March 28, 2012

EPA-HSRB-12-01

Lek Kadeli, Acting Assistant Administrator
Office of Research and Development
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: January 26, 2012 EPA Human Studies Review Board Meeting Report

Dear Mr. Kadeli,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of one new protocol for a study involving intentional exposure of human subjects to pesticides: a proposed Agricultural Handler Exposure Task Force, LLC (AHETF) scenario measuring dermal and inhalation exposure of workers who perform mixing, loading and application of pesticides using powered (gasoline or electric) handgun/hand wand equipment in greenhouses and nurseries (AHE-600).

The Agency also requested that the HSRB review a completed study of dermal and inhalation exposure of professional janitorial workers who clean indoor surfaces with an antimicrobial pesticide product using hand-held pressurized aerosol canisters, conducted by the Antimicrobial Exposure Assessment Task Force II (AEATF II). This study (AEA-04) was conducted after publication of the EPA's expanded final rule for protection of subjects in human research. 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 wipe indoor surfaces with antimicrobial pesticides.

The enclosed report provides the Board's response to EPA charge questions presented at the January 26, 2012 meeting.

Assessment of Proposed AHETF Research Study AHE-600: Mixing, Loading, and Applying Liquid Pesticides in Managed Horticultural Facilities Using Powered Handgun Equipment.

Science

- 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 generate high quality, reliable and useful data for assessing worker's pesticide exposures in horticultural settings.

- The Board provided several additional comments or suggestions with respect to the use of personal protective equipment (PPE), the potential effect of unanticipated incidental

exposures and other variables on proportionality, and the utility of existing European Crop Protection Association (ECPA) data.

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 AEATF II Research Study AEA-04: Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using a Pressurized Aerosol Can for Indoor Surface Disinfecting.

Science

- The Board concurred with the Agency's assessment that this study provides scientifically valid results for estimating the dermal and inhalation exposure of those who apply liquid antimicrobial pesticide products for indoor surface disinfecting using a pressurized aerosol can, but noted several issues, limitations and concerns with the data and proposed analyses.

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.

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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Human Studies Review Board Staff

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

* Not present on January 26, 2012.
† Participated in the January 26, 2012 meeting via telepresence.

INTRODUCTION

On January 26, 2012, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning one new protocol for research involving human participants: a study measuring dermal and inhalation exposures associated with the mixing, loading and application of pesticides using powered (gasoline or electric) handgun/hand wand equipment in greenhouses and nurseries. In accordance with 40 CFR 26.1601, EPA sought HSRB review of this proposed study. This study is discussed more fully below.

In addition, the Agency has data from one completed study measuring dermal and inhalation exposure of professional janitorial workers who clean indoor surfaces with an antimicrobial pesticide product using hand-held pressurized aerosol canisters. In accordance with 40 CFR 26.1602, EPA sought HSRB review of this completed study. This study is discussed more fully below.

REVIEW PROCESS

On January 26, 2012, 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 248, 80938).

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 mixing, loading and application of pesticides using powered (gasoline or electric) handgun/hand wand equipment in greenhouses and nurseries, and one completed study measuring dermal and inhalation exposure of professional janitorial workers who clean indoor surfaces with an antimicrobial pesticide product using hand-held pressurized aerosol canisters.

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

Ms. Megan Boatwright, Analytical Coordinator, Golden Pacific Laboratories.
Dr. Victor Cañez, Technical Chair, Agricultural Handler Exposure Task Force.
Dr. Richard Collier, Administrative Committee Chair, Agricultural Handler Exposure Task Force.
Mr. William McCormick III, Clorox, on behalf of the Antimicrobial Exposure Assessment Task Force II.
Mr. Robert Testman, Vice-President, Golden Pacific Laboratories.

Public oral comments were provided by:

Dr. Victor Cañez, Technical Chair, Agricultural Handler Exposure Task Force

Dr. Richard Collier, Administrative Committee Chair, Agricultural Handler Exposure Task Force.
Mr. Robert Testman, Vice-President, Golden Pacific Laboratories.

One written public comment from a New Jersey resident was submitted, but the substance of that comment was not directly related to the two studies under review by the HSRB at the January 26, 2012 meeting.

