specifically the Board noted that any generalizations to moppers and wipers in other parts of the country and in other kinds of buildings would be based on expert opinion, and that such generalizations would not be statistical generalizations. The Board cautioned the Agency regarding the 3x6 design in the protocols, suggesting future scenario designs for the AEATF- II program would likely have three clusters and six time durations, with the justification being the Board's recommendation of these protocols. The Board also concluded that the task duration time frame was not adequate to characterize daily exposure. The Board recommended that the work time frame be expanded to exceed the 95th percentile of the International Sanitary Supply Association survey findings. The Board noted that if, instead of time, the number of Ai units handled were the measure that defined each person's participation, the data would more likely lend themselves to a proper assessment of the assumption of proportionality.

Finally, the Board encourages modifications of future related protocols based on the lessons learned from this initial submission. Such adjustments are anticipated to improve the study design and subsequent results, leading to a more accurate characterization of pesticide handler exposure.

Ethics

The Board concurred with the initial assessment of the Agency that if the proposed mop and wipe scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, the research would meet the applicable requirements of 40 CFR part 26, subparts K and L.

ICR Protocol: A 382

Science

If amended in a manner consistent with the Board's concerns and recommendations, and with particular modification to subject ethnicity, the Board concluded that the protocol ICR A382 studying the efficacy of two formulations of picaridin for repelling stable flies would be sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of these formulations against stable flies.

Ethics

The Board concurred with the initial assessment of the Agency that, if the protocol is revised as suggested by EPA and the HSRB, the study submitted for review by the Board would meet the applicable requirements of 40 CFR 26, subparts K and L.

Carroll-Loye Biological Research Completed Studies: SCI 001.4 and SCI 001.5

Science

The Board concluded that the study on the efficacy of LipoDEET 320 and Coulson's Duranon shows efficacy of both products in repelling mosquitoes, and agreed with the Agency that the study was sufficiently sound, from a scientific perspective, to be used to accurately calculate the complete protection time for repelling mosquitoes.

Ethics

The Board concurred with the initial assessment of the Agency that the study submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L. However, the Board expressed concern regarding a pattern of deviations from IRB approved protocols apparent in this study and previous submissions by the investigator. Implications of this concern are noted below.

Over several meetings, including the April 2008 meeting, the Board has expressed concern with EPA submission for HSRB review of completed studies in which planned protocol deviations were conducted prior to IRB review and following HSRB review of the originally approved protocol. Such actions are in violation of 40 CFR 26, Subpart K Sec. §26.1108 IRB functions and operations.

Subpart K Sec. §26.1108 IRB functions and operations.
"In order to fulfill the requirements of this subpart, each IRB shall:
(a) Follow written procedures:
(1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;
(2) For determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;
(3) For ensuring prompt reporting to the IRB of proposed changes in research activity; and
(4) For ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects."

The Board reached consensus regarding its future review procedures under such conditions:

1. Any study executed prior to IRB approval of the Informed Consent Form and the protocol, or changed in ways that were not approved by the IRB will be judged by the Board as failing to meet the applicable requirements of §40 CFR 26, subparts K.
2. If the EPA submits to the Board for review a completed protocol with scientific deviations from the original protocol reviewed by the Board, the EPA review of the completed protocol should provide the Board with EPA's opinion regarding why the deviation did not meet the requirement for re-review and why the protocol still meets the applicable regulations.

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

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* Not in attendance at April 9-10, 2008 Public Meeting

INTRODUCTION

On April 9-10, 2008, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning: Sampling strategies in proposed pesticide handler research, Antimicrobial Exposure Assessment Task Force (AEATF) Governing Document, EPA Review of AEATF-II Mop and Wipe Scenarios, ICR Protocol: A382, and Carroll-Loye Biological Research Completed Studies: SCI 001.4 and SCI 001.5 Each of these topics is discussed more fully below. In addition, EPA's Office of Pesticide Programs provided a follow-up on pesticide specific HSRB recommendations. Finally, EPA's Office of Research and Development provided an update on revisions to its document "Scientific and Ethical Approaches for Observational Exposure Studies." Each of these topics is discussed more fully below.

1. Proposed AEATF Research on Exposure of Subjects Using an Antimicrobial Pesticide in Mopping and Wiping Activities

The HSRB has previously considered issues related to the design and conduct of research to measure the levels of exposure received by people when handling (i.e., mixing, loading, or applying) pesticides. Two industry Task Forces, the Antimicrobials Exposure Assessment Task Force II (AEATF) and the Agricultural Handlers Exposure Task Force (AHETF), have previously submitted materials for HSRB review. Based on the issues raised by the Board at its meeting in June 2006, EPA asked its FIFRA Scientific Advisory Panel (SAP), an advisory committee of independent expert scientific peer reviewers providing technical advice to EPA on pesticide and pesticide-related issues, to address a number of scientific issues at its January 2007 meeting. Drawing on the advice of the SAP, the Office of Pesticide Programs (OPP) presented additional issues relating to the proposed handler research again at the April and June 2007 HSRB meetings. In response to those reviews the Task Forces have extensively reworked their research proposals.

One issue, the design of the sampling strategies to be used by the Task Forces, has drawn particular attention. To resolve this question OPP has consulted with experts both within and outside EPA, and has carefully considered information presented by the Task Forces. Based on these interactions, OPP has decided to accept data developed through "hybrid" sampling strategies, i.e., strategies that use a basic purposive diversity sampling design but which incorporate random elements whenever feasible. OPP provided background documents on these interactions on December 5, 2007 to the HSRB for subsequent consideration. Those same background documents are provided again in this transmittal for the Board's convenience in preparing for the April 2008 HSRB meeting.

The AEATF has submitted two proposals. Each includes both a scenario-specific design document and the associated field study protocol, along with supporting documentation, for EPA and HSRB review. One proposal would measure inhalation and dermal exposure of subjects applying an antimicrobial pesticide by mopping floors. The other would measure exposure of subjects who apply an antimicrobial pesticide by wiping vertical and horizontal hard surfaces in two distinct scenarios—one using a spray-and-wipe technique, and the other using ready-to-use impregnated wipes.

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. Because the research proposed by the AEATF involves scripted exposure, it meets the regulatory definition of "research involving intentional exposure of a human subject", and thus these cited provisions of regulation apply to it.

EPA has reviewed the AEATF proposals and has concluded that, with a number of required revisions, they appear likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L. EPA has also concluded that the proposed hybrid sampling designs for all three proposed exposure scenarios effectively incorporate elements of randomization, consistent with EPA's guidance to the AEATF. Because the sponsor wishes to initiate testing pursuant to these protocols as soon as possible to meet regulatory requirements in other countries, and since EPA finds the protocols can meet applicable scientific and ethical standards, EPA presented this protocol for review at the Board's April 2008 meeting.

