January 11, 2012

EPA-HSRB-11-03

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

Subject: October 19-20, 2011 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 protocols for studies involving intentional exposure of human subjects to pesticides: a proposed Antimicrobial Exposure Assessment Task Force II (AEATF) scenario to determine dermal and inhalation exposures associated with the manual pouring of liquid antimicrobial products (AEA-05); and a proposed Agricultural Handler Exposure Task Force, LLC (AHETF) scenario measuring dermal and inhalation exposure of workers who perform closed system loading of liquid pesticides in non-returnable and returnable containers.

The Agency also requested that the HSRB review a completed study of insect repellent efficacy conducted by Carroll-Loye Biological Research, Inc. (CLBR). This study (No Mas-003) 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, and was reviewed favorably at the HSRB's October 2010 meeting.

Finally, the Agency asked the Board to review a published study involving intentional human exposure study measuring dermal absorption of nanosilver (Moiemen et al. 2011). The Agency proposes to rely on this study, conducted after publication of the EPA's expanded final rule for protection of subjects in human research, for regulatory actions.

The enclosed report provides the Board's response to EPA charge questions presented at the October 19-20, 2011 meeting.

Assessment of Proposed AEATF Research Study AEA05: A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of a Liquid Containing an Antimicrobial.

Science

- The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Leighton, Sherman and Cohen 2011) and HSRB recommendations, is likely to

generate scientifically reliable data, useful for assessing the exposure of individuals who manually pour liquid antimicrobial products.

- In addition to providing several additional comments or suggestions, the Board also pointed out two limitations not identified either within the protocol or by the Agency: 1) the wider range of exposures that could occur while pouring products outdoors than only indoors as proposed; and, 2) the unknown impact of potential differences in exposures between consumers and professionals.

Ethics

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

Assessment of Proposed AHETF Research Study AHE500: Exposure Monitoring of Workers During Closed System Loading of Returnable and Non-Returnable Containers in the United States.

Science

- The Board concurred with the Agency's assessment that the proposed AHETF scenario and field study proposal AHE500, if revised as suggested in EPA's review and performed as described, is likely to generate scientifically reliable data, useful for assessing the exposure of workers using closed systems to load liquid pesticide products from returnable or nonreturnable containers.

- The Board provided an additional set of recommendations for the Agency and study sponsors to consider when collecting and analyzing data concerning the exposure of workers using such closed load systems.

Ethics

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

Assessment of Completed 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 concurred with the Agency's assessment that this study provides scientifically valid results to assess the repellent efficacy against mosquitoes for the formulation tested.

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.

Assessment of Published Research Study MRID 48607501: Moiemen et al. (2011) Acticoat Dressings and Major Burns: Systemic Silver Absorption.

Science

- Despite several deficiencies identified with the study design, the small number of subjects, and the interpretation of the data, the Board agreed with the Agency's assessment that the Moiemen et al. (2011) study provides some potentially useful baseline information on the dermal absorption of silver from nanosilver-containing wound dressings.

- The Board concluded that the Moiemen et al. (2011) study could be used to support the Agency's conclusion that the dermal absorption of silver is less than 0.1% as part of the overall weight of evidence, but recommended that: 1) the Agency clarify its assumptions in estimating the dermal absorption of silver from nanosilver; and 2) that the Agency consider alternatives for estimating dermal absorption based on this study.

Ethics

- The Board concurred with the Agency's assessment that there was sufficient information regarding value of the research to society, subject selection, risks and benefits, independent ethics review, informed consent, respect for potential and enrolled subjects to conclude that the study was conducted in substantial compliance with procedures at least as protective as those in subparts A - L of EPA's regulation at 40 CFR Part 26.

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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[*] Not present on October 19, 2011.
[†] Participated in the October 19-20, 2011 meeting via telepresence.
[§] Not present on October 20, 2011.

INTRODUCTION

On October 19-20, 2011, 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 for research involving human participants: one new study measuring dermal and inhalation exposures associated with the manual pouring of liquid antimicrobial products, and one new study measuring dermal and inhalation exposure of workers who perform closed system loading of liquid pesticides in non-returnable and returnable containers. In accordance with 40 CFR 26.1601, EPA sought HSRB review of these two proposed studies. Each of these studies is discussed more fully below.

In addition, the Agency has data from one completed study measuring the efficacy of an insect repellent containing para-menthane-3,8-diol (PMD) and lemongrass oil against mosquitoes under field conditions. In accordance with 40 CFR 26.1602, EPA sought HSRB review of this completed study. This completed study is discussed more fully below.

Finally, the Agency sought HSRB review of one published study of dermal absorption of silver (Ag) from silver nanoparticle-impregnated wound dressings used to treat major burns. This study, conducted after publication of the EPA's expanded final rule for protection of subjects in human research, was identified by Agency scientists from the peer reviewed literature. This study, which the Agency proposes to rely upon for regulatory actions, is discussed in detail below.

REVIEW PROCESS

On October 19-20, 2011, 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" (76 Federal Register 187, 59697).

Following welcoming remarks from Agency officials, the Board heard presentations from EPA on the following topics: one new study protocol to measure dermal and inhalation exposures associated with the manual pouring of liquid antimicrobial products, and one new study protocol to measure dermal and inhalation exposure of workers who perform closed system loading of liquid pesticides in non-returnable and returnable containers. A completed study measuring the efficacy of an insect repellent containing PMD and lemongrass oil against mosquitoes under field conditions was also reviewed, as was one published study measuring dermal absorption of silver (Ag) from silver nanoparticle-containing wound dressings applied to severely burnt human skin.

The Board also asked clarifying questions of several study sponsors and/or research investigators, including:

Dr. Michael Bartels, Scientist, Dow Chemical Company (representing the Antimicrobial Exposure Assessment Task Force II)
Dr. Victor Cañez, Technical Chair, Agricultural Handler Exposure Task Force
Dr. Scott Carroll, Study Director, Carroll-Loye Biological Research

Dr. Richard Collier, Administrative Committee Chair, Agricultural Handler Exposure Task Force
Mr. Shawn King, Director of Operations, Carroll-Loye Biological Research
Ms. Leah Rosenheck, President, LR Risk Consulting, Inc. (representing the Antimicrobial Exposure Assessment Task Force II)

Public oral comments were provided by:

Dr. Michael Bartels, Scientist, Dow Chemical Company
Dr. Victor Cañez, Technical Chair, Agricultural Handler Exposure Task Force
Dr. Scott Carroll, Principal, Carroll-Loye Biological Research

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 AEATF Research Study AEA05: A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of a Liquid Containing an Antimicrobial.

Overview of the Study

AEATF II liquid pour protocol (AEA05) is designed to measure a typical occupational handler's daily exposure to various antimicrobial products whose use and application requires the pouring of a liquid product (e.g., an antimicrobial concentrate that may be measured and diluted with water prior to use). This proposal presents two different occupational exposure scenarios: one involving pouring of liquids from conventional containers and one involving the use of containers designed to reduce splashing.