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 AHETF Research Study AHE-600: Mixing, Loading, and Applying Liquid Pesticides in Managed Horticultural Facilities Using Powered Handgun Equipment.

Overview of the Study

This proposal presents an agricultural handler exposure scenario involving mixing, loading and application of pesticides using powered (gasoline or electric) handgun/hand wand equipment in greenhouses and nurseries. Pesticides can be formulated as either liquids or as wettable powders.

A total of 30 participants (described in the protocol as "Monitoring Units" [MUs]) will be observed; three volunteers from each of ten geographically distinct growing regions will be enrolled using a purposive sampling method (with some elements of random selection). For each scenario, volunteers will be randomized to mix and load a defined amount of active ingredient within one of three strata: 0.5 to 1.6 pounds, 1.6 to 4.8 pounds of active ingredient, or 4.8 to 15 pounds of active ingredient. After mixing and loading the pesticide, participants will use powered equipment to treat ornamentals and nonbearing fruit trees in nurseries, or ornamentals and vegetables grown in greenhouses, using spray patterns that include downward, outward and upward directions.

For this protocol, all participants will wear long sleeved shirts, long pants, and shoes plus socks. In addition, all participants will wear chemical resistant gloves. Additional personal protective equipment (PPE) may be required depending on product labeling directions, including the use of chemical-resistant aprons when mixing and loading the pesticide, and chemical-resistant headgear when making overhead applications.

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. For study participants wearing

chemical-resistant headgear, patches placed inside and outside of the headgear will be employed to estimate dermal exposure of the protected portions of the body covered by these garments.

Airborne concentrations of the surrogate will be monitored in the participant's breathing zone using an OSHA Versatile Sampler (OVS) tube 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 powered handgun 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 mix, load and apply pesticides using powered handgun equipment.

Science

Charge to the Board

If the AHETF 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 mixing, loading and applying pesticides in managed horticultural facilities using powered handgun equipment?

Board Response to the Charge

HSRB Recommendation

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 generate high quality, reliable and useful data for assessing worker's pesticide exposures in horticultural settings.

Several comments or suggestions were made by the Board with respect to the use of PPE, the potential effect of unanticipated incidental exposures and other variables on proportionality, and the utility of existing European Crop Protection Association (ECPA) data.

HSRB Detailed Recommendations and Rationale

This protocol, a study designed to measure dermal and inhalation exposure of agricultural workers who mix, load and apply pesticides in nurseries or greenhouses using a hand-held sprayer or gun, was well thought out and well designed. The study sponsors (Collier 2011) found no suitable existing information that could constitute some of the MUs for this particular scenario; consequently, the entire scenario has to be conducted. The design requires ten (10)

regions with three (3) MUs per region, for a total of 30 MUs. The rationale for this design is that there are relatively few nurseries and greenhouses that would be suitable for this scenario in most, if not all, regions of the United States. Similarity restrictions will be imposed to assure diversity. The investigators consulted several information sources to identify locations with suitable nurseries or greenhouses that could be venues for the conduct of this scenario. The areas of the country selected represent a variety of climatic and geographic conditions, likely providing the representativeness and diversity sought for the scenario. Given these factors and considerations, the Board determined that the proposed study design is reasonable.

The scenario will include several tasks: mixing/loading of the pesticide product, open pouring of the formulated product, application of the product to the plants, and potentially some cleaning. The objective is to demonstrate proportionality between the amount of active ingredient handled (AaiH) and exposure level. One concern that was raised by the Board was that proportionality may not be observed due to the high variability of unanticipated incidental exposures (e.g., accidentally touching a treated plant or contaminated part of spray equipment in some settings but not others), and these sources may contribute substantially to participants' exposure levels. Because workers may be close to some of the sprayed plants in a setting such as a nursery, it seems likely that unintended contact of workers with these plants might easily occur. In scenarios where unanticipated incidental exposures are likely to occur, it will be important for researchers to observe and document all unintentional contacts with treated plants or other events that might contribute to the exposure levels. However, even if proportionality is not seen -- particularly if the results are attributable to observed unanticipated exposures -- this scenario will still provide valid information about worker exposure when using a powered handgun or hand wand in a horticultural setting.

