EPA-HSRB-10-02

Paul Anastas, PhD
EPA Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: October 27-28, 2010 EPA Human Studies Review Board Meeting Report

Dear Dr. Anastas,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of two new and one revised protocols for studies involving intentional exposure of human subjects to pesticides: a proposed Carroll-Loye Biological Research, Inc. (CLBR) insect repellent efficacy study (No Mas-003); a proposed Agricultural Handler Exposure Task Force, LLC (AHETF) scenario measuring dermal and inhalation exposure by pesticide applicators who use backpack sprayers or hand gun sprayers in utility rights-of-way (AHE-400); and a revised AHETF water-soluble packaging mixing and loading scenario and protocol (AHE-120) previously reviewed by the HSRB in June 2009.

The Agency also requested that the HSRB review a completed study of dermal and inhalation exposure of professional janitorial workers who clean floors with an antimicrobial pesticide product using a mop and bucket, conducted by the Antimicrobial Exposure Assessment Task Force II (AEATF II). This study (AEA-03) was conducted after publication of the EPA's expanded final rule for protection of subjects in human research (40 CFR 26) on February 6, 2006 (71 Federal Register 24, 6137). The data will be posted to the Biocide Handlers Exposure Database (BHED®), and used generically to estimate daily dermal and inhalation exposures of those who clean floors with antimicrobial pesticides using a mop and pail.

The enclosed report provides the Board's response to EPA charge questions presented at the October 27-28, 2010 meeting.

Assessment of Proposed Carroll-Loye Biological Research Study No Mas-003: Field Efficacy Test of 16% Para-menthane-3,8-diol (PMD) and 2% Lemongrass Oil Based Repellent 'No Mas' Against Mosquitoes.

Science

- The Board concluded that the protocol for the proposed field repellency study, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, is likely to generate scientifically reliable data, useful for assessing the efficacy of the tested material in repelling mosquitoes.

Ethics

- The Board concluded that the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

Assessment of Proposed AHETF Scenario and Protocol AHE-400: Backpack and Handgun Application of Liquid Sprays in Utility Rights-of-Way.

Science

- The Board concluded the proposed backpack and handgun application scenario, if revised as suggested and performed as described, is likely to generate scientifically reliable data that may be useful for assessing the exposure of workers who apply pesticides in utility rights-of-way using backpack or handgun sprayers.

Ethics

- The Board concluded that the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

Assessment of Revised AHETF Scenario and Protocol AHE-120: Water-Soluble Packaging Mixing and Loading.

Science

- The Board concluded the submitted protocol, if revised as suggested and performed as described, is likely to generate scientifically reliable data that may be useful for assessing the exposure of workers who mix and load pesticides in water-soluble packaging.

Ethics

- The Board concluded that the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

Assessment of Completed AEATF II Research Study AEA-03: 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 (MRID 48210201, MRID 48231201, MRID 48231901).

Science

- The Board concurred with the Agency's assessment that the research reported in the completed AEA-03 study report and associated supplemental documents was conducted

in a manner that was reasonably faithful to the design and objectives of the protocol and governing documents of AEATF-II.

- The Board concluded that the Agency has adequately, if not completely, considered the limitations on these data that should be considered when using the data in estimating exposure of those who apply antimicrobial floor-cleaning products with mop and bucket.

Ethics

- The Board concurred with the Agency's assessment that the study submitted for review was conducted in substantial compliance with subparts K and L of 40 CFR 26.

- In response to a request from the study sponsor for guidance on how to provide individual exposure data to participants once the study is complete, the Board elected to establish a working group that could draft proposed guidance for the Agency and sponsors, which would be reviewed by the full Board during a future HSRB meeting.

Sincerely,

Sean Philpott, PhD, MSBioethics
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. You may obtain further information about the EPA Human Studies Review Board from its website at http://www.epa.gov/osa/hsrb. You may also contact the HSRB Designated Federal Officer, via e-mail at ord-osa-hsrb@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.

US ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD

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Jim Downing, Executive Director, Human Studies Review Board Staff, Office of the Science Advisor, United States Environmental Protection Agency, Washington, DC

INTRODUCTION

On October 27-28, 2010, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning two new protocols and one revised protocol for research involving human participants: one new study measuring the efficacy of an insect repellent containing para-menthane-3,8-diol (PMD) and lemongrass oil against mosquitoes under field conditions; one new study measuring levels of exposure received by agricultural handlers when applying commercially-available pesticides using backpack sprayers or hand gun sprayers in utility rights-of-way, and a revised study measuring levels of exposure received by agricultural handlers when mixing and loading pesticides using water-soluble packaging under various conditions. In accordance with 40 CFR 26.1601, EPA sought HSRB review of these three proposed protocols. Each of these protocols is discussed more fully below.

In addition, the Agency has data from one completed study measuring levels of exposure received by janitorial workers when applying a commercially-available antimicrobial pesticide using a mop and bucket. In accordance with 40 CFR 26.1602, EPA sought HSRB review of this completed study. This completed study is discussed more fully below.

REVIEW PROCESS

On October 27-28, 2010, the Board conducted a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the Federal Register as "Human Studies Review Board; Notice of Public Meeting" (75 Federal Register 193, 61748).

Following welcoming remarks from Agency officials, the Board heard presentations from EPA on the following topics: one new study protocol to measure the efficacy of an insect repellent containing PMD and lemongrass oil against mosquitoes under field conditions; one new study protocol for measuring levels of exposure received by agricultural handlers when applying commercially available pesticides using backpack sprayers or hand gun sprayers in utility rights-of-way, and a revised study protocol measuring levels of exposure received by agricultural handlers when mixing and loading pesticides using water-soluble packaging under various conditions. In addition, a completed study for the measurement of potential dermal and inhalation exposure during application of a liquid antimicrobial pesticide product using a bucket and mop was reviewed.