A total of 18 participants (described in the protocol as "Monitoring Events" [MEs]) will be observed. Each volunteer will pour antimicrobial products from both conventional and "reduced splash" containers at a laboratory site in Concord, OH. Didecyl dimethyl ammonium chloride (DDAC; Maquat WP) and N-alkyl dimethyl benzyl ammonium chloride (ADBAC; Maquat DS 1412-10%) will be the antimicrobial materials used for the conventional pour and reduced splash scenarios, respectively. These two commonly used products can be distinguished analytically, thus allowing researchers to use a single participant to monitor dermal and inhalation exposure to antimicrobial agents under both a conventional pour and reduced splash scenario. For each scenario, the study participants will be randomized to pour different amounts of liquid; 40 ounces to 20 gallons in the conventional pour scenario, and 60 ounces to 30 gallons

in the reduced splash scenario. A variety of source and receiving containers will also be used, including 32 ounce spray bottles, 2 and 4 gallon buckets, and 10 gallon basins.

Participants will wear long sleeved shirts and long pants (provided by the researchers), and shoes plus socks (provided by the subject). The low toxicity and low concentration of the surrogate compounds used eliminates the need to have participants wear additional protective equipment, such as chemical resistant gloves or aprons.

Dermal exposure will be measured by a whole body dosimeter 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 the liquid pour 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 collect field notes, take photographs, and record video of participant activity throughout the monitoring event.

These data will be used by the Agency generically to estimate dermal and inhalation exposures and risks for other antimicrobial ingredients where the product is packaged as a liquid concentrate in conventional or reduced splash containers.

Science

Charge to the Board

If the AEATF liquid pour study proposal 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 individuals who manually pour liquid antimicrobial products?

Board Response to the Charge

HSRB Recommendation

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Leighton, Sherman and Cohen 2011) and HSRB recommendations, is likely to generate scientifically reliable data, useful for assessing the exposure of individuals who manually pour liquid antimicrobial products.

Several comments or suggestions were made by the Board with respect to the Agency's proposed revisions to the protocol, the Task Force's proposal to use a single participant and a single dosimeter to assess dermal and inhalation exposure in two scenarios, and the lack of information provided within the protocol on the source containers to be used.

The Board also pointed out two limitations not identified either within the protocol or by the Agency: 1) the wider range of exposures that could occur while pouring products outdoors

than only indoors as proposed; and, 2) the unknown impact of potential differences in exposures between consumers and professionals. These limitations are described in detail below.

HSRB Detailed Recommendations and Rationale

The AEATF-II liquid pour protocol is complicated and highly scripted, but seems to be a feasible way to generate scientifically reliable exposure assessment data that includes the effects of source container size, size and type of receiving container, use of measuring cups or not, and height of pouring. The Board had several recommendations, however, as to how the study might be improved.

1. Proposed Revisions to the Protocol.

   First, the Agency has proposed that the protocol be revised to randomize the use of a measuring cup by participants in monitoring Group 2 (Leighton, Sherman and Cohen 2011, 17). The Board has no substantive insight into the impact on dermal and inhalation exposures if Group 2 does or does not use a measuring cup. Indeed, the inclusion of the measuring cup appears to be more of a policy decision based on perceived future uses of the data than a question of science. Nonetheless, the Board made the following observations. Because using a 4 ounce measuring cup twice for each of 10 pours into a bucket means that only 80 ounces (~ ⅔ of a gallon) will comprise only 5-10% of the total of 7.5 to 14 gallons expected to be handled by each ME in Group 2, the effect of this difference on exposures may be slight in either direction. The ability to detect a slight difference within two subgroups of 3 MEs each is very small. Given this, two alternatives for assessing the effect of using a measuring cup were suggested by the Board. The first alternative is to consider having half of the participants in Group 2 use a measuring cup to transfer all of their assigned source volume into the receiving container, and the other half to not use the cup. Another alternative is for no one in Group 2 to use a measuring cup, but instead to test for a difference in the unit exposure values between Group 1 (all of whom use a measuring cup) and Group 2 (all of whom do not use a measuring cup).

   The second revision proposed by the Agency would be to allow study participants to "fill the spray bottles from the source container and with water in the order they would normally do as opposed to the researchers directing them to fill with water after pouring the concentrate from the measuring cup" (Leighton, Sherman and Cohen 2011, 17). This is probably a good revision. However, the Agency should also ensure that the protocol directs the handlers to follow the label instructions. The label information provided within this protocol was not complete, and the lack of more specific instruction should be confirmed among all applicable labels. Based on the information available, however, the Board concurs with this proposed revision. A related but separate comment was made that since the bactericidal solution to be used in the study has been pre-diluted by the study director(s), none of the labeling instructions that would normally be present on the original container will be present in the pouring containers within this study. The protocol thus should be amended to specify what label information will be made available to study participants.

Regarding the third revision proposed by the Agency -- to "provide a description of how the different size source containers will be randomly assigned to each ME" (Leighton, Sherman and Cohen 2011, 17) -- the Board suggested adding statistical constraints to the randomization process used to assign the different size source containers to each ME. Since the array of conditions is already scripted, it seems reasonable to avoid creating statistical outliers that might result from a completely random distribution. For example, the study director could generate the random array of size distributions beforehand and screen it to assure that all distributions fall within the "to-be defined" probability limits.

The Board concurs with the Agency's fourth proposed revision, namely to request that the Task Force "provide details about how the airflow in the laboratory room will be measured and what the target airflow will be (e.g., will the airflow be minimized?)" (Leighton, Sherman and Cohen 2011, 17). However, the focus of interest in ventilation should be on the local air flow between the pouring operation (the purported source of exposure) and the handler. Analyses of the pattern of exposures to applicators in the AEATF-II completed mopping protocol showed that the amount of room ventilation seemed to have virtually no effect on exposures (EPA HSRB 2010). Mopping is a mobile task, and moving throughout a room can balance the effects of localized air currents between the source of exposure and the handler. In contrast, someone pouring a liquid is likely to be relatively stationary. Thus, a consistent local air flow (its speed and especially its direction between the pouring operation and the handler) is likely to bias the measured exposures. Because air flow patterns generated by a Heating, Ventilation and Air Conditioning (HVAC) system are likely to be consistent, at the very least, that pattern should be measured before and/or after exposures and the orientation between the source and each handler should be documented for each ME. Alternatively, the room's setup and the orientation between the source and handler could be varied (e.g., rotated 90°) either within or among MEs; this approach may increase the variability in the resulting exposure data and is more likely to include the higher downwind exposures than having only one orientation for all MEs. Increasing the variability independent of the amount of the active ingredient handled (AaiH) may adversely affect the ability to detect proportionality, akin to the effect discussed herein regarding the Agricultural Handlers Exposure Task Force's Closed System Load Liquid (AHETF CSLL) study. In addition, it was pointed out that the airflow through laboratories is generally more than what would be expected in many other work rooms in which such pouring would take place; therefore, some steps to minimize the air flow should be considered. One possible, simple way to reduce the airflow through the room is to close the laboratory fume hood's sash door, although some fume hoods have a bypass that prevents the sash's position from affecting the HVAC airflow.

2. Proposal to Monitor Two Scenarios Using the Same Dosimeters.

The proposal for each ME to monitor two scenarios using the same set of dosimeters seems novel and efficient. There is no evidence to suggest that the plan as proposed will not work, and precedents for collecting and analyzing multiple active ingredients in the same environment were discussed. The Board suggested that consideration be given to ways of leveraging the data from two exposures to the same individual during the analysis of the results. However, the Board pointed out the potential for a portion of a dosimeter

(particularly an outer dosimeter) that becomes locally saturated by a significant spill or splash to behave differently from a fresh dosimeter in terms of its transmission and/or retention of the handled mixture. While such an event may not occur during the study, such wetting of the outer clothing is likely to be quite visible to the study observer. Thus, a suggestion was made to modify the protocol to allow the study observer to decide if someone's dosimeters should be changed between the two scenarios to avoid such a foreseeable event from confounding the sample results of the second scenario. Discussion pointed out that this flexibility should be implemented in a way that does not cause the handler to change his or her behavior. Finally, no rationale was provided for using DDAC in the conventional pour scenario and ADBAC in the reduced-splash pour scenario versus randomizing the two antimicrobial agents between the conventional and reduced splash containers.