The Board provided additional recommendations and advice to the Agency about personal protective equipment (e.g., chemical-resistant headgear), respirators, the many sources of diversity, and analysis of data. For example, the Agency was reminded that, should chemical-resistant headgear be worn, the use of patches inside the headgear should yield valid estimates of exposure for those participants wearing such a hat (an issue previously raised at the April 2011 HSRB meeting [EPA HSRB 2011]). However, this method may underestimate exposures if attempts were made to extrapolate these data to those not wearing such headgear. Such extrapolation may not be an explicit intent, but the Agency states its plans to use the head exposure data to develop mitigation strategies (e.g. Evans, Sarkar and Sherman 2011, 11). The effect of the protection afforded by the brim of the chemical-resistant headgear would negatively affect that use. Thus, the Board suggested that the sponsors consider: 1) having study participants use chemical-resistant headgear without a brim (but only if this is allowed by the Worker Protection Standards); or 2) add a third patch dosimeter against the head below the brim, as the density of deposition ($\mu g/cm^2$) onto this patch could be compared to the deposition onto the rest of the face to estimate the magnitude of protection afforded by such a brim.

The Board also discussed the use of respirators and half-masks in the scenario, and how to handle the impact that use of such PPE might have on dermal exposure levels. For example, the Board raised concerns about whether the measured skin exposure to the face would be adjusted upward in proportion to the area of the face/neck covered by a respirator. Although the

Agency responded affirmatively, this adjustment was not stated in the protocol or the Agency's review of the protocol.

Several Board members noted that there are many sources of diversity in this scenario. As a result, it may be difficult to test the numerous variables to the degree the Agency intends for identifying statistically significant differences. Variables that may influence the proposed exposure data include:

1. The predominant direction of spray (downward, outward, or upward);
2. Whether or not the MU does "minor clean-up";
3. Whether the MU uses a handgun or a hand wand;
4. Whether the MU applies the pesticide indoors or outdoors;
5. The width of the path through which the applicator must pass, as determined by facility type (i.e., ornamental greenhouse, vegetable greenhouse, nursery), which may or may not be a surrogate for the proximity of foliage;
6. The formulation type mixed (liquid or solid/wettable powder); and
7. The mixing sequence (pre-mix or tank mix).

The Board also considered issues related to the Agency's recommendation to include wettable powder by at least one participant in each cluster (Evans, Sarkar and Sherman 2011, 4). In particular, concerns were raised about the use of two formulation types (wettable powder and liquid) in the scenario; this could be seen as akin to conducting two studies. The lack of clarity as to how many participants would use the wettable powder in each cluster is problematic for assessing the recommended study design and field conduct. The number of MUs who would handle the powder versus liquid formation is critical for statistical and analytical questions to be fully answered. If both formulations are to be used, the Board recommended that the Agency conduct a separate analysis of each type before combining all of the data for analysis. If the intent is to maximize the power of detecting a difference attributable to this variable, then the sponsor could have 15 MUs use the powder formulation and 15 MUs use the liquid formulation. Alternatively, all MUs could use the wettable powder, as that formulation type is more likely to generate more conservative exposure data.

Finally, the Board cautioned the Agency and the sponsors that the justification for the study may be weak. In particular, the Board raised a question about the utility of ECPA data. The Agency's rationale for not using those data was that the proposed AHETF scenario involves individual workers performing both mixing/loading and application activities, whereas the ECPA exposure data was collected from agricultural handlers involved only in the application of pesticides. The Board was not convinced, however, that this difference precludes the use of existing ECPA data. While there may be other scenario or data quality issues with the ECPA data, the Board recommended that the Agency consider the viability of combining the ECPA application-only exposure data with the Task Force's mixing/loading-only exposure data to satisfy the Agency's registration needs without further human exposure studies. Despite this, the Board noted that the amount of active ingredient handled might be very different for the proposed scenario and the existing ECPA data set; if true, then the existing data sets might not be useful in assessing worker exposure in this horticultural scenario.