The Board asked clarifying questions of several individuals attending the meeting, including:

Dr. Victor Cañez, Technical Chair, Agricultural Handler Exposure Task Force
Dr. Scott Carroll, Study Director, Carroll-Loye Biological Research
Mr. Shawn King, Director of Operations, Carroll-Loye Biological Research
Mr. Robert Roogow, Chief Operations Officer, Independent Institutional Review Board, Inc.
Dr. Sami Selim, Study Director, Selim & Associates

Public comments were provided by:

Dr. Victor Cañez, Technical Chair, Agricultural Handler Exposure Task Force
Dr. Scott Carroll, Principal, Carroll-Loye Biological Research
Dr. Hasmukh Shah, Manager, AEATF

No written public comments were submitted.

For their deliberations, the Board considered the materials presented at the meeting, oral comments, and Agency background documents (e.g., published literature, sponsor and investigator research reports, study protocols, data evaluation records, and Agency science and ethics reviews of proposed protocols and completed studies). A comprehensive list of background documents is available online at http://www.regulations.gov.

CHARGE TO THE BOARD AND BOARD RESPONSE

Assessment of Proposed Carroll-Loye Biological Research Study No Mas-003: Field Efficacy Test of 16% Para-menthane-3,8-diol (PMD) and 2% Lemongrass Oil Based Repellent 'No Mas' Against Mosquitoes.

Overview of the Study

This protocol describes a study to test the repellent efficacy of a lotion formulation containing 16% PMD and 2% lemongrass oil ('No Mas') against three species of mosquitoes in the field. As submitted to the EPA, the proposed study consists of two interdependent analyses: 1) a dosimetry study designed to determine the amount of lotion that typical users would typically apply; and 2) an efficacy study designed to measure the effectiveness of the compound as a repellent for those species of mosquitoes likely to be vectors for West Nile Virus (WNV) in the United States.

Dosimetry will be determined by direct measurement of compound application. The efficacy of the formulation as a mosquito repellent will be determined by measuring the ability of the formulations to prevent mosquito landings under field conditions at test sites in California's Central Valley. The efficacy study endpoint will be the "Landing with Intent to Bite" (LIBe), and the criterion for data to calculate complete protection time will be the first confirmed LIBe.

Science

Charge to the Board

If the proposed field repellency study protocol No Mas-003 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested material in repelling mosquitoes?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment that the proposed field repellency study protocol No Mas-003, if revised as suggested in EPA's review (Fuentes and Sherman 2010) and performed as described, is likely to generate scientifically reliable data, useful for assessing the efficacy of the tested material in repelling mosquitoes.

HSRB Detailed Recommendations and Rationale

Protocol No Mas-003 from Carroll-Loye Biological Research (Carroll 2010) will be conducted using methods similar to those presented to and commented on by the Board in the past. Apart from the new test material, the proposal is generally similar to previous Carroll-Loye field studies reviewed by the Board.

The study protocol was relatively clear and addressed adequately a number of key scientific issues, including: scientific justification, objectives, and data collection and compilation methods. The Board concurred with the Agency's assessment that the proposed field repellency study protocol No Mas-003 is likely to generate scientifically reliable data, useful for assessing the efficacy of the tested material in repelling mosquitoes. In addition, the Board recommended two minor changes to the protocol and associated study documents. First, the protocol should be amended to remove erroneous reference to spray repellents (e.g. the first sentence on page 79, under "Rationale"; Carroll 2010, 79). Second, the Board agreed with the Agency that reference to sample size standards is now irrelevant in light of recently released repellency testing guidelines. Rather than refer to a historical standard of 6 study participants, the proposed sample size should be large enough to be likely to yield a definitive answer to the research question and its size justified statistically in the protocol.

Ethics

Charge to the Board

If the proposed field repellency study protocol No Mas-003 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

HSRB Recommendation

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Fuentes and Sherman 2010) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendation and Rationale

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 the US EPA's Good Laboratory Practice (GLP) Standards described at 40 CFR 160, and the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (Carroll 2010). Requirements of FIFRA §12(a)(2)(P) also apply. The protocol was reviewed and approved by an independent human subjects review committee, Independent Institutional Review Board (IIRB), Inc. of Plantation, FL prior to submission. IIRB, Inc. is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). IIRB is also listed as an active Institutional Review Board (IRB) on the Office of Human Research Protection (OHRP) website (Reg. #IORG0002954). Minutes of IIRB, Inc. meetings (Carroll 2010) and a copy of IIRB, Inc. policies and procedures were provided to the Agency. These documents indicate that IIRB, Inc. reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

1. Except as noted below, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Fuentes and Sherman 2010). The proposed study is likely to meet the applicable ethical requirements for research involving human subjects, in accordance with the following criteria:

    a. Acceptable risk-benefit ratio. The risks as noted in the study protocol are fivefold: 1) allergic reaction to test materials themselves; 2) exposure to biting arthropods; 3) possible exposure to arthropod-borne diseases; 4) physical stress from the test conditions; and 5) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are justified by the potential societal benefits associated with data on the efficacy of the active ingredients, PMD and lemongrass oil, as mosquito repellents.

        - Based on toxicological data currently available for PMD and lemongrass oil, coupled with appropriate exclusion criteria, study participants are unlikely to be at risk of adverse side effects with exposure.

        - The study is designed to minimize the likelihood of mosquito bites, through the use of: LIBes rather than actual confirmed bites as a study endpoint; bite removal and joint observation; clear stopping rules; and limited periods of exposure to mosquitoes. Study participants will be trained in proper insect observation and handling techniques.

        - Mosquito bites, should they occur, are usually mild and easily treated with over-the-counter steroidal creams. The study will also exclude participants who have a history of severe skin reactions to such bites.

- Possible exposure to vectors of arthropod-borne diseases is minimized through the use of certified disease-free laboratory-reared insect populations, selection of field sites in low virus areas, and limited skin exposure.

- The potential risks to participants from environmental stress are minimized by the provision of a climate controlled rest area, food, water and medical supplies, and by careful monitoring for signs of dehydration, heat stress and hypothermia. Appropriate stopping rules and medical management procedures are in place.

- Minor and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. Only volunteers scored as non-pregnant will be allowed to participate. Information regarding pregnancy test results will be kept confidential.

b. Voluntary and informed consent of all participants

- There is the possibility that the participants in this study might represent particularly vulnerable populations, susceptible to coercion and undue influence. The study protocol, however, includes several mechanisms designed to minimize coercive recruitment and enrollment.