EPA provided the following materials concerning the AEATF Exposure Monitoring Program to the HSRB:

3. AEATF Exposure Monitoring Program

    a. General Documents

        (1) Volume 5 AEATF Governing Document (Revised 2/13/08)

        (2) AEATF Governing Document (Revised 2/13/08; track changes)

        (3) Summary of Changes to Governing Document of 2/13/08

        (4) Volume 6 AEATF SOPs (Revised 2/25/08)

    b. Documents specific to the Mop Scenario

        (1) Volume 1 AEATF Mop Scenario Design/Protocol: Primary Documentation (Revised 2/25/08)

        (2) Volume 2 AEATF Mop Scenario Design/Protocol: Secondary Documentation (Revised 2/25/08)

        (3) EPA Science and Ethics Review: AEATF Mop Scenario (3/10/08)

    c. Documents specific to the Wipe Scenarios

(1) Volume 3 AEATF Wipe Scenario Design/Protocol: Primary Documentation (Revised 2/25/08)

(2) Volume 4 AEATF Wipe Scenario Design/Protocol: Secondary Documentation (Revised 2/25/08)

(3) EPA Science and Ethics Review: AEATF Wipe Scenarios (3/10/08)

d. Background documents on the Sampling Strategy Issue distributed to the HSRB on December 5, 2007

(1) Memorandum from William Jordan to Dr. Celia Fisher Re: "Design of Sampling Strategies in Proposed Handler Research"

(2) AHETF Study Design, Logistics, and Conduct (10-17-07) Power Point presentation by David Barnekow and Victor Cañez

(3) AEATF Introduction and Background (10-17-07) Power Point presentation by Hasmukh Shah

(4) AHETF Membership Benefits and Incentives (10-17-07) Power Point presentation by Victor Cañez and David Barnekow

(5) AHETF and AEATF Concepts, Objectives, and Sampling Issues (10-17-07) Power Point presentation by Larry Holden

(6) Report of Dr. Tapabrata Maiti, Associate Professor of Statistics at Iowa State University, to EPA concerning sampling design issues in proposed handler exposure research (11-30-07)

(7) Letter from Debra Edwards, OPP director, to Hasmukh Shah, manager of the American Chemistry Council's Biocides Panel, concerning issues involving the AEATF's proposed handler research. (11-28-07)

(8) Summary of EPA/OPP Teleconferences with AHETF (11-28-07)

2. Proposed ICR Stable Fly Repellent Efficacy Study (A 382)

EPA requires submission of data from efficacy studies when a pesticide product is directed against organisms classified as public health pests. EPA's regulation, 40 CFR §26.1125, requires a 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 science and ethics reviews. In addition, EPA's regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the research proposal.

Insect Control & Research, Inc. (ICR) has submitted a proposal for new research to evaluate the efficacy of two conditionally registered products containing picaridin, to be conducted by Dr. William Gaynor. ICR protocol number G4330108001A382 (A382) describes a laboratory study of the efficacy of the test formulations against stable flies, a species classified as a public health pest.

EPA has reviewed ICR's protocol and has concluded that, with several 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 stable flies. In the interest of providing a thorough and timely decision on such applications, and since EPA finds the protocol can meet applicable scientific and ethical standards, EPA is presenting this protocol for review at the Board's April 2008 meeting.

EPA provided the following materials on the ICR repellent efficacy protocol A382 to the HSRB:

2. ICR Repellent Efficacy Protocol A382

    a. ICR Stable Fly Protocol A382 (Rvsd 2/1/08)

    b. EPA Science & Ethics Review (3/7/08)

3. Completed Insect Repellent Efficacy Studies (SCI-001.4 and SCI-001.5) of DEET Formulations

In its January 2007 meeting the HSRB reviewed protocol SCI-001 from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll, to test mosquito repellent efficacy of three controlled-release formulations of DEET in the field. The study was designed to measure the efficacy of the three test formulations and 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 amended the protocol to address a comment from the HSRB and to substitute a new, unregistered repellent formulation for one of those proposed in the protocol. Dr. Carroll then proceeded to conduct the research according to the amended protocol in July 2007, and submitted the results to EPA for review. At its October 2007 meeting, the HSRB reviewed the results of the research, determined that there were both scientific and ethical issues with the conduct of the research, and advised EPA not to rely on the data. Dr. Carroll further amended the protocol, obtained IRB approval for both the original and subsequent amendments, and re-executed the research in November 2007, testing only two of the originally proposed test repellents and omitting the comparison positive control formulation. Reports of this testing have been submitted to EPA by the study sponsor, Scientific Coordination, Inc., under study numbers SCI-001.4 and SCI-001.5. EPA is

presenting the results of the re-execution of protocol SCI-001 to the HSRB for review at this meeting.

The Agency's regulation, 40 CFR §26.1602, requires EPA to seek HSRB review of an EPA decision to rely on the results of these studies. The sponsor has submitted data in support of applications for amended registration for the two test materials. In order to facilitate review of these applications within the time allowed by statute, 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.

OPP has determined that the data are scientifically sound and that the research meets the standard in §26.1705. Therefore OPP proposes to rely on the results in considering the pending applications.

EPA provided the following materials on the completed insect repellent efficacy studies SCI-001.4 and SCI-001.5 to the HSRB:

1. Insect Repellent Efficacy Studies SCI-001.4 and SCI-001.5

    a. MRID 47322501 SCI-001.4: Test of DermAegis LipoDEET 302

    b. MRID 47322401 SCI-001.5: Test of Coulston's Duranon

    c. Supplemental correspondence IIRB↔CLBR 3/5/08

    d. EPA Science and Ethics Review (Protocol) SCI-001 (12/20/06)

    e. Changes in consent form version of 11-6-07

    f. EPA Ethics Review: SCI-001.4 and SCI-001.5 (3/7/08)

    g. EPA Science Review: SCI-001.4 and SCI-001.5 (3/7/08)

This report transmits the HSRB's comments and recommendations from its April 9-10, 2008 meeting.

REVIEW PROCESS

On April 9-10, 2008, 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 (73 Federal Register 46, 12413). At the public meeting, following welcoming remarks from Agency officials the Board then heard presentations from the Agency on the following topics:

- Update On Revisions To The EPA Document "Scientific And Ethical Approaches For Observational Exposure Studies
- EPA Follow-up on Pesticide Specific HSRB Recommendations
- Overview of EPA's Assessment of Proposed Pesticide Handler Research
  - Sampling Strategies in Proposed Pesticide Handler Research
  - Antimicrobial Exposure Assessment Task Force (AEATF) Governing Document
  - EPA Review of AEATF-II Mop and Wipe Scenarios
- ICR Protocol: A382
- Carroll-Loye Biological Research Completed Studies: SCI 001.4 and SCI 001.5

Oral comments

The following oral comments were presented at the meeting:

AEATF-II Mop and Wipe Scenarios

Jeff Driver, Ph.D. of infoscientific.com on behalf of the AEATF-II

Larry Holden of Sielken and Associates, Inc. on behalf of the AEATF-II

ICR Protocol: A382

William Gaynor, Ph.D. on behalf of ICR, Inc.

Robin Todd, Ph.D. on behalf of ICR, Inc.