Ethics

Charge to the Board

If the AHETF 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 (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 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) (Collier 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. (Collier 2011) and a copy of IIRB, Inc. policies and membership roster were provided (IIRB, Inc. 2010; 2011). 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, 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. Societal value of the proposed research. The clearly stated purpose of the proposed monitoring study is to develop data to determine the potential exposure for workers who mix, load, and apply liquid pesticides using powered handgun equipment in managed horticultural facilities in the United States. This mixing/loading/applying method is

applicable to a large variety of commercially important crops associated with the nursery and greenhouse industry across the US and Canada, and the existing exposure data are likely inadequate. This study will provide a partial answer to the question of what dermal and inhalation exposures are likely for workers who mix/load and apply pesticide products using handguns and hand wands in nurseries and greenhouses. EPA will use the results of this study to estimate the dermal and inhalation exposure likely for a wide range of agricultural pesticides mixed, loaded, and applied under this exposure scenario.

b. Subject selection and informed consent. The inclusion/exclusion criteria are complete and appropriate. Pregnant or nursing women are excluded from participation. Pesticide company employees and contractors to the AHETF 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 (Spanish or English) 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 it is preferable for recruitment discussions to take place away from the work site, to minimize the potential for coercion and that the protocol should describe the types of locations where recruitment discussions between researchers and potential subjects will take place, clarifying whether these discussions will take place at the work site or at locations that are away from the work site. 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.

Depending on the number of employees and size of the grower's facility, the Study Director or researcher may contact employees using an informational recruitment flyer posted in a common work area. Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the grower's employees who express interest in participation. Such recruitment meetings will always occur without supervisors being present. The Study Director or researcher will describe the AHETF Exposure Monitoring Program, the goals of this specific study, the procedures to be used in exposure monitoring, and the risks and benefits to participants. The subject eligibility factors listed in the consent form and SOP AHETF-11.B.6 are appropriate. Candidates who attend an individual interview will be paid $20 whether or not they agree to participate; enrolled subjects who put on the whole-body dosimeter will be paid $80 in addition to their usual pay, whether or not they complete participation.

c. Risks to subjects. The proposed test materials are EPA-registered products registered for nursery and/or greenhouse use and the specific application planned by the grower, 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 who self-report that they are in less than "good" health; alerting subjects to signs and symptoms of heat stress; monitoring heat index with associated stopping rules; 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 PPE. Provision is made for discrete handling of the pregnancy testing that is required of female subjects on the day of testing.

Five kinds of risks to subjects are discussed in the protocol, along with specific steps proposed to minimize them: the risk of heat-related illness; the risk associated with scripting of field activities; psychological risk; the risk of exposure to surfactants, and; the risk of exposure to surrogate chemicals. In this study, risks to subjects are classified as 'greater than minimal' since the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap the chemical) will be increased due to study participation. AHETF has adopted an extensive program to minimize these risks. Appropriate provision is made for safety and medical monitoring. The protocol also incorporates procedures to keep results of pregnancy testing private and to permit discrete withdrawal of a study subject. Finally, the protocol incorporates procedures to ensure that no photographs or videos will be taken in which a worker can be readily identified.

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 mixing, loading and application of pesticides using powered handgun equipment. 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. In particular, in the past the Agency and the Board have suggested that protocols and consent forms clarify the steps that participants should take if participants have an adverse reaction within 24 hours. This was not included in the materials provided by the AHETF, and the Board recommends that such information be included on the consent form.

- Introduction and Purpose:

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

- Procedures Before the Start of the Study:

  Modify the language per the protocol (p. 248/SOP II.D.2) to clarify that the pregnancy test will be taken prior to the start of the study:

8. If you are female, within 24 hours ~~of~~ prior to starting the study you will perform an over-the-counter pregnancy test. If there is a delay in the start of the study of more than 24 hours, another pregnancy test may be needed. The negative results of your pregnancy test will be verified by a female member of the study.

- Injury to Participants:

Add a line indicating the name and contact information of the Study Director or other individual to be contacted if the participant experiences an adverse event within 24 hours.

3. The Board agreed with the Agency that information about potential psychological and social harms related to unwanted disclosure of test results and breach of confidentiality associated with photographs or video may be included in the protocol (Evans, Sarkar and Sherman 2011). However, the Board recommended that this information not be included in the informed consent form as it might give participants the erroneous impression that these risks are particularly significant or that appropriate steps have not been taken to mitigate them.

Assessment of Completed AEATF II Research Study AEA-04: Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using a Pressurized Aerosol Can for Indoor Surface Disinfecting.