- The informed consent materials, if changed as recommended by the HSRB below, will adequately inform the subjects of the risks, discomforts and benefits from participation, and of their right to withdraw.

- Monetary compensation is not so high as to unduly influence participants.

c. Equitable selection of study participants

- The majority of research participants will be recruited from the University of California at Davis student population. Study participants are likely to represent the appropriate ethnic and racial diversity of individuals in and around the University, but the use of this convenience sample may limit the broad applicability of the study results to the general population. The investigators have noted this fact in the protocol (Carroll 2010).

2. The Board recommended that the study protocol be modified to address the concerns noted in the EPA's Ethics Review (Fuentes and Sherman 2010). In addition, the Board also raised the following concerns:

- The Board concurred with the Agency's recommendation that the protocol be revised to exclude as participants employees of the study sponsor. The Board added the recommendation that this exclusion also be extended to dependents of the study sponsor or sponsor employees.

- The consent form and protocol should be modified as follows:

1) Carroll-Loye should add "child/minor" to the list of exclusion criteria.

2) The term "treatment" is used ambiguously throughout the protocol and informed consent form to describe both the application of the test materials and treatment for research-related injuries. For example, on page 23 the protocol states that "application of a test material is considered a treatment" (Carroll 2010, 23). Elsewhere, however, the protocol states that "candidates are again encouraged to ask any questions they have about the study, which may include understanding … treatment and compensation for injury more fully" (Carroll 2010, 17, 238). This ambiguity should be resolved with the use of a different term to describe the application of test materials.

3) On page 16, the protocol states that "…dosimetry subjects may be consented before repellency subjects. Untreated control subjects for the repellency phase (field study) are consented before the treated subjects for that phase…" (Carroll 2010, 16). The verb "to consent" is an intransitive verb; from a grammatical point of view, someone cannot "be consented." From an ethical perspective, this infelicitous use of the verb also employs the passive voice, which is not best practice when the issue is to affirm that researchers will be accountable for obtaining informed consent. It is recommended that the protocol be modified to use alternate phrasing such as "Researchers may obtain informed consent from dosimetry subjects before repellency subjects …"

4) Carroll-Loye should spell out the acronym "PMD" when it is first used in the protocol and consent form.

5) On page 2 of the consent form, the phrase "You have been offered an opportunity to participate in this research study because …" (Carroll 2010, 199, 209, 219) be modified by Carroll-Loye to minimize the impression that participation in this intentional exposure study is somehow a beneficial or favorable occasion. A neutral alternative might be: "We are asking you to participate in this research study because…"

6) A description of the symptoms of heat stress and equine encephalitis should also be included in the consent form. Currently, only the symptoms of West Nile Virus are listed.

<u>Assessment of Proposed AHETF Scenario and Protocol AHE-400: Backpack and Handgun Application of Liquid Sprays in Utility Rights-of-Way.</u>

Overview of the Study

This proposal presents an agricultural handler exposure scenario involving backpack and handgun application of liquid pesticides along utility rights-of-way. The protocol calls for study participants to apply (and potentially load) four surrogate pesticides (fosamine, glyphosate, imazapyr and 2,4-D). A total of 21 participants (described in the protocol as "Monitoring Units"

[MUs]) will be observed for each scenario; three volunteers each from seven geographically distinct growing regions will be enrolled using a purposive sampling method (with some elements of random selection).

Dermal exposure will be measured by a whole body dosimeter (WBD) worn beneath the subject's outer clothing. Hand wash and face/neck wipe samples will also be collected prior to, during, and after completion of pesticide loading and mixing procedures. Airborne concentrations of the surrogate will be monitored in the participant's breathing zone using an OSHA Versatile Sampler (OVS) tube sample collector connected to a personal sampling pump. Additional measures will also record environmental conditions at the time of monitoring, and observers will make field notes, photographs and videos of participant activity throughout the monitoring event.

The results of sample analysis under the backpack and handgun application scenario will be posted to the AHED® database, where they will be available to the EPA and other regulatory agencies for statistical analysis. The proposed documentation will report a confidence-interval-based approach to determine the relative accuracy for the arithmetic mean and 95th percentile of unit exposures. The Agency proposes to use these data to estimate daily dermal and inhalation exposures of agricultural handlers who are applying pesticides using backpack and/or handgun applicators under a variety of scenarios.

Science

Charge to the Board

If the proposed AHETF Right-of-Way application scenario and field study proposal AHE400 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to generate scientifically reliable data, useful for assessing the exposure of workers who apply pesticides in utility rights-of-way using backpack or handgun sprayers?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment that the proposed AHETF Right-of-Way application scenario and field study proposal AHE400, if revised as suggested in EPA's review (Evans and Sherman 2010a) and performed as described, may generate scientifically reliable data useful for assessing the exposure of workers who apply pesticides in utility rights-of-way using backpack or handgun sprayers.

HSRB Detailed Recommendations and Rationale

Given the lack of existing reliable and sound data in this area, the Board concurred with the Agency's assessment (Evans and Sherman 2010a) that this protocol will likely generate data that may be useful for assessing the exposure of handlers who apply pesticides using backpack or handgun sprayers.

The study, if conducted as described, will provide newer exposure information on dermal and inhalation exposures of pesticide handlers using backpack sprayers and handgun sprayers treating utility rights-of-way in appropriate and distinct geographic locations; some study participants will be exposed during loading backpacks or tanks as well. The Board agreed with the Agency's assessment that the protocol adequately addresses a number of scientific questions, including having clear scientific objectives, a reasonable experimental design for achieving these objectives: appropriate quantification of test materials, adequate procedures for collecting, compiling and summarizing test results, appropriate justification for selection of test substances, sample size, and study site selection, and acceptable QA/QC procedures.