Ralph Piedmont, Ph.D. of Loyola College on behalf of ICR, Inc.

Carroll-Loye Biological Research Completed Studies: SCI 001.4 and SCI 001.5

Scott Carroll, Ph.D. and Mr. Shawn King on behalf of Carroll-Loye Biological Research

Written comments

Written comments were received by:

General

Stephen A. McFadden, Independent Scientific Research Advocates

AEATF-II Mop and Wipe Scenarios

American Chemistry Council on behalf of the AEATF-II

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 or study). 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

Update On Revisions To The EPA Document "Scientific And Ethical Approaches For Observational Exposure Studies

No Charge to the Board

EPA Follow-up on Pesticide Specific HSRB Recommendations

No Charge to the Board

Overview of EPA's Assessment of Proposed Pesticide Handler Research

Sampling Strategies in Proposed Pesticide Handler Research

No Charge to the Board

Antimicrobial Exposure Assessment Task Force (AEATF-II) Governing Document

No Charge to the Board

Board Recommendations on Review and Format of AEATF and AHETF Protocols

Overall recommendations

1. Random sampling designs are preferred.
2. When random sampling is not possible, a purposive diversity sampling (PDS) protocol must nonetheless have a well-developed sampling frame based on knowledge of the range of active ingredient concentrations and distribution of methods used in the field.
3. Each protocol should be individually assessed for the feasibility of random assignment. When random sampling is not possible, each protocol should be individually assessed for the adequacy of the PDS sampling frame.

Format of protocols for subsequent HSRB review

1. A detailed description of the methods and rationale for data collection (e.g., neck wipes).
2. If random sampling is not used, a detailed description of efforts made to incorporate random elements in each scenario-specific design and why it was not feasible (in terms of availability of information, costs, and time) to obtain a random sample.

3. For both random and PDS designs, a detailed description, rationale and justification for the scenario, selection of clusters, and what will be done within each cluster and why.
4. For all protocols, a detailed explanation of how data will be analyzed and interpreted by AHETF & AEATF.
5. For all protocols, a detailed explanation of how the data is anticipated to be analyzed by EPA and how it will be useful for EPA risk assessments.

Format of Agency presentations, specifically OPP presentations to the Board

1. OPP should develop a written glossary of terms (e.g., cluster, scenario) for HSRB and public reference. This glossary should be distributed but not summarized during OPP presentations.
2. For each protocol OPP should provide a brief (1 page if possible) abstract in terms appropriate for a lay audience describing the nature and purpose of the study and how EPA intends to use the data.
3. OPP's oral presentation should not focus on details. The Board believes that such detailed presentations distract from focusing attention on those aspects of the protocol for which OPP is eliciting Board feedback.
4. OPP's oral presentation on the science should not be a summary of the protocol, but a focused discussion of OPP's evaluation of why they think the study has sufficient scientific validity; the presentation should include questions regarding scientific validity that OPP wishes the Board to address.
5. OPP's oral presentation should also include a description of how the Agency plans to analyze and use the data.
6. Similarly, OPP's oral presentation should not focus on the details regarding the protection of human subjects as such details are described in the written materials. Rather, a brief oral presentation should identify those aspects of the design that OPP believes raise human subjects concerns.

AHETF and AEATF Comments at HSRB meetings:

1. Since the HSRB makes its recommendations to EPA and not directly to sponsors, it is the responsibility of the Agency to present the protocol to HSRB, along with EPA's critique and conclusions.
2. Sponsors have the opportunity to express their perspectives and clarify information during the public comment periods.
3. During Board discussion of protocols, sponsors should be available for additional clarifications that may be needed.
4. In addition, if sponsors believe that a specific point has not been adequately addressed they should have the opportunity to alert OPP to their concerns during the time allotted to the protocol; OPP in consultation with the Chair and DFO may recommend to the Board that the sponsor provide additional clarification on the issue(s).

EPA Review of AEATF-II Mop and Wipe Scenarios (due to similarities of the mop and wipe scenarios, both exposure scenarios were reviewed together)

Science

Charge to the Board

If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by mopping?

If the proposed research described in AEATF's proposed wipe scenario designs, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by wiping?

Board Response to the Charge

The two proposed human studies focus on handlers during floor mopping or surface wiping with a liquid antimicrobial pesticide product to determine potential dermal and inhalation exposures. The studies are (1) AEA03, "A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using Bucket and Mop Equipment for Cleaning Indoor Surfaces," and (2) AEA02, "A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product using Trigger Spray and Wipe or Ready to Use Wipes for Cleaning Indoor Surfaces." The protocols associated with these studies have many similarities. The Board's comments were therefore very similar for the two studies. All comments below can be applied to both studies, unless otherwise noted.

Study Objective

AEATF II stated that the primary purpose of the handler studies is to develop more accurate information on worker exposures to antimicrobials. AEATF II also presented information to indicate that existing human exposure data are inadequate. The Board concurred that existing data are inadequate and that the development of more accurate information is an appropriate goal.

Benefits and Risks

The Board concurred with the Agency that the generation of new data for mop and wipe activities would be of value in the assessment of risks for antimicrobial products. The Board concurred with the Agency that there are only minimal risks associated with the application of a dilute solution of didecyl dimethyl ammonium chloride (DDAC) as described in the study protocols.

Study Design Criteria

The Board was pleased by the amount of randomization included in the design of these studies. The investigators and the Agency have indicated that they are interested in knowing the statistical distribution of the exposure level, with an acceptable bound for the relative

accuracy of the estimated mean and 95 percentile. In both AEA03 (mop) and AES02 (wipe) studies, the same set of three sites will be used as clusters, each representing a random sample of one for three different types of buildings. In order to understand the spectrum of exposure, six volunteers will be randomly selected to fill each of six consecutive time durations. This configuration of three clusters of six handlers for each cluster is based on a simulation study under two-stage cluster sampling with an intra-class correlation coefficient of 0.3 and a geometric standard deviation (GSD) of 2.86. The sample size justification depends on these design parameters.

In an earlier mop study, conducted by the Chemical Manufacturers' Association (CMA), the estimated GSD was 3.53. It therefore appeared to the Board that the proposed AEA03 study design would not ensure three-fold relative accuracy (K=3) for the resulting estimated mean and the 95 percentile of the exposure distribution. Furthermore, in an earlier CMA wipe study the estimated GSD was 5.00, much larger than 2.86 assumed in the simulation study that was used to derive the sample size justification. Again, it appeared unlikely to the Board that the AEA02 study design would produce a three-fold relative accuracy for the resulting estimated mean and the 95 percentile of the exposure distribution.

The Board also noted that the stratified nature of selecting a cluster from each of three types of sites makes it impossible to assess the variability of exposure distribution from site to site. Likewise, because of the stratified nature of selecting one handler for each of six mopping/wiping durations, one cannot estimate the exposure distribution. The experimental design can be viewed as consisting of 18 design points with 18 data points, resulting in no degrees of freedom for estimation of variability as there are no replications at any design point.