3. Source Containers.

   The lack of information within the protocol about the source containers to be used was noted. Granted that the definition of reduced-splash non-refillable containers is performance based rather than product specific; however, neither the specific reduced-splash container(s) was to be used in this study not identified, nor were a list of candidate reduced-splash containers potentially to be used or a description of how the final container(s) will be chosen provided. A similar comment about the lack of candidates or specificity (other than size) applies to the refillable containers. It seems prudent to agree upon the selection process or final containers before beginning the study.

4. Additional Study Limitations.

   The Board also pointed out two limitations not identified either within the protocol or by the Agency: 1) the wider range of exposures that could occur while pouring products outdoors than only indoors as proposed, and; 2) the unknown impact of potential differences in exposures between consumers and professionals.

   First, pouring operations are likely to occur outdoors within three of the eight 'Use Categories' identified by the Agency at which a majority of liquid pouring operations are likely to occur (i.e., Agricultural, Swimming pools, and Aquatic areas), and it may occur outdoors in a fourth (III Commercial / institutional / industrial premises and equipment) (Leighton, Sherman and Cohen 2011, 5-6). Air velocity outdoors is likely to be more variable (particularly on the high-end) than indoors. The Agency should review and determine the importance of the limitation of not assessing exposures outdoors.

   Second, while pouring a liquid product from a container may not be a specialized task (see, e.g., Leighton, Sherman and Cohen 2011, 25), the experience of a user may reduce the incidence of high exposure events. This pattern leads to the hypothesis that a consumer (or less experienced handler) may have a higher exposure on any given pour than a professional (or more experienced handler). Despite this, the Board did not disagree with Agency's conclusion that "because of greater quantities of antimicrobial, professional handler exposure is expected to be greater than that of consumers" [sic] (Leighton, Sherman and Cohen 2011,

8). Professionals seem to be the appropriate group upon which to later assess chronic risk, but having data only from highly experienced (and nominally more proficient) handlers may underestimate the acute hazards experienced by consumers who have potentially higher but less frequent exposures.

Ethics

Charge to the Board

If the AEATF liquid pour study proposal 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 (Leighton, Sherman and Cohen 2011) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendations 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 of the US EPA's Good Laboratory Practice (GLP) Standards described at 40 CFR 160, and, for research conducted in California, the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (AEATF 2011). Requirements of FIFRA §12(a)(2)(P) also apply. Researchers who participate in the study and interact with study participants will be required to undergo ethics training. The training will include the successful completion of the course from the National Institutes of Health (Protecting Human Research Participants) and/or the Basic Collaborative IRB Training Initiative Course.

The protocol was reviewed and approved by an independent human subjects review committee, 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, Inc. is also listed as an active Institutional Review Board (IRB) on the Office of Human Research Protection (OHRP) website (Reg. #IORG0002954). Copies of all correspondence with IIRB, Inc. (Shah 2011b, 2011c) and a copy of IIRB, Inc. policies and membership roster were provided (IIRB, Inc. 2011a; 2011b). These documents indicate that IIRB, Inc. reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

1. 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, Sherman and Cohen 2011). The proposed study is likely to meet the applicable ethical requirements for research involving human subjects, in accordance with the following criteria:

a. Societal value of the proposed research. The clearly stated purpose of the proposed monitoring study is to determine potential dermal and inhalation exposures to occupational workers and consumers associated with the manual pouring of liquid antimicrobial products. Many consumers and workers pour antimicrobial products, so the research question is important and cannot be answered with confidence without new monitoring data meeting contemporary standards of quality and reliability.

b. Subject selection and informed consent. The inclusion/exclusion criteria are complete and appropriate. Pregnant or nursing women are excluded from participation. Employees or relatives of employees of the investigators and of cleaning product manufacturers are also excluded from participation. Protections are adequate even if a subject were from a vulnerable population. Informed consent will be obtained from each prospective subject and appropriately documented in the language preferred by the subject. Recruitment materials and interactions with potential subjects will be conducted in English or Spanish, depending on subject preference; the Board agrees with EPA's suggestion that AEATF identify the recruiting newspapers and specify "Spanish" rather than "second alternate language." Subjects will be recruited through newspaper advertisements, which will minimize the potential for coercion or undue influence, and the proposed monetary compensation is not so high as to unduly influence participation. Candidates and subjects will be repeatedly informed that they are free to decline to participate or to withdraw at any time for any reason, without penalty.

c. Risks to subjects. The proposed test materials are EPA-registered for the use proposed, are of low toxicity to mammals, and will be used in full compliance with the approved labels. All identified risks are characterized as of low probability, and risks are further minimized by exclusion of candidates known to be sensitive to quaternary ammonium compounds or in poor health or with broken skin on hands, face, or neck; testing in a controlled-temperature environment; alerting subjects to signs and symptoms of heat stress; monitoring heat index with associated stopping rules; allowing subjects to rest whenever they want or need to; close observation of subjects; training of experienced technicians to minimize embarrassment; incorporation of procedures to keep results of pregnancy testing private and to permit discrete withdrawal; provision of appropriate work clothing and Personal Protective Equipment (PPE). Provision is made for discrete handling of the pregnancy testing that is required of female subjects on the day of testing. The Board agreed with the Agency's suggestion to clarify the steps that participants should take if participants have an adverse reaction within 24 hours.

d. Benefits to participants. This research offers no direct benefits to the subjects. The principal benefit of this research is likely to be reliable data about the dermal and inhalation exposure of people pouring liquid antimicrobial products from conventional and reduced-splash containers. These data are intended to be used by EPA and other regulatory agencies to support exposure assessments for a wide variety of antimicrobial products and their uses.

e. *Risk/benefit balance*. Risks to subjects have been thoughtfully and thoroughly minimized in the design of the research. The low residual risk is reasonable, in light of the likely benefits to society from new data supporting more accurate exposure assessments for antimicrobial products.

2. In addition to this analysis, the Board recommended a few edits to improve the clarity of the Informed Consent Form. These are listed below, organized according to the section within the Informed Consent Form in which they appear:

   • Introduction:

   "~~If you do~~ In order to take part in this study, you must read and sign this consent form" (Line 4).

   • Purpose of this Study:

   "This study is being funded by the American Chemistry Council's Antimicrobial Exposure Assessment Task Force II (AEATF II) ~~which~~. The AEATF II is a …" (Line 1).

   • Purpose of this Study:

   The last sentence of this section currently reads: "If you cannot read or understand English, a Spanish speaking member of the research team will read the Spanish translation to you and answer your questions." It is not clear what translated document(s) are being referred to here. The protocol indicates that the forms and supporting documents will be available in either English or Spanish and literacy is required, thus it is not clear why someone would need to read to the participant. The Board suggests clarifying this sentence.