However, the Board noted a few weaknesses in the proposed study design. In particular, the variability in individual dermal and inhalation exposure levels may be extremely high because of the diversity of terrains and locations selected for the study and the opportunity for large (but potentially categorical) personal differences in application practices. As such, results may not be reproducible should the study be repeated. The proposal to impose a minimum exposure duration of at least 4 hours will also create opportunities for the applicator's exposures to be influenced by variables that by their nature are likely to be unrelated to the amount of active ingredient handled (AaiH). Should this diversity yield high variability in the data sets, then the proportionality of exposure with AaiH may not be apparent. If the 4-hour minimum is not removed, the Task Force may want to ensure that field notes are adequate to report time-on-task as a fraction of the total monitored time for use in later data analysis and usage within AHED. The rationale for having and using this "fraction" is discussed more fully in the Board's discussion of protocol AHE120 below. Even if the proportionality hypothesis is not supported by the resultant data sets, these data are likely to still be useful and relevant to assessing the levels of exposure to workers applying pesticides to utility rights-of-way.

Ethics

Charge to the Board

If the proposed AHETF Right-of-Way application scenario and field study proposal AHE400 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

HSRB Recommendation

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Evans and Sherman 2010a) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendation and Rationale

The submitted documents assert that the revised 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 the US EPA's GLP Standards described at 40 CFR 160 (AHETF 2010a; Collier

2010a). FIFRA §12(a)(2)(P) also applies. The protocol was reviewed and approved by an independent human subjects review committee, IIRB, Inc. of Plantation, FL prior to submission. Minutes of IIRB, Inc. meetings and a copy of IIRB, Inc. policies and procedures were provided. This IRB is fully accredited by AAHRPP and listed by OHRP (see details above).

1. Except as noted below, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Evans and Sherman 2010a). The proposed study is likely to meet the applicable ethical requirements for research involving human subjects, in accordance with the following criteria:

    a. Acceptable risk-benefit ratio. Risks as noted in the study protocol are four-fold: 1) heat-related illness; 2) injury associated with scripted field activities; 3) allergic reaction to surfactants used for hand washing; and 4) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are justified by the potential societal benefits, particularly data for new exposure assessments for occupational risks associated with spraying pesticides to rights-of-way using backpack and handgun sprayers.

        - Only experienced pesticide handlers, with specific experience with the type of application equipment to be used, and who consider themselves to be in good health, will be enrolled.

        - Risk of heat-related illness is minimized appropriately. Heat index will be monitored with an associated stopping rule. A medical professional will be on site to observe the workers and provide urgent care. Nearby medical facilities have been identified in case of emergency, and transportation to medical treatment will be provided, if needed.

        - Subjects will be reminded about safe chemical handling practices and procedures, wearing appropriate personal protective equipment (PPE), and will be monitored for any accidental or unintended product exposure.

        - Minors and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential stigma resulting from study exclusion due to pregnancy is appropriately minimized.

    The Board disagreed with the AHETF conclusion, however, that "the risk of toxicity from pesticide handling [is not] strictly due to study participation [and therefore], the risk of surrogate toxicity will not be listed in consent forms or this protocol" (Collier 2010a, 309). This study is subject to 40 CFR 26 subparts K and L precisely because it is considered to be a study in which the subjects are "intentionally exposed," for research purposes, to pesticides. Given its scripted nature, the AHETF protocol influences the behavior of workers and their employers in a number of ways. That a particular agricultural worker will be applying a particular pesticide on a particular day is due, to a

large extent, to the fact that the study is being conducted. Accordingly, the risk from exposure to the pesticides being applied should clearly be categorized as a risk of study participation.

The Board does agree, however, that the risk from exposure to those pesticides is a reasonable one, and that it has been appropriately minimized. The products being used in this study are ones already registered by EPA for vegetation control in rights-of-way, and will be applied in accordance with label requirements.

b. Voluntary and informed consent of all participants

- There is the possibility that the participants in this study might represent particularly vulnerable populations, susceptible to coercion and undue influence. The study protocol, however, includes several mechanisms designed to minimize coercive recruitment and enrollment.

- The informed consent materials, if changed as recommended by the HSRB below, will adequately inform the subjects of the risks, discomforts and benefits from participation, and of their right to withdraw.

- Monetary compensation is not so high as to unduly influence participants.

- Spanish translations of the informed consent documents, informational packets, and recruitment flyers were provided. Researchers will be working with local Spanish-speaking community members to ensure that the appropriate regional dialect of Spanish is used (AHETF 2010b).

c. Equitable selection of study participants

- The study is designed to recruit an appropriately diverse population of participants who represent skilled workers in the study locations.

- The study will first involve identifying and contacting the employers involved in right-of-way application of pesticides. Only employees of these employers are eligible to be recruited. The recruitment process has been carefully designed to assure that employees will not be coerced into participating: recruitment will take place using brochures and meetings with employees at which the employer and supervisors will not be present.

2. The Board recommended that the study protocol be modified to address the concerns noted in the EPA's Ethics Review (Evans and Sherman 2010a). In addition, the Board also raised the following concerns:

- As noted above, the Board concluded that the risk of toxicity from pesticide handling is indeed a risk of participating in the study, and accordingly it should be described as such, and discussed appropriately, in the consent form.

- The consent form should explain that the pregnancy test will be provided by the researchers, and explain when it will take place.

- There appears to be a discrepancy between the exclusion criteria stated in the EPA review (Evans and Sherman 2010a, 36), which refer to training in handling pesticides, and the AHETF-provided consent form (AHETF 2010a, 267), which notes that the subject might need only to confirm that "you are not required to take this training." This discrepancy should be clarified.

- Study participants will undergo hand washes prior to eating anything, which will reduce their risk of accidental ingestion of the surrogate compounds. As many of the adults in the US still smoke, however, hand washes should also occur before any smoking break to further reduce participant's risk of accidental pesticide ingestion.

Assessment of Completed AEATF II Research Study AEA-03: 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 (MRID 48210201, MRID 48231201, MRID 48231901).