In light of these concerns, the Board recommended that the Agency reconsider the design of the study, or develop an explicit statement of the limitations on the use of data that will be collected under the proposed design.

Site selection

The studies will take place in Fresno, California, in three buildings: an office building, a retail building, and a building with large meeting spaces. The way in which the clusters have been defined suggests that they represent a fixed effect factor (i.e., building type) rather than a random effect factor. The proposed study design will not replicate this fixed effect by having more of than one building of each type. The Board acknowledged the practical considerations that led to the decision to have both studies in the same city, using the same buildings. However, it must be realized that any generalizations to moppers and wipers in other parts of the country and in other kinds of buildings would be based on expert opinion, and that such generalizations would not be statistical generalizations. Nevertheless, the Board concurred with the Agency that some generalizations from these data would seem to be reasonable at this point in time.

Sample size

The proposed sample size of 18 observations for each scenario did not appear to have a statistical justification, as indicated above. The Board was concerned about recommending this sample size and the 3x6 design (three sites, six workers per site) on which it is based. The concern is that all that all future scenario designs for the AEATF- II program are likely to have three clusters and six time durations, with the justification being the Board's recommending these protocols. The Board has seen this happen with insect repellency studies repeatedly. That is, a new protocol has justified its sample size by reference to a previously submitted protocol. The adequacy of the proposed sample size for future studies will be informed by the data collection and analysis of this first set of studies. In general, the Board will not consider a new protocol that has justified its sample size by reference to a previously submitted protocol.

Task duration

AEATF-II's protocol for mopping proposed that handlers mop for a maximum of 90 minutes. This value was derived from a survey conducted by the International Sanitary Supply Association (ISSA). AEATF-II calculated an average mopping duration to 83 minutes from the ISSA study data. The Board understood that this value was calculated in the following manner:

- ISSA data indicated that handlers spend, on average, 12 minutes to mop 1000 square feet.
- It was assumed that a hospital room consists of a 240 square feet (12x20) main room and a 36 square foot (6x6) bathroom for a total floor area of 276 sq ft.
- It was assumed that a worker would mop 25 such rooms for a total of 6,900 sq feet.
- Thus, 6900 square feet x 12 minutes per 1000 square feet = 82.8 minutes

A similar calculation was made for the wipe scenarios, resulting in an estimated average wiping time of 212.75 minutes.

The Board concluded that the task duration time frame was not adequate to characterize daily exposure. The Board recommended that the work time frame be expanded to exceed the 95th percentile of the ISSA survey findings.

The Board also noted that the lengths of mopping (or wiping) would be consistently tested from the longest time period to the shortest time period for each site. For this to be a valid approach, one must be willing to assume that there is no "carry-over" effect from one testing period to another. One factor that could lead to a carry-over effect would be whether residues from earlier mopping (or wiping) could affect the measurements on later study participants, especially respiratory effects. The Board recommended that these concerns be reflected in the protocols.

The Board found the explanation of potential analyses that the Agency would conduct based on these studies to be very helpful. A basic assumption for these analyses is that the distribution of exposure/unit handled is the same regardless of the number of active ingredient (Ai) units handled or the time spent mopping (or wiping). However, the mean exposure/Ai

unit and/or variance of the exposure/unit is likely to increase with the number of units due to fatigue. This assumption could be at least partially checked by plotting exposure/Ai unit by Ai unit, though such an analysis might conflict with the second analysis identified: the assessment of the assumption of proportionality. A regression would likely be conducted for this second analysis. If the distribution of exposure/unit handled were constant or increased with the number of units handled and proportionality was demonstrated, then both the mean and the variance would be expected to increase with the number of units handled. In simple linear regression, the variance is assumed to be constant for all values of x. Thus, a weighted regression, not a simple linear regression would be needed. Because the protocol does not ensure that there will be replication of exposures for the same number of units, whether a simple or weighted regression would be more appropriate could not be fully evaluated. If, instead of time, the number of Ai units handled were the measure that defined each person's participation, the data would more likely lend themselves to a proper assessment of the assumption of proportionality.

Participation Criteria

AEATF plans to recruit subjects from among identifiable and willing professional janitors. A rationale for this decision was provided. AEATF also assumes that these professionals would have higher exposures than consumers. One Board member expressed the view that professionals have substantial experience and perhaps training in how to minimize exposure, and that consumers might have higher exposures per Ai unit handled. AEATF-II plans to recruit subjects through service providers. The Board suggested that unions also be considered in the development of the recruitment procedures.

Measurement Criteria

The Board noted that inhalation exposure from vapors would likely be low in these studies due to the relatively low volatility of the active ingredient used in the scenarios. However, the extent to which liquid aerosols generated in the mop protocol would contribute to aggregate exposure is not known. It was not clear what particle size range was expected to be generated in these studies, nor was it clear what particle size range would be captured by the sampling method. The Board suggested that a laboratory study that measured aerosol size under varying environmental conditions would be helpful in clarifying these uncertainties.

The following are key variables that will have an effect on inhalation exposure:

- Ventilation
- Temperature
- Total area treated
- Duration
- Volume of the enclosed space

The protocols state as follows: "light level, air temperature, and relative humidity of the work area for the duration of exposure monitoring will be documented with automated instrumentation logging and recording at intervals appropriate for the duration of the work period. Monitoring equipment will be calibrated or standardized according to the cooperating

contractors' SOPs. HVAC will be described in detail and the air turnover rate will be measured or estimated." The Board recommended that the equipment and procedures used to characterize these environmental factors be described in greater detail, either in the protocols or in the SOPs. The Board also asked investigators to explain how the effects of such factors as ventilation, temperature and the volume of the enclosed space would be used to modify or interpret study results.

AEATF-II proposed to use dermal exposure assessment methods similar to those used by the Agricultural Handler Exposure Task Force studies; i.e., cotton garments on most of the body, handwashing, and face/neck wiping. As in its previous reports, the Board noted that these methods have the potential to underestimate exposure. The Board supported the use of a double layer of socks to capture potential exposure from spills or splashes.

Laboratory and Field Conditions

The Board considered the quality assurance and quality control procedures that accompanied these protocols to be of high quality. The Board appreciated the attention to detail provided by the investigators.

The Board raised several concerns regarding field conditions.

These studies will use DDAC, contained in the product Sani-Care Lemon Quat™ as the chemical of interest. The Board agreed that the choice of DDAC as the antimicrobial material for these studies was appropriate, given its wide use, availability, and the existence of a reliable and sensitive analytical method.

The Board encouraged the Agency and the investigators to ensure that work activities be as realistic as possible. For example, a worker should use a bucket of the disinfectant solution until it becomes dirty; the worker should then empty the bucket and pick up a fresh bucket. All of this could be done without the involvement of study staff. In general, the Board viewed the activities of the study staff described in the current protocols to be too disruptive of "usual practices". The Board recommended that the protocols be revised to provide a more detailed description of what the workers will actually do, and that the presence of staff during the exposure period be kept to a minimum.