   • Study Procedures:

   The numbered list under "Here's exactly what will happen" sequences the pregnancy test prior to checking for cuts and scrapes on the hands. Some (though not all) Board members were concerned that this ordering might subject female participants to an unnecessary pregnancy test and recommended that the sponsors consider conducting the skin check earlier than any pregnancy test since evidence of any exclusion factors here would make the pregnancy test unnecessary.

   • Benefits:

   Regarding the section of the informed consent form that discusses return of results as a possible benefit of the study, the Board discussed:

   - Whether this adequately covers the issue of return of research results to participants;
   - Whether this topic deserves its own section in the informed consent form under "Receiving your Research Results";
   - Whether it should be presumed that receiving the results would be a benefit; and

- Whether the Board would recommend that the AEATF not offer to return research results to participants.

Based on this discussion, the Board determined that at this time there is neither a positive nor a negative duty to provide results to participants of this study as there is not a clear rationale or benefit to participants. The Board concluded that it would not be objectionable if the Sponsor and the Agency decided not to return individual research results and removed language relating to this from the Informed Consent form. Likewise, if the sponsor chooses to return individual research results to participants, the Board would offer guidance regarding language in the Informed Consent form and to provide the sample letter drafted and discussed during the May 2011 teleconference (EPA HSRB 2011b).

- Right to Withdraw:

The Board recommended revising language consistent to clarify that "If you withdraw from the study after the exposure monitoring begins, you will still be paid for your time."

- Questions about this Study:

The Board recommends adding information to clarify what the IIRB is and does (e.g., "The organization that reviewed and approved this study meets requirements for the protection of research subjects").

3. The Board recommended that EPA and the sponsors consider breach of confidentiality associated with photographs taken or video recorded as a potential risk associated with study participation. For future studies, this risk should be listed on the informed consent form and should be considered by the Agency in its ethics review.

Assessment of Proposed AHETF Research Study AHE500: Exposure Monitoring of Workers During Closed System Loading of Returnable and Non-Returnable Containers in the United States.

Overview of the Study

This proposal presents two agricultural handler exposure scenarios involving loading of liquid pesticides packaged in non-returnable containers and returnable containers respectively. The scenario calls for study participants to mix and load one of thirteen possible surrogate pesticides[1] using closed systems, which are defined by the Agency's Worker Protection Standard (WPS; 40 CFR 170) as mixing and loading systems that are "designed by the manufacturer to enclose the pesticide to prevent it from contacting handlers or other people while it is being handled."

[1] Possible surrogate pesticides include carbaryl, chlorothalonil, Dacthal (DCPA), fosamine, glyphosate, imazapyr, imidacloprid, Malathion, simazine, sulfur, thiophanate-methyl, 2,4-Dichlorophenoxyacetic acid, and 4-(2,4-dichlorophenoxy)butyric acid. The choice of surrogate pesticide will be determined by the preference of the grower involved in the study and the pest pressure on the crop at the time of monitoring.

A total of 21 participants (described in the protocol as "Monitoring Units" [MUs]) will be observed for the non-returnable container scenario; three volunteers from each of seven geographically distinct growing regions will be enrolled using a purposive sampling method (with some elements of random selection). For the returnable container scenario, a total of 15 participants (three volunteers from each of five geographically distinct growing regions) will be observed; these data will be combined with existing exposure data from two pre-Rule studies involving two participants in California and seven participants in Texas (see Collier 2011, 23-25). For each scenario, volunteers will be randomized to mix and load a defined amount of active ingredient within one of three strata. For the non-returnable container scenario, these strata are: 12 to 30 pounds, 31 to 310 pounds, or 311 to 800 pounds of active ingredient, respectively. For the returnable container scenario, these strata are: 60 to 119 pounds, 120 to 1200 pounds, or 1201 to 2400 pounds of active ingredient.

Although the use of closed mixing loading systems permits handlers to wear less PPE than required by pesticide labeling for open mixing/loading, including not wearing chemical resistant gloves in some cases, for this protocol all participants will wear long sleeved shirts, long pants, and shoes plus socks. Chemical resistant gloves and protective eyewear will also be required when the study participants are using closed systems that operate under pressure.

Dermal exposure will be measured by a whole body dosimeter 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 OVS tube connected to a personal sampling pump. Additional measures will also record environmental conditions at the time of monitoring, and observers will collect field notes, take photographs, and record video of participant activity throughout the monitoring event.

The results of sample analysis under the closed system scenario will be posted to the Agricultural Handlers Exposure Database (AHED®), 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 mixing and loading pesticides using closed systems.

Science

Charge to the Board

If the AHETF closed system loading study proposal 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 using closed systems to load liquid pesticide products from returnable or nonreturnable containers?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment that the proposed AHETF scenario and field study proposal AHE500, if revised as suggested in EPA's review (Evans et al. 2011) and performed as described, is likely to generate scientifically reliable data, useful for assessing the exposure of workers using closed systems to load liquid pesticide products from returnable or nonreturnable containers. The Board raised a number of additional concerns, however, for the Agency and study sponsors to consider when collecting and analyzing the exposure data.

HSRB Detailed Recommendations and Rationale

The Board concluded that the research is likely to generate scientifically reliable data, useful for assessing the exposure of handlers who using closed systems to load liquid pesticide products from returnable or nonreturnable containers. However, five additional concerns were raised by the Board.

First, the Board was concerned that the pre-Rule exposure study conducted in 1991 (referred to as AH501 in the AHETF submission [Collier 2011, 23-25]) might not have been conducted with similar attention to detail (e.g., careful observation and recording data about the workers, work practices and equipment) as the proposed studies. The quality of the older data might therefore not match the quality of the data collected in the proposed studies. The Board thus urged the Agency and sponsors to be cautious about including these older data in the AHED exposure data, particularly if they are substantially different from the data collected using the proposed design and protocols.

Second, there is some concern that the proportionality premise regarding levels of residues and amount of active ingredient handled might not hold for these scenarios. These scenarios are somewhat reminiscent of the completed study of the closed cab scenario that the HSRB reviewed at its January 2011 meeting (EPA HSRB 2011a). In the closed cab scenario, the pesticide residues detected on the study participants' hands and clothing appeared to be more related to incidental exposures than to the amount of active ingredient handled. If, as designed, the engineering controls of the closed systems used in this proposal are effective in restricting worker exposure to pesticides, it would not be surprising if similar results were obtained here. Therefore, the HSRB strongly supports the EPA's recommendation (Evans et al. 2011) that detailed observations should occur during the conduct of the exposure so that any incidental worker contacts with contaminated surfaces are noted. Furthermore, the Board suggested that the sponsors and Agency consider the value of measuring surface contamination at the start of the study; if there were a background residue present prior to the conduct of the study, this existing residue would contribute to the total exposure and should be quantified. Because the proportionality objective (objective 2) is crucial to the proposed analysis, as described in Section C12 of the AHETF Governing Document (AHETF 2010, 150), exposure and normalized exposure is interpretable only when the proportionality constants are zero and one. The effect of assuming the proportionality constant is one (or zero), when in fact it may not be, should be also considered. Diversity selection will lead to exposures being more uniformly spread than what

would be observed from random selection (e.g., Figure B2 in the AHEFT governing document [AHETF 2010, 119]). However, under the assumed model, it is not evident that the normalized exposures would also have a more uniform spread.