Overview of the Study

The objective of this study was to measure individual exposures to a surrogate antimicrobicidal pesticide (didecyl dimethyl ammonium chloride; DDAC) while mopping floors and emptying mop buckets. Eighteen volunteers participated in the study, mopping floors in one of three building types (an office building, a Rite Aid pharmacy building, or a retired teacher's memorial building in Fresno, CA) for one of six pre-determined mopping times (30-40, 40-50, 50-60, 60-70, 70-80 and 80-90 minutes total mopping time, respectively).

Dermal and inhalation exposure monitoring was conducted while study participants mopped floors and emptied the mop buckets; all participants wore long-sleeved shirts, long pants, shoes, socks, and no gloves. Dermal exposure was measured by inner and outer body dosimeters. Airborne concentrations of the surrogate compound were monitored in the participant's breathing zone using an OSHA Versatile Sampler (OVS) tube sample collector connected to a personal sampling pump. Environmental conditions were also recorded at the time of monitoring, and observers made notes, photographs and videos of participant activity throughout the mopping period.

These exposure data will be used to populate a database representing inhalation and dermal exposure during a number of antimicrobial handler scenarios. A scenario is defined as a pesticide handling task based on activity (e.g., application) and equipment type (e.g., mop & bucket, ready-to-use wipes, pressure treatment of wood facilities, painting). These data will be used by the Agency to estimate dermal and inhalation exposures of antimicrobial handlers who are applying pesticides using a mop and bucket under a variety of scenarios.

Science

Charges to the Board

1) Was the research reported in the Antimicrobial Exposure Assessment Task Force II (AEATF–II) completed study report AEA-03 and associated supplemental reports faithful to the design and objectives of the protocol and governing documents of AEATF-II?

2) Has the Agency adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply antimicrobial floor-cleaning products with mop and bucket?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Leighton 2010) that the research reported in the completed AEA-03 study report and associated supplemental documents (Selim and Taylor 2010a, 2010b, 2010c) was conducted in a manner that was reasonably faithful to the design and objectives of the protocol and governing documents of AEATF-II. The Board also concluded that the Agency has adequately, if not completely, considered the limitations on these data that should be considered when using the data in estimating exposure of those who apply antimicrobial floor-cleaning products with mop and bucket.

HSRB Detailed Recommendations and Rationale

The study was conducted in a manner that was reasonably faithful to the design of the protocol and governing documents. The study report (Selim and Taylor 2010a) contains sections that adequately describe the test substance, recruitment procedures, field procedures, sample collection and handling, sample analysis, and data analysis. Previous Board recommendations (EPA HSRB 2008) for the use of a double layer of socks and provision of more detail about staff activities during the observation period were adopted. Appropriate rationale for changes in key elements of the study design, including justification for the purposive sampling of monitoring events (MEs) and the sample size of 18, was also provided. Finally, assuming that only one participant was present in the cluster when an ME was conducted, it also appears that no participant observed another participant's activities during the study, as previously recommended. However, some of the issues raised by the Board in its initial review of the mop and bucket scenario (EPA HSRB 2008) were not addressed, including: the bases for the 90-minute maximum mopping period choice, the possibility (or not) of "carry-over effects" between MEs, and the interaction between aerosolized particles, heating, ventilation and air conditioning (HVAC) systems, and inhalation exposure estimates. Although the importance of measuring the impact of HVAC systems on inhalation exposures was mentioned in the protocol (Selim and Taylor 2010a, 28), it was not given appropriate attention nor were HVAC operations consistently documented during the conduct of the study.

The study was also conducted in a manner that was reasonably faithful to the objectives of the protocol and governing documents. As stated in the final report, the study was conducted

primarily to "determine potential dermal and inhalation exposures to professional janitorial workers when mopping indoor surfaces with a liquid antimicrobial pesticide product containing didecyl dimethyl ammonium chloride (DDAC)" (Selim and Taylor 2010a, 28). Dermal exposures were reported, with estimates based on total collected residue from all matrices (face and hand wipes, socks, and all parts of the inner dosimeter). Dermal exposures were expressed as micrograms of active ingredient (AI) handled per subject and as milligrams of AI per subject/pound of AI applied. Inhalation exposure was also presented as units of concentration. However, sufficient data is available (i.e., the duration of each exposure) to express those results in the same units as dermal exposures if an average respiratory minute volume for the applicators is also applied to the calculation.

The overall study objective was listed differently in the Agency's scientific review than in the protocol, stating it as: "the study objective is to monitor inhalation and dermal exposures to be used as inputs in exposure algorithms to predict future exposures to persons mopping floors." (Leighton 2010, 5). The Agency added two sub-objectives not found in the protocol: "to be 95% confident that key statistics of normalized dermal exposure are accurate within 3-fold" and "to evaluate the presumption of proportionality between exposure and amount of active ingredient handled," respectively. The Agency provided a thorough assessment of their first sub-objective supporting the sample size and analyses used to achieve the 3-fold accuracy goal. However, although the presumption of proportionality was demonstrated for dermal exposure and the amount of AI handled, the rationale supporting the presumption of proportionality for inhalation exposure needs to be recalculated to include duration of exposure.

The Agency's scientific review (Leighton 2010) discussed the limitations of the dermal and inhalation exposure data. The Agency also presented alternative models for estimating dermal and inhalation exposures, evaluated the impacts of non-detects and of assigning low limits of quantification (LOQs) at 3 different values (0, ½ and full LOQ). The Agency concluded that dermal exposures and pounds of active ingredient are related in a proportional manner, while accounting for sampling efficiency and normalizing the data in terms of milligrams/pounds of active ingredient applied. The Agency also discussed the dermal exposure estimates in relationship to its sub-objectives of the study (accuracy within 3-fold and proportionality). Their assessment acknowledged that some estimates included a high level of uncertainty and some bias. The Board concluded that the Agency adequately, if not completely, considered limitations in its interpretation and subsequent estimates of dermal exposure data. The Agency should carefully examine the handwash data, however, to ensure that it does not overcorrect for face and neck residue estimates. Additionally, the model may not always support the conclusion of proportionality for all clothing configurations.