The Board was also concerned with what is sometimes called the "Hawthorne Effect". That is, workers will change behavior consciously or unconsciously when they are aware that they are being observed. The current protocols indicate that there will be constant surveillance of workers, including video recording. The Board urged the Agency and the investigators to minimize these observations and to train staff to be as unobtrusive as possible.

Finally, the Board requested that the protocol provide more specificity as to where study subjects will be located while waiting to participate in the study. There was a concern that observation of some study subjects by other study subjects could alter behavior.

HSRB Consensus and Rationale

The Board considered the AEATF-II study protocols to successfully address many design challenges. The Board appreciated particularly the clarity of the protocols, the attention to detail, and the thorough description of quality assurance and quality control procedures. The Board concurred with the Agency that existing data on handler exposures to antimicrobials are inadequate and that the development of more accurate information is an appropriate goal. The Board also concurred with the Agency that there are only minimal risks associated with the application of a dilute solution of didecyl dimethyl ammonium chloride as described in the study protocols.

While the Board concluded that the research could produce scientifically reliable data, the Board identified several contextual factors that may limit the generalizability of the findings. The Board recommended that the Agency reconsider the design of the study, or develop an explicit statement of the limitations on the use of data that will be collected under the proposed design. The Board noted that any generalizations to moppers and wipers in other parts of the country and in other kinds of buildings would be based on expert opinion, and that such generalizations would not be statistical generalizations. The Board cautioned the Agency regarding the 3x6 design in the protocols, suggesting future scenario designs for the AEATF- II program would likely have three clusters and six time durations, with the justification being the Board's recommendation of these protocols. The Board concluded that the task duration time frame was not adequate to characterize daily exposure. The Board recommended that the work time frame be expanded to exceed the 95th percentile of the International Sanitary Supply Association survey findings. The Board noted that if, instead of time, the number of Ai units handled were the measure that defined each person's participation, the data would more likely lend themselves to a proper assessment of the assumption of proportionality.

In regard to inhalation exposure assessment, the Board suggested that a laboratory study that measured aerosol size under varying environmental conditions would helpful in clarifying uncertainties regarding particle size and sampling methods. The Board raised several concerns regarding the field conditions for these studies: ensure that any carry-over effect in buildings is avoided; ensure that work activities be as realistic as possible; revise protocols to provide a more detailed description of what the workers will actually do; keep the presence of staff and intrusive observation of workers during the exposure period to a minimum; and, provide more specificity as to where study subjects will be located while waiting to participate in the study..

Finally, the Board encourages modifications of future related protocols based on the lessons learned from these initial submissions. Such adjustments are anticipated to improve the study design and subsequent results, leading to a more accurate characterization of pesticide handler exposure.

Ethics

Charge to the Board

If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation 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?

If the proposed research described in AEATF's proposed wipe scenario designs, protocol, and supporting documentation 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 to the Charge

Brief Overview of the Studies

Each of these scenarios (mop and wipe) has been designed to develop data for a database of exposure monitoring information which will be used by the EPA for making regulatory decisions about future exposures to a variety of antimicrobial products and their active ingredients. The sponsor of both scenarios is the Antimicrobial Exposure Assessment Task Force II (AEATF-II) of the American Chemistry Council. The scenarios will be conducted on behalf of that entity by Golden Pacific Laboratories, LLC, of Fresno, California. For each of the scenarios, there will be three field sites in Fresno, California.

According to the protocols, these studies are intended to comply with the ethical standards contained in 40 CFR Part 26, subparts K and L, in addition to the requirements of FIFRA § 12(a)(2)(P), and Title 3, § 6710 of the California Code of Regulations. Both scenarios were reviewed and approved by a commercial IRB, the Independent Investigational Review Board, Inc. (IIRB, Inc.) of Plantation, Florida.

For each scenario, the protocols include detailed explanations of how the buildings in which the scenarios take place will be chosen, how the subjects will be recruited, how the informed consent of those subjects will be obtained, and what will take place during the conduct of the scenarios.

Each of the protocols requires that the subjects be at least 18 years of age, and they exclude female subjects who are pregnant or lactating.

The test substance that will be used in both scenarios is diluted Sani-Care Lemon Quat. Its two active ingredients are didecyl dimethyl ammonium chloride (DDAC) and n-Alkyl dimethyl benzyl ammonium chlorides (ADBAC).

Critique of Studies

The Board concurred with the factual observations of the ethical strengths and weaknesses of the studies, as detailed in the EPA's Science and Ethics Reviews (Carley 2008a and 2008b).

In general, the research described in these two protocols appears to comport with the applicable requirements of 40 CFR Part 26, subparts K and L. The risks to study participants,

in general, will be minimal and would appear to be justified by the likely societal benefits, specifically the production of data that could be used by the EPA in determining acceptable exposures to antimicrobial products used in certain mopping and wiping activities.

The test compound contains two active ingredients, DDAC and ADBAC, both of which have been extensively tested in animals. The subjects will only be exposed to concentrations of the test compound at the label dilution rates. At those dilutions, animal testing has shown the compound to have low acute toxicity and a low chronic hazard profile. Both of the active ingredients have already been approved by the EPA for use in many formulations, and in many janitorial products. In addition, the test compound itself, Sani-Care Lemon Quat, has been approved by the EPA, and will only be used in the scenarios in conformity with its approved labeling. All of the subjects will be professional janitors with extensive experience in using these products, and thus unlikely to misuse them in a way that might increase their likelihood of being harmed.

Although the risks to subjects from exposure to the test compound appear very low, it should be noted that in terms of the purposes of these scenarios, it is not actually necessary that subjects be exposed to an antimicrobial product. The scenarios are intended to measure only the amount of skin, clothing and inhalation exposure when someone is engaged in certain activities relating to applying an antimicrobicide. They are not measuring the actual effects to the test subject from that exposure. Thus, it might be possible to design scenarios in which instead of an antimicrobicide, some less toxic tracer substance might be used. It would be appropriate for protocols to discuss this possibility for further minimizing risks, and to indicate why (if it is true) such an option would not allow the needed information to be collected.

Another possible risk is that of heat-related illness, given that the subjects will be required to wear two layers of clothing during the scenario activities. That risk is being minimized by the fact that those activities will take place indoors in temperature-controlled environments. In addition, subjects will be given appropriate breaks. The breaks will not only minimize the likelihood of heat-related illness, but also reduce the likelihood of cardiovascular harms.

With regard to subject selection, EPA observed that “[n]o potential subjects are from a vulnerable population” (Carley 2008a and 2008b). In this regard, it should be noted that 45 CFR § 46.111(b) states that “economically or educationally disadvantaged persons” may constitute a vulnerable population. Accordingly, given that this study is recruiting from a population of individuals who may not have substantial education, who may be relatively disadvantaged from an economic viewpoint, and many of whom may not speak or read English, it would be appropriate not to dismiss the possibility that the subjects in this study might be vulnerable to coercion and undue influence, but rather to instead recognize that there are sufficient safeguards in the design of the study to protect the subjects, even if they are vulnerable.