Third, Board members raised some concerns about the necessity for and the appropriateness of upper limits to the AaiH for those handlers to be included in these studies. While the rationale for the proposed upper limit on study participants using closed systems to load liquid pesticide products from returnable containers seemed sound (particularly since existing data from the two pre-Rule studies was collected from participants with very high AaiH values), it was suggested that no upper limit be imposed on the AaiH of participants using closed systems to load liquid pesticide products from nonreturnable containers. Expanding their range will increase the potential pool of acceptable participants, expand the power of demonstrating proportionality, and also have the potential to yield a better match in the AaiH from this portion of the study with the data coming both from this study and from the previously reviewed AHE80 open pour wettable powder mixer/loader protocol (EPA HSRB 2011a).

Fourth, the Board recommended that criteria be developed before the conduct of the study to ensure that the closed systems included within these studies comply with the provision within the Agency's WPS that such systems must be functioning properly. These criteria should describe how 'proper function' will be (or were) determined and by whom. Such criteria are expected to be a part of scientifically reliable data collection process and to ensure compliance with the WPS.

Finally, a suggestion was made to consider the addition of cotton gloves, to be worn over the handlers' chemical protective gloves. While the Board did not question the rationale to place the focus of these studies on hand exposures inside chemical protective gloves, it felt that being able to measure both unprotected and protected hand exposures would greatly increase the value of this study. In this case, such cotton gloves would need to be tested to see if they would fit over the chemical protective gloves and not interfere with the work tasks.

Ethics

Charge to the Board

If the proposed AHETF scenario and field study proposal AHE500 is revised as suggested in the EPA's review and if the research is performed as described, is the research likely to meet the applicable requirements of 40 CFR 26, subparts K and L?

Board Response to the Charge

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Evans, Sarkar and Sherman 2011) 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 of the US EPA's Good Laboratory Practice (GLP) Standards described at 40 CFR 160, and, for research conducted in California, the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (AHETF 2010; Collier 2011). Requirements of FIFRA §12(a)(2)(P) also apply. Researchers who participate in the study and interact with study participants have or will undergo appropriate ethics training.

The protocol was reviewed and approved by an independent human subjects review committee, IIRB, Inc. of Plantation, FL, prior to submission. As described previously, IIRB, Inc. is fully accredited by AAHRPP, listed as an active IRB on the OHRP website, and reviewed this protocol and associated documents pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A. Copies of all correspondence with IIRB, Inc. (Collier 2011) and a copy of IIRB, Inc. policies and membership roster were provided (IIRB, Inc. 2011a; 2011b).

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, Sarkar and Sherman 2011). 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 described in the study protocol are fivefold:

        1) The risk of heat-related illness. The study will likely involve an increased risk of heat-related illness due to study participation. All participants in the study will be wearing an extra layer of clothing that they would not normally wear using closed systems to load liquid pesticide products from returnable or nonreturnable containers. In addition, loading activities might occur indoors or outdoors and some locations and dates are likely to result in hot and/or humid conditions.

        2) The risk associated with scripting of field activities. In order to ensure all monitoring units (MUs) fall within one of the AaiH strata, AHETF may ask some workers to load more or less product than usual. For some, this might lead to a slightly longer work period for those workers which may increase the risks of acute toxicity associated with exposure to the surrogate chemical or of heat-related illness.

        3) Psychological risks. Participating in AHETF exposure monitoring studies involves activities that are unusual and might cause subjects psychological distress. These include performing an over-the-counter pregnancy test prior to participation (females only) and allowing a researcher to assist with the removal of the whole body dosimeter.

        4) Exposure to surfactants. A very dilute surfactant solution (0.01% v/v sodium dioctyl sulfosuccinate in water) is used as a surfactant for face/neck wipes and hand washes

for all MUs. This surfactant is in a very dilute solution and its use represents a very short exposure period, but the undiluted surfactant causes mild to moderate skin and eye irritation in animals.

5) Risk of exposure to surrogate chemicals.

AHETF has proposed several procedures to minimize these risks:

1) Monitoring and stopping procedures will be instituted. The AHETF will monitor ambient conditions to determine the heat index near the mixing/loading station and base monitoring decisions on the current heat index. Exposure monitoring will be discontinued if the heat index cutoff of 105º F (adjusted for direct sun, if applicable) is reached or exceeded. The Study Director or other researcher shall stop the monitoring and/or move the worker to a cooler environment until monitoring can be resumed. If necessary, some monitoring will take place at night or early in the morning to avoid excessively hot and humid conditions.

2) Clear inclusion/exclusion criteria have been established. Only experienced pesticides handlers who consider themselves in good health will be included in the study. Experience with the mixing/loading equipment to be used in the study will be required of all participants. Participants must also understand Spanish or English, and appropriate provisions have been made for participants who have low levels of literacy.

3) Workers will be reminded of safe chemical handing practices and research staff will practice the face wipe and hand wash procedures with each participant before pesticide handling begins. The use of PPE is required of all participants, and in some cases will exceed the minimum requirements established by the WPS.

4) Appropriate medical management procedures are in place. Eye rinse stations will be on hand in case of an accidental exposure. Medical treatment facilities will be identified in case of an emergency. A medical professional will be on site to observe study participants and provide urgent care.

5) Minors and pregnant or lactating women are excluded from participation, with pregnancy status confirmed by over-the-counter pregnancy testing within 24 hours prior to study participation. All female volunteers will be notified that an additional pregnancy test may be required if there are any delays in the planned start of the study. Only non-pregnant volunteers will be allowed to participate.

6) Procedures have been instituted to decrease psychological risks. Pregnancy tests will be conducted in a private place and information regarding pregnancy test will be kept confidential. Private dressing areas will be provided and researchers of the same gender will be available to assist study participants.

These risks are minimized appropriately and are justified by the potential societal benefits associated with gathering data to determine the potential exposure for workers who mix and load liquid pesticides using closed systems in five regions of the United States.

b. Voluntary and informed consent of all participants:

1) There is the possibility that the participants in this study might be vulnerable (i.e., susceptible to coercion and undue influence). The study protocol, however, includes several mechanisms designed to minimize coercive recruitment and enrollment.

2) 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.

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

c. Equitable selection of study participants:

1) AHETF will first determine a pool of growers and/or commercial pesticide application companies who are eligible to participate in this study. Agricultural workers who work for these eligible businesses will be recruited as study participants. Employers will be required in writing to affirm that they will not influence their employees' decisions about whether to participate in this study. AHETF has developed complete and appropriate inclusion/exclusion criteria.

2. The Board recommended that the study protocol be modified to address the concerns noted in the EPA's Ethics Review (Evans et al. 2011). In addition, the Board raised additional concerns:

a. The Board concurred with the Agency's recommendation (Evans et al. 2011) that a standard operating procedure (SOP) needs to be developed which specifies the criteria by which study investigators will decide that a participant is "too sick to make a decision about getting medical treatment" (Collier 2011, 378). As mentioned in previous HSRB reviews of similar AHETF protocols (e.g., EPA HSRB 2011a), appropriate criteria for determining decision-making capacity can be found in the clinical and clinical ethics literature (e.g., Appelbaum 2007) and generally include all the following: The patient a) can appreciate the situation and its consequences; b) can understand the relevant information; c) can reason about the treatment decision; and d) can communicate a choice.

b. With regard to the return of exposure results to study participants, the Board reiterated its opinion that there is neither a clear positive nor a clear negative duty to provide results to participants at this time. Although the Agency and sponsors have argued that the return of individual exposure results may benefit research participants, based on current debate within the bioethics community regarding the return of individual study results, the Board felt that it was still unclear whether or not this was indeed the case. Thus, the Board

currently neither recommends nor discourages the return of individual study results. The Board remarked that it would not be objectionable should the study sponsors chose to return individual exposure results to study participants, nor would it be objectionable should they chose not to do so. However, if the sponsor did elect to return individual exposure results to study participants, the Board recommended that they look to the letter developed by an HSRB working group (as discussed during the Board's May 2011 teleconference [EPA HSRB 2011b]) for an example of how such information might be provided.