With respect to limitations of the inhalation exposure data due to study deviations, some (but not all) of the limitations that need to be considered when estimating inhalation exposure were discussed. In its initial 2008 review (EPA HSRB 2008), the Board noted several factors that could influence these estimates, including: ventilation, room temperature, total area mopped, duration of mopping, and volume of the enclosed space and respiration rate of the study participants. Although the final study report provides some of these data for the facilities in which mopping activities were conducted (Selim and Taylor 2010a, 105-7), neither ventilation data nor a discussion of these factors were provided, thus limiting the Board's and Agency's

ability to interpret fully the reported environmental data. Furthermore, the rationale for the Agency's conclusion that air changes per hour was not a significant factor influencing inhalation exposure estimates, based on the low vapor pressure of DDAC and the LOQs observed, does not recognize fully how HVAC parameters could have affected reported air concentrations from mopping activities. The Agency also failed to consider whether the limited areas available for mopping in Clusters 1 and 3 could have compromised the study design or affected inhalation exposure estimates. Similarly, although surface areas of the floors mopped were noted, the ceiling heights were not reported. The Agency's review also fails to consider the impact that ceiling height and room volume may have had on the reported air concentration data. The respiration rates of study participants were not discussed by the Task Force researchers or the Agency; ignoring this factor could introduce important uncertainties into exposure estimates. Finally, the Board's previous recommendation to consider particle size (e.g., whether DDAC is aerosolized) and its potential impact on inhalation exposures were not addressed by the Agency. Although not discussed in detail by the Board at the October 2010 meeting, several of these factors are discussed in a separate report (submitted independently by an HSRB member to the Agency).

Ethics

Charge to the Board

Does available information support a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Carley 2010) that the study was conducted in substantial compliance with subparts K and L 40 CFR 26.

HSRB Detailed Recommendation and Rationale

The documents provided by Golden Pacific Laboratories, LLC, under Project No. AEA-03, state that the study was conducted in compliance with the requirements of 40 CFR 26 subparts K, L and M; FIFRA § 12(a)(2)(P); and the California Code of Regulations Title 3, Section 6710 (Selim and Taylor, 2010a, 2010b, 2010c). The protocol was reviewed and approved by an independent human subjects review committee, IIRB, Inc. of Plantation, FL prior to submission. Minutes of IIRB, Inc. meetings and a copy of IIRB, Inc. policies and procedures were provided. This IRB is fully accredited by AAHRPP and listed by OHRP (see details above).

1. The Board concurred with the conclusions and factual observations relating to the study, as detailed in the EPA's Ethics Review (Carley 2010) and summarized briefly below.

    a. Prior HSRB and Agency Review. Because this study was initiated after 7 April 2006, prior submission of the protocol and supporting materials to EPA was required by 40 CFR §26.1125. The requirements of 40 CFR §26.1125 for prior submission of the

protocol to EPA and of §26.1601 for HSRB review of the protocol were satisfied. The scenario design and study were approved by IIRB, Inc. and submitted to the EPA in February 2008. The HSRB discussed the protocol at its April 2008 meeting, concurring with the Agency's assessment that the proposed mop and wipe scenario, if revised as suggested by the Agency and the HSRB, would meet the applicable requirements of 40 CFR part 26, subparts K and L.

b. Responsiveness to HSRB and Agency Recommendations.

The Agency's initial ethics review noted two deficiencies to be corrected before the study was initiated. The first focused on measures to improve the informed consent process for Spanish-speaking candidates. The Agency called for the candidate interviews for Spanish speakers to be conducted by a member of the research team fluent in Spanish, rather than an independent translator. The second deficiency focused on references in the informed consent forms to "normal business hours". The Agency asked that the researchers revise the consent form to show hours for calling in local (Pacific) time.

In the revisions submitted to IIRB, Inc. in February 2009, the researchers addressed these ethical concerns. Because the study was conducted in California, the approval of the California Department of Pesticide Regulation (CDPR) was also required. CDPR granted final approval of the amended protocol and supporting documents in April 2009.

c. Responsiveness to HSRB and Agency Reviews. The Agency's and HSRB's comments were satisfactorily addressed in the revisions approved by the IIRB in March 2009 (Selim and Taylor 2010a).

At its April 2008 meeting, the HSRB made several specific recommendations for refinements of the study. As noted in Amendment 4 of the Agency's ethics review (Carley 2010), the investigators addressed fully most of these recommendations, addressed partially some of these recommendations, and did not address two of these recommendations. The Board agreed with the Agency conclusion, however, that the investigators' failure to address all of the recommendations did not violate applicable ethical standards for the protection of human participants of research.

d. Substantial Compliance with Reporting Requirements (40 CFR §26 subpart M).

The study sponsor initially did not provide adequate documentation to demonstrate that they had satisfied the requirements of §26.1303. The initial report (Selim and Taylor, 2010a) contained several reporting deficiencies, including: inadequate documentation of interaction between the investigators and the overseeing IRB, incomplete study chronology, and a lack of tracked consent forms showing how they were revised to address Agency and HSRB concerns. These deficiencies were corrected by the submission of supplemental documents (Selim and Taylor, 2010b, 2010c).

IRB minutes documenting discussion and review of these revised documents were not provided for review. All IIRB, Inc. reviews subsequent to the HSRB's April 2008

meeting were conducted using an expedited procedure and did not require a full meeting of the IRB. Neither the IRB roster nor the operational procedures were submitted as part of the study documents.

The HSRB agreed with the Agency that these deficiencies in the conduct and the documentation of the research did not compromise the ethical conduct of the study, and concluded that the requirements of 40 CFR §26.1303 were satisfactorily addressed. The HSRB did recommend, however, that the Agency require the submission of reports for all research that undergoes expedited IRB review in the future.

2. The Board concluded that this study, as conducted, met all applicable ethical requirements for research involving human participants, in accordance with the following criteria that had been stated in the Board's prior review of this protocol (EPA HSRB 2008).

   a. Acceptable risk-benefit ratio. The risks to study participants were minimized appropriately and were justified by the potential societal benefits, particularly data on the dermal and inhalation exposure of professional janitorial workers to antimicrobial pesticides as they mopped indoor floors and disposed of spent mop water. These data could be used to develop mechanisms to protect future users of these antimicrobial pesticides.