The study protocols included several mechanisms designed to minimize coercive recruitment and enrollment, including the fact that subjects were not recruited directly from their employers, but instead would themselves respond to flyers that have been posted.

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 under the age of 50 to undergo a urine pregnancy test). 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.

With regard to the eligibility criteria, the Board believes that the requirement for females under the age of 50 to take a pregnancy test could be refined. It would be possible to design criteria that created a better fit between which female subjects might be able to get pregnant, and which of them are being asked to take that test. By doing this, the researchers would be showing greater respect for this group of subjects.

The protocol might provide a greater justification for why subjects older than 65 are excluded.

Most of the issues raised by the Board relate to informed consent and recruitment. With regard to the consent forms, as a general matter, given the population from which subjects are being recruited, it would be appropriate to make sure that the consent forms are at an appropriate level of readability. In at least some places, there appears to be room for further simplification.

The consent forms do not appear to describe adequately the procedures discussed in the protocol relating to (a) still photography of the subjects, (b) videotaping of the subjects, and (c) observation of the subjects by members of the study team. All of these procedures pose possible risks to the privacy and confidentiality of the subjects. The fact that each of these procedures will be part of the protocols should be adequately explained in the consent forms. That explanation should include the details relating to who will be observing and who will be taking the photographs (e.g., members of the study team, outside contractors, other subjects). In addition, both the protocol and the consent forms should explain what procedures will be in place to make sure that the photographs and videos will be stored in a way that adequately protects both the confidentiality and the privacy of the subjects, and explains what harms to subjects might result if those protections are not adequate. If subjects will be accorded the right to opt out of being photographed, that should be explained in the consent form.

In the Purpose section of the consent form, it should be explained that the underlying purpose of the study will be to collect information that will be provided to the EPA, and that the EPA would use that information to determine the appropriate standards for allowable exposures to products such as the test compound.

The consent form in one instance (the paragraph numbered 4 under Study Procedures) uses the term "same-sex person." That confusing term should be replaced with the descriptions used elsewhere in the form, such as "a researcher of your own sex."

In the description of risks to subjects from exposure to the test compound, it is merely stated that the risks are low. If there is a known risk from getting the compound in a person's eyes, for example, that risk should be explained.

The approved version of the consent form, under the Pregnancy Risks heading, begins with "We don't know the risks to the unborn from exposure to SANI-CARE LEMON QUAT **and may be hazardous** . . ." There is a word or words missing in this sentence, and it therefore needs to be revised. More significantly, the "and may be hazardous" language differs from the language that appears in the versions of the consent forms submitted to the IRB by the researchers. The Board was not able to determine how this change in language took place. There is not documentation that the IRB asked for the change, or that the change was initiated by the researchers themselves, and that they submitted a copy of the consent form with this change to the IRB. This circumstance raises some concerns regarding whether the EPA was provided with the full documentation of what went on during the IRB approval process. The Board believes it would be appropriate for the EPA to determine how this change occurred. In addition, some members were concerned that this lack of documentation might relate to the operation of IIRB, Inc., which might reinforce prior Board concerns about the operation of that IRB.

With regard to the recruitment brochure, it would appear appropriate for that document to mention that the product which will be used in the study is Sani-Care Lemon Quat. At the beginning of that document, it fails to mention that the study will look not only at how much of the product "gets on" the workers, but also how much of it they inhale. Under the eligibility criteria, it states that subjects must be "Male or non pregnant, non or nursing female." This language needs to be corrected. And in the last sentence, the brochure incorrectly states that the EPA will use this information to reduce risks to workers. The statement should be revised to more accurately state the EPA will use the information to determine how much of the product workers will be exposed to; it is not true that it will necessarily lead to a reduction in risks to workers.

The phone texts that are used for calls to employers, and for calls to workers making inquiries, fail to mention that the study will be looking at inhalation risks in addition to risks relating to getting the compound on the worker's skin and clothing.

With regard to recruiting and obtaining the informed consent of Spanish-speaking persons, the Board agrees with the changes recommended by the EPA (Carley 2008a and 2008b). It would also be appropriate for the protocol to include a more detailed discussion of how the researchers will obtain appropriate community involvement (such as, for example, discussions with unions representing janitorial workers).

With regard to the translations into Spanish of the various documents, the Board believes that it is important to make sure that the appropriate dialect of Spanish is being used in he translations. The translation of the consent form, for example, was provided by someone from Miami, Florida, yet the study will be taking place in California. The Spanish-speaking communities in Miami and California might well use significantly different dialects of Spanish.

It was also not clear from the documents who was producing the Spanish-language version of some of the materials, such as the recruitment brochure.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that if the proposed mop and wipe scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, the research does appear to meet the applicable requirements of 40 CFR part 26, subparts K and L.

ICR Protocol: A382

Science

Charge to the Board

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 stable flies?

Board Response

Protocol A382 outlined a laboratory test to evaluate the efficacy of picaridin against stableflies when applied dermally as a 20% cream or spray product. The purpose of the study was clearly defined (i.e., efficacy testing), and the use of human subjects was adequately justified. Briefly, the proposed study will involve a total of 13 subjects, 12 of whom are designated for treatment with the picaridin spray and cream, with one additional subject designated as the negative control. The negative control will be selected at random and serves to establish the aggressiveness of each cage of stable flies to be used in the test. The first phase of the planned study will determine the average dose applied under normal use conditions, but will not exceed 4 mg/cm^2. The second phase of the study is the repellency test in which subjects' arms will be treated with measured amounts of both products (one product on each forearm), after which they will expose their treated forearms to stableflies for a 5 minute period every half hour for up to 10 hours. The submitted protocol proposed to use the time to first confirmed bite on both arms (both products) as the quantitative measure of repellent efficacy. The Sponsor provided a thorough statistical justification for the protocol design, including the determination that a minimum of 7 subjects would be required to achieve a 95% confidence interval for assessing protection up to 8 hours with a $\pm$ 2-hour confidence limit.

There was general consensus that the protocol was well written and a sound scientific rationale was provided. There were several minor issues that were identified during the course of the HSRB discussion, representing issues that can easily be addressed in a revised protocol. These included: (1) clarifying the protocol to specify that there are 13 subjects, representing 1 negative control and 12 treated individuals; (2) providing some information as to what activities are permitted during the 25 minute intervals when subjects are not actively on test and specifying what activities are precluded by being involved in the test; (3) ensuring the

accuracy of the margin of exposure (MOE) assuming a maximum application rate of 4 mg/cm^2 ; and (4) recommending that the Sponsor design the test to randomize the treatment modalities (spray or cream) on the left and right arms and to ensure that the professional staff involved in the conduct of the study are blinded to the treatments. The HSRB recommends that these modifications should be made to the protocol and study conduct.