Assessment of Completed 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

No Mas-003 was a field-based study to measure the effectiveness of a lotion containing 16% PMD and 2% lemongrass oil ('No Mas') as a repellent against three genera of mosquitoes (*Culex*, *Anopheles* and *Aedes*). It 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, and was reviewed favorably at the HSRB's October 2010 meeting (EPA HSRB 2010).

A total of 32 participants (selected from a pool of 92 volunteers diverse in age and ethnicity) participated in this study. There were 10 participants (5 female and 5 male) in the dosimetry phase. Twenty treated volunteers, 4 untreated experienced volunteers, and 6 alternates participated in the field-based efficacy test. One female and 2 male volunteers participated in both the dosimetry phase and the field-based efficacy test. The two untreated experienced volunteers from Site 1 also participated as treated subjects at Site 2. Finally, one of the female alternates for the field-based efficacy test also participated in the dosimetry phase of the study.

Dosimetry data was collected from 10 participants (5 female and 5 male). Each participant received an average of 1.20 $\mu l/cm^2$ of product when applied to the arms, and 1.04 $\mu l/cm^2$ when applied to the legs. This is equivalent to 1.14 mg/cm^2 and 0.99 mg/cm^2 of active ingredient for the arms and the legs, respectively. Margin of Exposure (MOE) calculations were based on an assumed 70 kg participant and an acute dermal LD50 value for PMD at the limit dose of greater than 5,000 mg/kg. For the arms, the MOE was greater than 583 and for the legs the MOE was greater than 287, both exceeding a target MOE of 100.

The effectiveness of 'No Mas' as a mosquito repellent was determined in a study conducted at two diverse field sites in the Central Valley of California. Site 1 (Glenn County) was mature floodplain forest surrounding some marshy areas with standing water; only *Aedes* spp. of mosquitoes were detected at this site. Site 2 (Butte County) was a relatively open landscape with hedgerows of willows growing along an active stream; all three genera of mosquitoes were detected at this site, with *Aedes* spp. predominant. Participants at Site 1 were treated approximately 3.2 hours before field exposure, whereas participants at Site 2 were treated approximately 6 minutes prior to field exposure.

Prior to the field-based efficacy tests, each study participant received training in proper observation and aspiration of mosquitoes using pathogen-free laboratory-raised insects. During the field-based test, 10 participants (5 female and 5 male) at each site exposed a treated limb to mosquitoes for one minute every 15 minutes. Two additional experienced volunteers (1 male and 1 female) served as untreated controls to measure mosquito biting pressure. Participants were partnered in groups of two and each partner monitored the front of their own exposed limb and the back of their partner's exposed limb. Mosquitoes landing with intent to bite (LIBe) were recorded, aspirated into containers, and identified in the laboratory. Participants remained in the test until the repellent failed as determined by the first confirmed LIBe, or until the end of the test period, whichever came first. The time at which the repellent failed equaled the Complete Protection Time (CPT) for each subject.

All 10 of the treated volunteers at Site 1 experienced a confirmed LIBe, versus 4 of the treated volunteers at Site 2. Weibull mean CPT values were not significantly different at the two sites, with mean CPT calculated at 9.8 hours (h) (lower and upper 95% = 9.0 h and 10.6 h) at Site 1 and 10.2 h (lower and upper 95% = 8.2 h and 12.5 h) at Site 2. The normal mean CPT values were 9.2 h (lower and upper 95% = 8.1 h and 10.2) and 8.5 h (lower and upper 95% = 7.8 h and 9.2 h) at Sites 1 and 2, respectively. Kaplan-Meier median CPT was 9.6 h (lower and upper 95% = 6.4 h and 10.5 h) at Site 1. Neither the Kaplan-Meier median CPT nor the upper 95% confidence limit could be determined for Site 2, but the lower 95% confidence limit was estimated to be 6.8 h.

Science

Charge to the Board

Is the CLBR completed study No Mas-003 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Fuentes 2011) that this study provides scientifically valid results to assess the repellent efficacy against mosquitoes for the formulation tested.

HSRB Detailed Recommendations and Rationale

The Board agreed in full with the Agency's assessment (Fuentes 2011) of the completed CLBR study No Mas-003. The study was conducted consistently with the protocol and produced results which are sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection provided by the tested repellent against three genera of mosquitoes.

During the meeting, the Agency also asked the Board to consider the question of which of statistical methods -- parametric (with Weibull distribution or normal distribution) or non-parametric (Kaplan-Meier) -- would be appropriate to calculate the CPT for the No Mas repellent. The Board considered the fact that parametric methods based on a normal distribution are not suitable to estimate the CPT due to right-censored and heavily skewed data. Because of this, the HSRB previously recommended the use of survival analysis methods to estimate the mean CPT and its confidence intervals (CI) (see, e.g., EPA HSRB 2010).

The Board concluded that Parametric Survival Analysis based on a Weibull distribution is one form of survival analysis methods and is suitable for predicting right-censored CPT if the Weibull distribution assumption is validated before estimating the mean CPT and its confidence intervals. This type of parametric analysis can be performed using SAS/STAT LIFEREG or SAS/QC PROC Reliability procedures. However, if the Weibull distributional assumption is not confirmed, a Non-Parametric right-censored Survival Analysis method based on the product-limit method (also called the Kaplan-Meier method) should be used to estimate the CPT median and percentiles and the 95% CI, with relatively smaller samples (10 subjects/group or stratum). Furthermore, a separate survivor function can be estimated for each stratum, and tests of the homogeneity among the groups can be conducted using this method. This type of non-parametric analysis can be performed using SAS/STAT LIFETEST procedures.

Ethics

Charge to the Board

Does available information support a determination that the studies were 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 (Sherman 2011a) that the studies submitted for review was conducted in substantial compliance with subparts K and L of 40 CFR Part 26.

HSRB Detailed Recommendation and Rationale

The documents provided by Carroll-Loye Biological Research (Carroll 2011) state that the study was conducted in compliance with the requirements of the US EPA Good Laboratory Practice Regulations for Pesticide Programs (40 CFR 160); 40 CFR 26 subparts K, L and M; FIFRA § 12(a)(2)(P); and the California Code of Regulations Title 3, Section 6710. The study was reviewed and approved by a commercial human subjects review committee, Independent Institutional Review Board Inc. (IIRB, Inc.) of Plantation, FL. Documentation provided to the EPA indicated that IIRB, Inc. reviewed this study pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A) and found it in compliance (Carroll 2011; IIRB, Inc. 2010; IIRB,

Inc. 2011). IIRB, Inc. also reviewed and approved Amendment 1 of November 15, 2010 (Carroll 2011; Sherman 2011a).