      - Minors and pregnant or lactating women were excluded from participation, with pregnancy confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential of stigma resulting from study exclusion was also appropriately minimized.

      - Clear stopping rules and medical management procedures were in place, and no adverse events or other incidents of concern related to product exposure were reported.

      - The study was designed to minimize the risks of exposure to the test compounds.

   b. Voluntary and informed consent of all participants

      - The study protocol included several mechanisms designed to minimize coercive recruitment and enrollment.

      - Monetary compensation was not so high as to unduly influence participation.

3. Three minor protocol deviations were reported. These included: 1) most study participants declining to take rest breaks or taking less than the 10 minutes provided for in the protocol; 2) full facial photographs taken of participants at one monitoring site; and 3) enrollment of participants who self-reported that their health was only "fair," despite the requirement that all participants be in "good health" (Selim and Taylor, 2010b, 31). The Board concluded, however, that these minor deviations did not affect the integrity of the research or the safety of participants. The Board did recommend, however, that sponsors clarify the criteria used to establish participants' health status prior to study enrollment.

Assessment of Revised AHETF Scenario and Protocol AHE-120: Water-Soluble Packaging Mixing and Loading.

Overview of the Study

This revised proposal presents an agricultural handler exposure scenario involving mixing/loading of pesticides enclosed in water-soluble packets (WSP). The original protocol, which was favorably reviewed by the Board at its June 2009 meeting (EPA HSRB 2009), called for study participants to mix and load one of two WSP-enclosed surrogate pesticides (acephate and carbaryl) into a variety of tanks containing water in a variety of agricultural spraying operations. Carbaryl in water-soluble packaging is no longer being produced by pesticide manufacturers; however, the AHETF proposed substituting three additional surrogate compounds for carbaryl: dithiopyr, imidacloprid, and thiophanate-methyl. Because of use patterns of these surrogate compounds, the AHETF also identified additional study sites. The previously reviewed study was to be conducted at three cool dry sites in Michigan, New York, and Washington State, one hot humid site in Louisiana, and one hot dry site in California. The revised protocol will also be conducted at five sites, including two cool dry sites in New York and North Dakota, two hot humid sites in Florida and Louisiana, and one hot dry site in California.

A total of 25 participants (described in the protocol as "Monitoring Units" [MUs]) will be observed; five volunteers each from five different growing regions will be enrolled using a purposive sampling method. Dermal exposure will be measured by a whole body dosimeter (WBD) worn beneath the subject's outer clothing. Hand wash and face/neck wipe samples will also be collected prior to, during, and after completion of pesticide loading and mixing procedures. Airborne concentrations of the surrogate will be monitored in the participant's breathing zone using an OSHA Versatile Sampler (OVS) tube sample collector connected to a personal sampling pump. Additional measures will also record environmental conditions at the time of monitoring, and observers will make field notes, photographs and videos of participant activity throughout the monitoring event.

The results of sample analysis under the mixing/loading of water-soluble packets scenario, and will be posted to the AHED® database, where they will be available to the EPA and other regulatory agencies for statistical analysis. The Agency proposes to use these data to estimate daily dermal and inhalation exposures of agricultural handlers who are mixing/loading pesticides in water-soluble packets under a variety of mixing and loading scenarios.

Science

Charge to the Board

If the revised AHETF scenario and field study proposal AHE120 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who mix and load pesticides in water-soluble packaging?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Evans and Sherman 2010b) that this protocol will generate data that are scientifically valid and that may be useful for assessing the exposure of handlers who mix and load soluble or wettable powder pesticides in water-soluble packaging. The Board cautioned, however, that these data might not be useful for creating distributions of worker exposure that are scientifically accurate or that are precise.

HSRB Detailed Recommendations and Rationale

The protocol is largely the same as when it was first reviewed by the HSRB in June 2009 (EPA HSRB 2009). The major changes are that one of the surrogate active ingredients (carbaryl) was deleted and three other active ingredients (dithiopyr, imidacloprid, and thiophanate-methyl) were added. This change necessitated revising the geographical regions in which the study could be conducted and a slight lowering of each of the five strata in the amounts of active ingredient handled.

Each of these changes seems justified. Assuming that the AHETF can provide adequate evidence of the validity of the analytical methods for each of the new compounds, the revised study protocol still allows a good probability of the study successfully obtaining its primary and secondary objectives (i.e., "that selected lognormal-based estimates of normalized dermal exposure distribution be accurate to within 3-fold, at least 95% of the time," and the ability to distinguish "a proportional from an independent relationship between exposure and AaiH," respectively [Evans and Sherman 2010b, 28-9]).

However, the Board pointed out that many of the same concerns it raised in June 2009 remain for the revised protocol. Of particular note is the conflict between the non-random, purposive study design and the statistical methods proposed to analyze the exposure data. Moreover, the protocol does not control for ecological, engineering, and statistical factors that may obscure a linear relationship between AaiH and worker exposure. Previously the Board said that "there is no statistical theory that can be applied to non-random samples of this type. Thus, the statistical analyses proposed, including mixed model approaches, are not valid" (EPA HSRB 2009, 34). In contrast to the prior version, this protocol indicates that AHETF will not statistically analyze the monitoring data; that begs the question as to what statistical methods are appropriate to use on these data.

The Board also raised one new concern regarding the potentially adverse impact of the protocol's exposure duration of at least 4 hours for all of the MUs. This constraint seems unnecessary and may introduce unintended and undesired variability into the results. The Board noted that scripting activities to include more time than would otherwise be required to apply the amount of active ingredient in the designated stratum is likely to change the applicator's exposures by introducing variables that by their nature are unrelated to the AaiH. In particular, other tasks within those hours are likely to result in the transfer of active ingredient either to or from other surfaces from or onto the subject. For this study, the fraction of the total monitored time

that is time on-task is likely to be highly variable, probably among strata (particularly if the artificial constraint on the minimum time monitored affects the low AaiH preferentially) and potentially even within strata. While omitting this time constraint would avoid these random variables, the Board recommended that all field notes for this study report the time on-task as a fraction of the total monitored time, and that the total monitored time and the fraction of the total time on-task be tabulated for this study. This fraction can be used later by the Agency, sponsors and AHED users to reliably extrapolate from the time-weighted average concentrations or rates of exposure measured by the existing protocols to task-specific concentrations or rates of dermal and inhalation exposure per AaiH.