There were however, three additional matters concerning the protocol design for which there was additional board discussion and more significant changes recommended to the proposed study. These issues were as follows:

1. It was noted during the Board's discussion that the Sponsor specified that the subject pool was exclusively Caucasian. There was concern as to whether the results obtained from such a constrained population could be generalized to other races, and there was a minority, but strongly voiced opinion that the protocol was not scientifically sound given this limitation. The HSRB recommended that the subjects used in this study should not be homogeneous, but rather, that there should be diversity across the subjects used for the test. The Board did not provide a specific recommendation on how diverse the test population should be, but suggested that, at a minimum, it should reflect the diversity of the region from which the possible subjects are drawn. The Board agreed that the Sponsor must address this scientific issue prior to executing the study.

2. OPP staff recommended that a positive control be used in this study, suggesting that it would improve the overall scientific validity of the test. In its discussion, the HSRB concluded that the inclusion of a positive control was not essential to the protocol, and the Board recommended against requiring a positive control in the study.

3. The protocol was designed to evaluate repellent efficacy using the accepted paradigm of time to first confirmed bite for each treatment (cream or spray product). As such, this design would result in a total of 4 bites per subject upon loss of repellency (first bite to be followed by a confirming bite for each treatment). In consideration of the biology of stable flies, there was general consensus among the HSRB that the study would be scientifically valid if the time to first bite, requiring only one bite per treatment, was used as the endpoint for evaluating the efficacy of the repellent.

HSRB Consensus and Rationale

If amended in a manner consistent with the Board's concerns and recommendations, and with particular modification to subject ethnicity, the protocol ICR A382 studying the efficacy of two formulations of picaridin for repelling stable flies would be sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of these formulations against stable flies.

Ethics

Charge to the Board

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

The Board concurred with the factual observations of the ethical strengths and weaknesses of the proposed study, as detailed in the EPA's Science and Ethics Review (Carley and Sweeney 2008).

Overall, this is a well written protocol, consent document, and application, answering many of the questions that HSRB has asked when reviewing in other studies. The risks to study participants were minimal and were justified by the likely societal benefits, including data on the efficacy of these new formulations as repellents against stable flies.

The 20% concentration of picaridin in the products to be used in this study is "higher than the marketed and EPA-registered formulation." Based on toxicological data currently available, however, picaridin has low acute toxicity. The potential risks include irritation or allergic response to the product. Individuals known to be sensitive to insect repellents or skin care products are excluded from the study. In addition, subjects will be monitored for signs of reaction to the products during the dosimetry portion of the study as well as during the repellent phase of the study.

While stable fly bites are acutely painful, the flies are not known to transmit any diseases to humans. Individuals known to be sensitive to stable fly bites are excluded from the study. Topical lotions and rubbing alcohol will be available to subjects to help relieve the itching from the bites.

The study protocol also included several mechanisms designed to minimize coercive recruitment and enrollment, compensation ($11/hour, time-and-a-half over 9 hours) was not considered to be so high as to unduly influence participation, and minors and pregnant or lactating women were explicitly excluded from enrolling (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test "shortly before any treatment with a test article"). The potential stigmatization resulting from study exclusion was minimized by the use of 'alternate' participants, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

Several ethical issues were raised, and can be categorized as they relate to the Belmont Principles of Respect for Persons, Beneficence and Justice. The Board concluded that all of the issues could be addressed with additional explanations or minor protocol modifications. Concerns were raised relating to the Justice principle. Subjects greater than 70 years of age are excluded without adequate justification. Subjects who cannot "read, speak, and understand English" are also excluded, without a description of how that will be assessed or a justification of why reading English is required for this study. The recruitment pool of potential subjects is overwhelmingly Caucasian. While ICR will "look for recruits from the Afro-American

community," there are no plans presented to assure racial/ethnic diversity of the study population, which would be more appropriate given that these products, if marketed, will be marketed to the general diverse population.

Issues related to the Respect for Persons principle include the requirement that women not of child-bearing potential, such as women who have had a hysterectomy or who are post-menopausal, are nevertheless required to undergo a pregnancy test. Some HSRB members found this disrespectful, but a minority of other members did not.

While most issues related to the Beneficence principle were addressed, the question of whether or not the stable flies to be used in this study would be given bovine blood at any time prior to the study remained unanswered. Because bovine blood carries with it a potential risk to humans of Creutzfeld-Jacob disease or exposure to bovine leukemia virus, the Board recommended that this question of whether or not the stable flies would receive bovine blood prior to their opportunity to bite human volunteers and the attendant risks be addressed. In addition, the scientific issue of using unblinded ICR staff to measure the outcome variable (stable fly bites) may jeopardize the scientific validity of the study, and thus alter the risk-benefit assessment. The HSRB recommended randomizing which product is applied to which arm, and using a blinded evaluator to measure the outcome variable.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that, if the protocol is revised as suggested by EPA and the HSRB, the study submitted for review by the Board meets the applicable requirements of 40 CFR 26, subparts K and L.

Carroll-Loye Biological Research Completed Studies: SCI 001.4 and SCI 001.5

Science

Charge to the Board

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

Board Response

The active ingredient DEET in two lotion formulations was tested for its ability to repel mosquitoes from the arms of volunteers by the protocol presented and modified by Carroll-Loye in two separately described studies which were conducted simultaneously using common sites and negative controls. This was a repeat of two products previously tested but not accepted for ethical reasons at the October, 2007, HSRB meeting. The protocol had been modified based on the suggestions and input of EPA and HSRB. The results were reported in SCI.001.4, DermaAegis LipoDEET 302, and SCI.001.5 Coulston's Duranon. The results on these two products were not compared to a positive control substance nor to one another. Because of the common elements between the two studies, they are discussed together in this

report. All experiments were conducted using Good Laboratory Practices. Margins of exposure were high.

The dosimetry for the two products was done in the laboratory on November 7-9, 2007. The field tests were conducted on November 10, 2007, at Site 1 in Glenn County, a forest habitat, and on November 11, 2007, at Site 2 in Butte County, a grassland habitat, both in California. Slightly different mosquito species composition occurred at the two sites, but overall the species composition of the two sites was similar. Ten subjects were used for the dosimetry tests. Ten subjects were used for each of the two products. The subjects were required to be above 18 years of age and no more than 55 years of age, and active in rural outdoor settings. Only arms were tested in this study. There were two experienced persons serving as negative controls (i.e., without any repellent product) to confirm mosquito landing pressure (and landing pressure was maintained throughout the period of the study, defined as at least one Landing with Intent to Bite, LIBe, per min during the period of exposure). LIBe's were monitored in experimental subjects during a one min interval each 15 min, until the First Confirmed LIBe (FCLIBe) could be determined. Stopping rules were employed. No evidence of West Nile Virus was present in either test site from sentinels prior to conduct of the study. Mosquitoes landing were taken to the laboratory for later identification, and for screening for West Nile, Western Equine Encephalitis, and St. Louis Encephalitis viruses, and all mosquitoes were negative. All subjects wore Tyvek coverall, head nets and surgical gloves. Observation was initiated 150-180 minutes post application. Complete protection time (CPT) was measured, defined as the time to the FCLIBe. The data were presented as mean ± standard deviations. Because of the low number of repellency failures observed, a Kaplan-Meier analysis (suggested at previous HSRB meetings) was not conducted.