1. The Board concurred with the conclusions and factual observations relating to the study, as detailed in the EPA's Ethics Review (Sherman 2011a). Specifically:

    a. Prior HSRB and Agency Review. 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 study (Carroll 2011) was conducted in accordance with the protocol previously reviewed by the Agency (Fuentes and Sherman 2010) and by the HSRB (EPA HSRB 2010). Neither the Agency's nor the HSRB's ethics reviews identified significant deficiencies requiring correction relative to 40 CFR 26, subparts K and L, or to FIFRA § 12(a)(2)(P) (Carley 2010a). Because the study was conducted in California, the approval of the California Department of Pesticide Regulation (CDPR) was also required before the study could be initiated. CDPR granted final approval of the amended protocol and supporting documents on March 21, 2011.

    b. Responsiveness to HSRB and Agency Reviews. Following the HSRB review, the protocol and consent form were modified through Amendment 1 of November 15, 2010 (Carley 2010a; Carroll 2010c). This amendment incorporated changes responsive to the comments of EPA, the HSRB, and CDPR, as well as additional corrections initiated by the investigators. Only two Agency and HSRB suggestions were not incorporated into the revised protocol: the addition of "child/minor" to the list of exclusion criteria and the definition of the acronym 'PMD' in the protocol and informed consent document. Failure to incorporate these suggestions into study protocol and informed consent documents, however, is unlikely to compromise the informed consent process or place the study participants at risk. IIRB, Inc. granted approval to Amendment 1 and supporting documents on November 16, 2010 (Carroll 2011; Sherman 2011a).

    c. Substantial Compliance with Reporting Requirements (40 CFR Part 26 subpart M). CLBR's submission (Carroll 2011), along with the separately submitted documents describing the procedures and roster of the IRB (IIRB, Inc. 2010; 2011), fully meet the requirements of 40 CFR §26.1303 to document the ethical conduct of the research were fully satisfied.

2. The Board concluded that this study 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 study protocol:

    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 efficacy of these new formulations as personal insect repellents.

        • 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.

- Based on toxicological data currently available for 'No Mas', coupled with appropriate exclusion criteria, study participants were unlikely to be at risk of adverse side effects with exposure.

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

- The study was designed to minimize the likelihood of mosquito bites.

- The field-based trials were conducted only in areas where known vector-borne diseases like West Nile Virus had not been detected by county and state health or vector/mosquito control agencies for at least two weeks. Mosquitoes collected during the field studies also were subjected to molecular analyses to confirm that they were free of known pathogens.

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. There was one minor protocol deviation reported: use of a reformatted lotion dosimetry data form without prior IRB review. The Board concluded, however, that this deviation did not affect the integrity of the research or the safety of participants.

Assessment of Published Research Study MRID 48607501: Moiemen et al. (2011) Acticoat Dressings and Major Burns: Systemic Silver Absorption.

Overview of the Study

In the Moiemen et al. (2011) study, 6 human volunteers being treated for severe burns (defined as burns covering greater than 20% of the total body surface area) were exposed to antimicrobial wound dressings containing silver in nanocrystalline form. The study was conducted at the Selly Oak Hospital Burns Unit (also known as the Midlands Burn Center) in Birmingham, United Kingdom (UK), between May 2006 and May 2007. One female subject and five male subjects, ranging from 22 to 56 years of age, were enrolled. As part of their treatment, participants' burns were dressed with either Acticoat® antimicrobial barrier dressings and/or Acticoat® Absorbent; this represents standard of care for patients with severe burns.

Acticoat dressings consist of an absorbent inner core of rayon and polyester fabric sandwiched between two layers of silver-coated, low adherent polyethylene mesh. Acticoat Absorbent is a silver-coated calcium alginate fabric. Both products release silver slowly over

several days. Silver nanoparticles are an effective microbiocide, and Acticoat and Acticoat Absorbent have established antimicrobial efficacy and are licensed for use as wound dressings.

Serum levels of silver were determined prior to enrollment in the study, during treatment with wound dressings, and after treatment discontinuation. Hematology, clinical chemistry, and clinical observations were also performed in order to identify any adverse effects of treatment with the wound dressing. No treatment related adverse effects on hematology, clinical chemistry, wound healing, or clinical signs of toxicity were observed.

Serum levels of silver increased during the wound dressing treatment periods, but there was no apparent relationship between the Total Body Surface Area (TBSA) of the wound and the amount of silver absorbed. Serum levels of silver also remained elevated after discontinuation of wound dressing treatment, suggesting continued systemic absorption of skin-associated silver and/or slow clearance of circulating serum silver. The study authors calculated a median half-life of 46.4 days for elimination of serum silver, which was extrapolated to give a median reduction of 1.5% per day.

Using the data reported in the Moiemen *et al.* (2011) study, in conjunction with *in vitro* data from the Larese *et al.* (2009) study, EPA scientists have estimated that the maximum amount of silver absorbed from nanosilver on human skin is approximately 0.1% per day. The Agency proposes to use this estimated 0.1% absorption factor as part of the overall weight of evidence to estimate dermal exposure for pesticide formulations that contain nanosilver.

Science

Charge(s) to the Board

1) Is the Moiemen *et al.* (2011) study scientifically sound, providing reliable data?

2) If so, can the Moiemen *et al.* (2011) study be used to support the Agency's conclusion that the dermal absorption factor for silver from nanosilver on human skin is less than 0.1%?

Board Response to the Charge

HSRB Recommendation

Despite several deficiencies identified with the study design, the small number of subjects, and the interpretation of the data, the Board agreed with the Agency's assessment that the Moiemen *et al.* (2011) study provides some potentially useful baseline information on the dermal absorption of silver from nanosilver-containing wound dressings.

The Board noted that the calculated values for the dermal absorption of silver from nanosilver in the Moiemen *et al.* (2011) study were higher than values previously reported by another study using *in vitro* intact and abraded skin (Larese *et al.* 2009). Despite this, the Board concluded that the Moiemen *et al.* study could be used to support the Agency's conclusion that the dermal absorption of silver is less than 0.1% as part of the overall weight of evidence.

The Board recommended, however, that the Agency clarify its assumptions in estimating the dermal absorption of silver from nanosilver. The Board also suggested that the Agency consider alternatives for estimating dermal absorption based on the Moiemen *et al.* (2011) study, such as using the less-conservative approach suggested by one Board member and which will be detailed in a separate memorandum to the Agency.

HSRB Detailed Recommendations and Rationale

The estimates for dermal absorption of silver from nanosilver-containing wound dressings in patients with various degrees of skin burns reported in the Moiemen *et al.* (2011) are within the range of values previously reported in some articles but higher than that seen in others (see, e.g., Larese *et al.* 2009). This may be due to limitations in the design and execution of the study, as well as the interpretation of the results, as described in detail below:

1. *Study design and execution.* The authors did not include hematologic and blood chemistry data in their article, so it was difficult to assess whether or not changes in normal organ physiological and biochemical functions (e.g., liver or kidney) may have influenced plasma values of silver for each patient. Although the Agency had access to this information, it was not at liberty to share it with the Board. However, based on their review of these data, the Agency believed that no treatment related adverse effects on hematology, clinical chemistry, wound healing or clinical signs of toxicity were observed.

   The Board noted that the clustering of patients with partial thickness and full thickness wounds might have masked any potential dose-response relationship. Unfortunately, the number of patients in each of these two main categories of wound thickness seemed insufficient to study them separately.