Ethics

Charge to the Board

If the revised AHETF scenario and field study proposal AHE120 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

HSRB Recommendation

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Evans and Sherman 2010b) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendation and Rationale

The submitted documents assert that the revised 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 the US EPA's GLP Standards described at 40 CFR 160 (AHETF 2010c; Collier 2010b). FIFRA §12(a)(2)(P) and the California State EPA Department of Pesticide Regulation's study monitoring requirements (California Code of Regulations Title 3, Section 6710) also apply. The protocol was reviewed and approved by an independent human subjects review committee, IIRB, Inc. of Plantation, FL prior to submission. Minutes of IIRB, Inc. meetings and a copy of IIRB, Inc. policies and procedures were provided. This IRB is fully accredited by AAHRPP and listed by OHRP (see details above).

1. Except as noted below, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the revised study, as detailed in the EPA's Ethics Review (Evans and Sherman 2010b). The proposed study is likely to meet the applicable ethical requirements for research involving human participants, in accordance with the following criteria:

    a. Acceptable risk-benefit ratio. Risks as noted in the study protocol are four-fold: 1) heat-related illness; 2) injury associated with scripted field activities; 3) allergic reaction to surfactants used for hand washing; and 4) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are

justified by the potential societal benefits, particularly data on occupational exposure of agricultural workers to pesticides during mixing and loading activities.

- The greatest risk to participants is that of heat-related illness, given that the participants will be required to wear two layers of clothing during the scenario activities. This risk is lessened but not eliminated by the application of appropriate stopping rules (including cessation of all monitoring activities when the ambient heat-index exceeds 105°F) and frequent monitoring of participants. Participants will be given frequent breaks, access to ample amounts of water or sports drinks, and educated about the dangers and symptoms of heat-related illness. Appropriate medical management procedures are also in place.

- The surrogate materials consist of four common pesticides: acephate, dithiopyr, imidacloprid, and thiophanate-methyl. The participants will only be exposed to concentrations of the surrogate compound at accepted exposure thresholds.

- Participants will be selected from volunteers with experience handling these or similar compounds in WSP mixing and loading scenarios. Thus, all of the participants will have extensive experience in using these or similar products, and thus will be unlikely to misuse them in a way that might increase their likelihood of being accidentally exposed.

- Participants will be reminded about safe handling practices and procedures, about wearing appropriate PPE, and will be monitored for any accidental or unintended product exposure.

- Allergic reactions to the surfactants used in hand washing are usually mild and easily treated with over-the-counter steroidal creams. The study will exclude participants who have a history of severe skin reactions to such detergents.

- Minors and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential stigma resulting from study exclusion due to pregnancy is also appropriately minimized.

Several members noted, however, that exposure to the surrogate chemicals is no longer listed as a potential risk to study participants in either the protocol or in the informed consent documents. Study volunteers, it was argued, are likely to handle these chemicals as part of their daily activities and the possibility of exposure is thus a risk of employment and not a risk of study participation. However, because of the nature of the study (including scripted handling of specific amounts of chemical), the Board felt that exposure to the surrogate chemicals was a potential risk of study participation and recommended that the sponsor explicitly list this risk in the protocol and informed consent documents.

b. Voluntary and informed consent of all participants

- There is the possibility that the participants in this study might represent particularly vulnerable populations, susceptible to coercion and undue influence. The study protocol, however, includes several mechanisms designed to minimize coercive recruitment and enrollment.

- Monetary compensation is not so high as to unduly influence participants.

- Spanish translations of the informed consent documents, informational packets, and recruitment flyers were provided. Researchers will be working with local Spanish-speaking community members to ensure that the appropriate regional dialect of Spanish is used (AHETF 2010d).

c. Equitable selection of study participants

- The study is designed to recruit an appropriately diverse population of participants who represent skilled agricultural workers in the five study locations.

- Community representatives and advocates are appropriately involved in the recruitment and enrollment of study participants.

2. The Board recommended that the study protocol be modified to address the concerns noted in the EPA's Ethics Review (Evans and Sherman 2010b). In addition, the Board also raised the following concerns:

- The Board raised concerns that the revised water-soluble packaging protocol was reviewed by IIRB, Inc. using an expedited procedure. Future protocol revisions that involve major changes like substitution of surrogate compounds and/or change in study site should be reviewed under full-board procedures and reflected properly in the IRB minutes.

- As noted above, the Board recommended that accidental exposure to the surrogate chemicals be listed in the protocol and that the informed consent form also list surrogate exposure as a potential risk of study participation.

- The protocol excludes participants who normally wear additional personal protective equipment (such as chemical-resistant clothing) that is not required by the chemical label and that might impact the objectives of the study. The Board recommended that this assessment be done in a non-directive way, so as not to encourage participants to wear less PPE than they would normally in order to participate in the study.

- Study participants will undergo hand washes prior to eating anything, which will reduce their risk of accidental ingestion of the surrogate compounds. As many of the adults in the U.S. still smoke, however, the Board recommended that hand washes also occur before any smoking break to further reduce their risk of accidental pesticide ingestion.

- The informed consent document states that “you may refuse medical treatment unless you get sick from too much exposure to pesticides or from getting too hot, or if we believe you are too sick to make a rational decision about getting medical treatment” (Collier 2010b, emphasis added). It was unclear how this determination of rationality will be made, however. The protocol and informed consent document should be more explicit as to who will make this determination, and what criteria would be used.

- The Board raised some concerns about how the Task Force plans to release individual exposure data to individual study participants who request this information. For example, the Board encouraged the sponsor to consider how this information might be provided to participants who do not speak English and/or are illiterate. The Board also recommended that the request for individual study results be included as a check box on the informed consent document. The HSRB will be establishing a small working group to develop some guidance for the Agency and sponsors regarding the release of individual exposure data to study participants.

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