LipoDEET 302 is 30% DEET on lipid spheres designed to improve the durability and to improve the cosmetic properties. It yielded a CPT of 11.25 ± 0.0 hr in Site 1 (no repellency failures) and 11.28 ± 0.79 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. It yielded a CPT of 11.25 ± 0.0 (no failures) in Site 1 and 10.78 ± 1.3 hr in Site 2.

The report was clearly written. 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, none of which negatively impacted the scientific validity. Discussion was related to a lack of positive control (this was not considered a flaw and did not impact the usefulness of

the data); the deviation of a lag time between application of the repellants and the initiation of monitoring (this was probably related to the short day length available for testing in November and the necessity of applying the repellant early to assure a sufficiently long observation period before dark); and the allowance of an application of repellant on the day before the study (it was clarified in the previous HSRB meeting that the repellant was washed off after dosimetry or testing, and the target skin was washed again prior to a new study, thereby insuring that there was no carry-over to compromise data).

HSRB Consensus and Rationale

The Board concluded that the study on the efficacy of LipoDEET 320 and Coulson's Duranon shows efficacy of both products in repelling mosquitoes, and agreed with the Agency that the study was sufficiently sound, from a scientific perspective, to be used to accurately calculate the CPT for repelling mosquitoes.

Ethics

Charge to the Board

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?

Board Response

Brief Overview of the Study

The basic protocol for these studies (SCI-001) was initially reviewed at the January 2007 HSRB meeting, 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. Most, although not all, of these suggestions were incorporated into a revised protocol, submitted to the IRB of record (Institutional Review Board, Inc., [IIRB, Inc.] of Plantation, FL) for re-review, and approved (Carley 2008; Carroll 2008).

Using the revised protocol and consent documents for SCI-001, Carroll-Loye Biological Research conducted dosimetry and field trials of three compounds in July 2007: DermAegis LipoDEET 302, DermAegis LipoDEET 3434, and Coulston's Duranon Personal Insect Repellent. At the October 2007 meeting of the HSRB, the Board recommended that the data obtained in July under protocol SCI-001 not be accepted for regulatory decision-making purposes (EPA HSRB 2007). The Board concluded that the use of a previously unapproved pesticide formulation (DermAegis LipoDEET 3434) violated the applicable requirements of 40 CFR Part 26.

The data presented to the Board in April 2008 represents the results of new dosimetry and field trials of two compounds in November 2007: DermAegis LipoDEET 302 and Coulston's Duranon Personal Insect Repellent. The documents provided by Carroll-Loye

(Carroll 2007a; Carroll 2007b) specifically state that each study was conducted in compliance 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, Inc. Documentation provided to the EPA by IIRB, Inc. indicates that it reviewed these studies pursuant to the standards of the Common Rule (45 C.F.R. Part 46, Subpart A) and determined them to be in compliance with that Rule.

As submitted to the EPA, each completed study consists of two interdependent analyses: 1) a dosimetry study designed to determine the amount of an insect-repelling compound (30% 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. The two studies, SCI-001.4 and SCI-001.5, 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 was manufactured and supplied by DermAegis, Inc. of Rockford, Illinois; Duranon was manufactured and supplied by Sawyer Products of Safety Harbor, Florida.

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 whom tested both formulations. Each efficacy study enrolled 10 subjects for each formulation at each of the two field sites. Many volunteers participated in multiple analytic phases, both dosimetric and effective. In total, 29 volunteers participated in at least one analytic phase of SCI-001.4 and SCI-001.5. 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 of Study

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA’s Science and Ethics Review (Carley 2008).

In general, the research described in SCI-001.4 and SCI-001.5 comported with the applicable requirements of 40 CFR Part 26, subparts K and L. 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% DEET in liposomal capsules and 20% DEET in protein capsules) as personal insect repellents.

Based on toxicological data currently available for DermAegis LipoDEET 302 and Coulston's Duranon Personal Insect Repellent, compounds registered with the EPA, the subjects enrolled in this study were unlikely to be at increased risk of experiencing adverse side effects upon exposure. Higher concentrations of DEET are commercially available and have been used as repellents for years.

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 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 West Nile Virus, 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.

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 compromising their confidentiality. There was some question as to the appropriate timing of such testing (Carley 2008), but no female participant was exposed to product without first undergoing pregnancy testing. Future trials conducted by Carroll-Loye Biological Research, however, should use protocols and informed consent documents that explicitly outline the nature and timing of pregnancy testing for female participants.

Several Board members raised ethical and procedural concerns about the numerous protocol changes present in the documents submitted to the EPA (Carroll 2007a, 2007b) but which were not presented to the Board prior to the conduct of the study. For example, in its initial review of Protocol SCI-001 in January 2007, the HSRB approved a protocol that involved the experimental administration of four compounds (three sponsor-submitted test compounds and one comparator [3M Ultrathon; 34.34% polymerized DEET]). The study, as completed, used only two test compounds and no comparator. Many HSRB members

considered this to be a major change in study design, a change to which the Board was unaware until the study was completed and the data submitted for review. In light of these concerns, the Board recommended that the EPA review existing regulations and establish clear guidelines as to when modified protocols should be submitted to the Board for re-review.

Finally, several Board members also voiced concerns about the type and nature of the protocol deviations reported by Dr. Carroll to IIRB, Inc. Many of these same deviations have occurred in completed studies previously submitted to the Agency and the Board for review, raising questions about the unanticipated nature of these protocol changes. It is clearly stated in Federal regulations for research involving human subjects that the only protocol changes that can be made without prior IRB approval are those that are unanticipated and which are necessary to protect the safety of trial participants. No protocol changes, reported or not, are allowed for reasons of expedience, as appeared to be the case here.

HSRB Consensus and Rationale

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

Board Decision Regarding Future Review of Protocols with Planned Deviations from Prior IRB Review

Over several meetings, including the April 2008 meeting, the Board has expressed concern with EPA submission for HSRB review of completed studies in which planned protocol deviations were conducted prior to IRB review and following HSRB review of the originally approved protocol. Such actions are in violation of 40 CFR 26, Subpart K Sec. §26.1108 IRB functions and operations.

Subpart K Sec. §26.1108 IRB functions and operations.
"In order to fulfill the requirements of this subpart, each IRB shall:
(a) Follow written procedures:
(1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;
(2) For determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;
(3) For ensuring prompt reporting to the IRB of proposed changes in research activity; and
(4) For ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects."

The Board reached consensus regarding its future review procedures under such conditions:

1. Any study executed prior to IRB approval of the Informed Consent Form and the protocol, or changed in ways that were not approved by the IRB will be judged by the

Board as failing to meet the applicable requirements of §40 CFR 26, subparts K.

2. If the EPA submits to the Board for review a completed protocol with scientific deviations from the original protocol reviewed by the Board, the EPA review of the completed protocol should provide the Board with EPA's opinion regarding why the deviation did not meet the requirement for re-review and why the protocol still meets the applicable regulations.

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