2. *Interpretation.* The authors of the Moiemen *et al.* (2011) study calculated a plasma half-life for silver of 46.4 days and a median elimination rate of 1.5% per day upon cessation of Acticoat treatment; in other words, after treatment was stopped, the daily reduction rate of serum silver levels was estimated to be at 1.5% of the total amount measured in blood. In its discussion of these estimated half-life and median elimination rates, however, the Board viewed the lack of urinary excretion measures as a shortcoming. Urine data are needed to obtain an accurate measurement of the total amount of chemical actually absorbed by the worker via all routes (see, e.g., AEATF 2011, 52). Any estimation of dermal absorption from blood serum samples would be more reliable if urinary excretion data are available.

   The pattern of silver elimination from plasma for most patients was described as biphasic. The study investigators concluded that this apparent biphasic elimination involved biliary excretion at low serum silver levels and urinary excretion levels greater than 100 µg/L[2]. The Agency considered the possibility that this biphasic response may reflect competing processes of systemic absorption of any skin-associated silver present after the wound

[2] This value is the same as that originally reported by Coombs *et al.* (1992) in a prospective clinical study that determined the absorption and effects of the silver ion from sliver sulfadiazine in the context to hepatic and renal function.

dressings were removed. The Board argued that, for this biphasic response to be valid, saturation of biliary excretion pathways should occur under the conditions reported in the study. As this is unlikely when considering the maximal plasma levels of silver achieved and that the fraction of silver eliminated daily was ~1.5% of what was present in blood, the Board suggested two alternative interpretations.

First, the biphasic mode of elimination suggests that two forms of silver -- silver nanoparticles and silver ions -- were being absorbed from the skin. The particles can be subjected to uptake and storage in a tissue compartment(s) from which these particles can be dissociated, leading to a slow release of silver ions into the blood, while the silver ions absorbed from the skin provide the more rapid phase of elimination. The authors did not report whether they considered the likelihood that two forms of silver were being absorbed from the wound dressing.

Alternatively, deposition of ionic silver itself (not necessarily nanoparticles) in tissue reservoirs may explain the apparent biphasic elimination mode. A recent review article by Lansdown (2010) describes how ionic silver that is absorbed into the body readily binds to intracellular proteins, such as serum albumin and macroglobulin, and to intracellular cysteine-rich proteins like metallothioneins. Bone is also described as a potentially relevant storage site for silver -- along with soft tissues such as the eye, brain, liver, kidney spleen, and bone marrow -- following systemic absorption. Slow release from these tissues/cellular reservoirs can contribute to the slow elimination phase of silver seen in the Moiemen *et al.* (2011) study.

The dermal absorption analysis described in Appendix 1 of the Agency's science review (Ryman 2011) was based on the conservative assumption that the blood serum silver levels on any given day are due to that day's absorption. Implicit in that assumption is that each prior day's serum silver is removed from the blood and sufficient new silver is absorbed to reach the next day's level. As described above, such an assumption is not based on a realistic pharmacokinetic model and its results are inconsistent with the median of 9.5 days that it took for patients' serum levels to reach their maximum level and with the estimated 46.4-day half-life serum levels after treatment was discontinued.

Despite these limitations, this absorption factor calculated by the Agency appears to be greater than any of the absorption factors estimated by Board members using alternative approaches, or the absorption factors seen in other studies in the current literature. Use of such a conservative dermal absorption factor is likely to provide greater protections when used for regulatory decision-making purposes. Thus, the Board concluded that the Moiemen *et al.* (2010) study could be used as part of a weight-of-evidence approach to support the Agency's conclusion that the dermal absorption factor for silver from nanosilver on human skin is equal to or less than 0.1%.

Ethics

Charge to the Board

Is there adequate information to support a determination that the study was conducted in substantial compliance with procedures at least as protective as those at subparts A-L of 40 CFR Part 26?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the EPA's Ethics Review (Sherman 2011b), that there was sufficient information regarding value of the research to society, subject selection, risks and benefits, independent ethics review, informed consent, respect for potential and enrolled subjects to conclude that the Moiemen et al. (2011) study was conducted in substantial compliance with procedures at least as protective as those in subparts A-L of EPA's regulation at 40 CFR Part 26.

HSRB Detailed Recommendations and Rationale

This is the second time that the Agency has asked the HSRB to review a study that was located in the public literature and which was conducted after promulgation of the Final Human Studies Rule in April 2006 (c.f. EPA HSRB 2011a). This study was conducted in Britain and was reviewed and approved by the Sandwell and West Birmingham Local Research Ethics Committee, in accordance with the policies and procedures of the British National Research Ethics Service.

1. Standards Applicable to EPA's Reliance on the Research.

   As noted in the EPA's Ethics Review (Sherman 2011b), the Agency's Final Human Studies Rule (40 CFR part 26 subpart Q) defines standards for EPA to apply in deciding whether to rely on research—like this study—involving intentional exposure of human subjects. The applicable acceptance standards are:

   > §26.1703. Prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children. Except as provided in §26.1706, in actions within the scope of §26.1701 EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
   >
   > §26.1705 Prohibition of reliance on unethical human 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, or if conducted in a foreign country, under procedures at least as protective as those in

subparts A through L of this part. This prohibition is in addition to the prohibition in §26.1703.

2. Compliance with Applicable Standards.

As noted in the EPA's Ethics Review (Sherman 2011b), this research did not involve intentional exposure of any pregnant or nursing female subjects or any children. Reliance on the research is therefore not prohibited by 40 CFR §26.1703.

EPA is forbidden by 40 CFR §26.1705 to rely on data from research involving intentional exposure—such as this study— "unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of [40 CFR part 26], or if conducted in a foreign country, under procedures at least as protective as those in subparts A through L of [40 CFR part 26]." This research was approved by an independent ethics review committee, the Sandwell and West Birmingham Local Research Ethics Committee and conducted in accordance with requirements under the UK Central Office for Research Ethics Committees and the Medicine for Human Use Clinical Trial Regulations. The Board observed that the protocol provides that the research "will be performed in accordance with the guidelines of the Declaration of Helsinki (1964) and subsequent revisions," but noted that the Declaration of Helsinki is not regulatory in nature. Rather, the fact that the protocol was reviewed and performed in accordance with specific UK requirements for the conduct of ethical research ensures that the research was conducted under procedures as at least as protective as subparts A through L of the Agency's Final Human Studies Rule.

EPA's regulations governing third-party human research for pesticides at 40 CFR part 26 subpart K permit consent for a subject's participation in research to be given by the subject's "legally authorized representative" when the subject lacks the capacity to consent for himself or herself. Subpart K is consistent with the Common Rule, which was drafted to protect subjects in a wide variety of research settings, including, for example, research into emergency procedures to save lives of unconscious patients.

3. Additional Board Comments and Concerns.

In order to ensure that quality of data regarding Acticoat absorption, the protocol prohibited the use of other silver-based products in these burn patients. One question that was raised concerned whether or not the quality of care provided to these patient/subjects may have been adversely affected because of this prohibition. Based on clinical information on silver-based products in burn care, and additional research by the Agency and Board members regarding standard-of-care for burn patients, the Board was satisfied that the silver-based wound dressing being tested would have been the only silver-based product used. All study participants were thus treated using an appropriate standard of care.

Finally, one member of the Board observed that the reference in this study to obtaining "retrospective consent" is a misnomer. Informed consent is a prospective decision made by

and individual or surrogate to consent for treatment and/or study participant. It is not possible for a study participant or their surrogate to agree to something that happened in the past.

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