Overview of the Study

AEATF II aerosol spraying scenario was designed to measure a typical occupational handler's daily exposure to an antimicrobial spray (containing C14 alkyl dimethyl benzyl ammonium chloride [ADBAC]) packaged in a commercially-available pressurized aerosol spray can.

Eighteen (18) professional janitors were enrolled in the study, and applied (but did not wipe) the product on surfaces at one of three motels in the Fresno, CA area. Study participants were randomized to apply different amounts of product, from one (1) to four (4) cans of product in 1/2-can increments (i.e., 1 to 1.5 cans, 1.5 to 2 cans, and so on up to 3.5 to 4 cans).

Participants wore a variety of clothing combinations, ranging from short pants and short sleeved shirts with shoes plus socks, to long pants and long sleeved shirts with shoes plus socks. No participant wore gloves, but participants were given the option of wearing a respirator during product application; all 18 subjects elected to wear respirators during monitoring. All participants wore inner and outer sets of whole-body dosimeters that were sectioned and analyzed separately.

Dermal exposures were measured using whole-body dosimeters (inner and outer), and hand and face washes. Dermal unit exposures (reported in mg/lb AaiH) were calculated by dividing the summed total exposure by AaiH. The study sponsor report normalized the dermal

exposures by milligrams (mg) of active ingredient applied, but these exposure data were recalculated by the Agency and expressed as mg/lb of active ingredient applied.

Inhalation exposures were measured using a personal air sampling pump and OVS tubes plus a separate pump used to run a RespiCon™ Particle Sampler. This allows for collection and analysis of inhalation exposure monitoring results as total particles, as inhalable particles (<100 μm), as thoracic particles (<10 μm), and as respirable particles (<2.5 μm). Inhalation unit exposures (reported in mg/m^3/lb AaiH) were calculated by dividing the air concentrations by AaiH.

The data will be posted to the Biocide Handlers Exposure Database (BHED®). The Agency plans to use these data generically to estimate dermal and inhalation exposures and risks for other antimicrobial ingredients where the applied product is packaged in a pressurized aerosol spray can. Although the scenario as performed did not include the subsequent wiping of the aerosol spray solution, the Agency believes that dermal and inhalation exposure that results from the subsequent wiping of sprayed antimicrobial solutions can be determined by combining the results of this study with the results of the previously AEATF II conducted ready-to-use (RTU) wipe study (favorably reviewed at the April 2011 HSRB meeting; EPA HSRB 2011).

Science

Charges to the Board

Was the research reported in the AEATF II completed aerosol study report faithful to the design and objectives of the protocol and governing documents of the AEATF?

Has EPA adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating the exposure of professional janitorial workers who apply liquid antimicrobial pesticide products to indoor surfaces using pressurized aerosol cans?

Board Response to the Charge

HSRB Recommendation

The Board concluded that the research reported in the completed monograph, associated field study reports, 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 the AEATF.

The Board also concluded that the Agency has adequately, but not completely, considered the limitations in this study when using the data in estimating the dermal and inhalation exposure of those who apply liquid antimicrobial pesticide products for indoor surface disinfecting using a pressurized aerosol can. In particular, the Board noted several issues, limitations and concerns with the data and analyses. These are described in greater detail below.

HSRB Detailed Recommendations and Rationale

The Board concluded that the study (Testman and Boatwright 2011) was done thoroughly, yielding detailed and helpful data that appear to be reliable. Some data trends were not explained in the accompanying Agency analysis, but overall the diversity of subjects and settings were strengths of the study.

The Board agreed with the Agency that the number of participants was adequate to achieve the primary benchmark accuracy goal. The Board also agreed that the modest diversity of application settings was a reasonable attempt to offset the practical limitation of recruiting and assessing all exposures within one geographic area. The documented diversity in application behaviors indicates the robust nature of the resulting exposure data.

The Agency's analyses of protocol deviations and of the blank, fortified field, and lab samples were acceptable. In addition to the deviations noted in the final report (Testman and Boatwright 2011, 1033-104) or by the Agency (Leighton 2012, 9), however, the Board identified a few more. For example, subject AE4 was apparently observed to be applying the product to surfaces at much heavier rates than usual. About 20% of the way into the sampling time, the study director instructed this subject to “lighten up” in their application (Testman and Boatwright 2011, 488). This intervention comprises an unknown limitation that may have had a large effect on reducing a potentially high exposure. Alternatively, it may have had no significant effect and was unjustified in terms of protecting the subject. Although no specific prohibition against such interventions was found in the protocol, such instructions regarding applicator behavior were counter to the intent of the protocol (i.e., that the study participants “spray surfaces as they would normally do” [Testman and Boatwright 2011, 18]). Thus, it is unclear whether this event actually qualifies as a protocol deviation. However, the lack of an explicit prohibition of study director intervention raised issues in this study’s analysis and interpretation. Guidance about how to handle interventions should be incorporated into future protocols and standard operating procedures (SOPs).

Subject AE18 (in cluster #1) was a borderline outlier without any indication in the field notes of intervention by the researchers. The Board did not disagree completely with the Agency’s conclusion that AE18’s data was not an outlier (Leighton 2012, 15), but believed that one particular combination of these data -- application rate -- reflects the characteristics of an outlier. However, the Board did not advocate excluding this data point from subsequent analyses. Rather, these sometimes substantial differences provide additional support for the diverse and therefore broadly representative nature of the subjects and the qualitatively robust nature of the study results.

The Board also discussed outliers in laboratory recovery data. These data were not used by the Agency to correct field samples; the Board agreed with the EPA’s approach. However, the lack of explicit procedures for handling outliers raised questions among Board members. Explicit discussions about when data should or should not be excluded should be incorporated into future protocols and SOPs.

The Board raised concerns that the 20% higher flow rates (or discharge rates) from the batch of aerosol cans used in the first four MEs, as compared with the flow rates from those cans used in the last 14 MEs, could cause an appreciable difference in exposure (Leighton 2012, 9). Typically, a faster discharge rate through a given nebulizer produces smaller droplets. An analysis of variance for data in this study found a statistically significant difference between the average fraction of the a.i. <10 µm in the first four RespiCon™ samples and the last 14 samples (44% versus 55%, respectively; $p < 0.00001$). This difference is consistent with the expectation that the first batch of canisters may have produced particles with a mass median aerodynamic diameter just over 10 µm and the last batch particles with a mass median aerodynamic diameter just under 10 µm. The difference in particle size is more likely to have been due to the reported difference between flow rates than the difference in ADBAC concentration in the product. Notably, the impact of this probable shift to slightly smaller droplets is small in comparison to the much wider variation in flow rates and particle sizes among the many other products these studies are intended to represent.

The Board also raised concerns that the ventilation data presented were unclear, inadequately recorded, and inadequately interpreted (Testman and Boatwright 2011, 119-20). For example, "fresh air" was presented using different metrics (e.g., %, total fan cubic feet per minute [CFM], and CFM fresh air). Furthermore, the reported air changes per hour seem to differ from separately calculated values by factors of 1.5- to 3-fold. Analyses by one Board member suggest that the overall effect of the deficiencies may have been small; the amount of time that participants spent in each room was so short that airborne ABDAC was just beginning to accumulate by the time the subjects left the space, limiting the effect of ventilation on overall rates of exposure. However, the Board recommended that the Agency consider the potential limitations associated with the heating, ventilation and air conditioning systems in the test facilities.

The Agency requested the Board's advice on the use of RespiCon™ versus OVS results. The major advantage of the RespiCon™ air samples is their ability to look at the data by size ranges. A disadvantage of collecting RespiCon™ samples is the challenge of confronting the difference inherent in the entrance losses of any two air samplers. Such losses are a characteristic primarily of entrance diameters and flow rates, but also of the shape of those entrances and their orientation, and the air velocity and particle diameters in any given setting. These characteristics affect both the RespiCon™ and OVS samples. Unfortunately, it appears that no tests could be found in the literature comparing the OVS with the RespiCon™ sampler (e.g., Leighton 2012, 35-7). Thus, there is no reliable basis upon which to correct the RespiCon™ to the OVS data. For the purposes of calculating dose via inhalation, however, the Board recommends that the <10 micron-size results from RespiCon™ monitors be used because this size range represents the fraction that enters the respiratory tract and thus provides a more conservative estimate of inhalation exposure.

The Board suggested that the dermal and inhalation exposure data be combined to obtain total exposure results. The Board also questioned whether a slope of 1.5, with a confidence interval (CI) including one (1), should be considered as evidence of proportionality. Furthermore, a CI that does not include one may not provide adequate protection. The Board thus recommended that the Agency always clarify coefficients over one. Finally, the Board

recommended that the Agency and the Task Force refrain from using the word 'proportional' without preceding it by an adjective such as 1:1 proportional or 1:2 proportional.

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 (Sherman 2012) that the study 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 prepared by Golden Pacific Laboratories, LLC, and submitted by American Chemistry Council Antimicrobial Exposure Assessment Task Force II under Project No. AEA-04, state that the study was conducted in compliance with the requirements of the EPA's Good Laboratory Practice (GLP) Standards; FIFRA §12(a)(2)(P); and the applicable subparts of 40 CFR 26 (Testman and Boatwright 2011).

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 registered with OHRP (see details above). 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 (IIRB, Inc. 2010; 2011).

1. The Board concurred with the conclusions and factual observations relating to the study, as detailed in the EPA's Ethics Review (Sherman 2012). 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 (Testman and Boatwright 2011) was conducted in accordance with the protocol previously reviewed by the Agency (Leighton, Walls and Sherman 2009) and by the HSRB (EPA HSRB 2009). Neither the Agency's nor the HSRB's ethics reviews identified any significant deficiencies requiring correction relative to 40 CFR 26, subparts K and L, or to FIFRA § 12(a)(2)(P) (Leighton, Walls and Sherman 2009). 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 April 19, 2010.

b. Responsiveness to HSRB and Agency Reviews. Following HSRB review, the protocol and consent form were modified to incorporate changes responsive to the all of the comments of EPA (Leighton, Walls and Sherman 2009) and the HSRB (EPA HSRB 2009). Additional corrections and amendments were also requested by CDPR. IIRB, Inc. granted approval to the amended protocol and supporting documents on April 6 and April 7-9, 2010, respectively (Testman and Boatwright 2011; Sherman 2012).

c. Substantial Compliance with Reporting Requirements (40 CFR Part 26 subpart M). The AEATF II's submission (Testman and Boatwright 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.

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 study protocol (EPA HSRB 2009):

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 compounds as they sprayed indoor surfaces with aerosolized pesticides. 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. 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.

3. Although the first study participants were enrolled in April 2010 and monitoring began in June 2010, shortly thereafter the study was placed on 'hold' as the result of an issue raised by CDPR. In response to a request from some participants to wear a respirator while engaged in study related tasks, the AEATF II decided to offer all study subjects the option of wearing a half-mask respirator fitted with organic vapor cartridges. This decision was made after consulting with the Agency and with the IRB, and the amended protocol and informed consent forms were reviewed and approved by the IRB. Upon receipt of the approved protocol amendment, CDPR requested that the study be halted temporarily until Golden Pacific Laboratories could conduct an additional review of its procedures for respirator use. CDPR granted approval for the amended protocol on May 11, 2011.

   This hold is unlikely to have affected the integrity of the research or the safety of participants. In fact, by allowing subjects to wear a respirator, the researchers further minimized potential risks to study participants. All 18 monitored subjects used a respirator, which was fitted by a trained study investigator and worn under the supervision of a registered study nurse.

4. Several minor deviations from GLP were reported by the study sponsors (Testman and Boatwright 2011, 3), but these were unlikely to have affected the integrity of the research or the safety of participants. Only one of these deviations bears further discussion, namely the enrollment of a participant who self-reported that his health was only "fair," despite the requirement that all participants be in "good health" (Testman and Boatwright 2011, 227). This same issue was discussed by the HSRB during its October 2010 and April 2011 meetings (EPA HSRB 2010; 2011), at which time the Board recommended that the study sponsors clarify the criteria used to establish participants' health status prior to enrollment. Enrollment of this particular participant, however, happened prior to those two Board meetings. Furthermore, although formally enrolled in the study, this participant was not one of the 18 subjects monitored. Thus, the Board concluded that this deviation did not put the participant at increased risk.

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