November 14, 2008

EPA-HSRB-08-03

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

Subject: June 24-25, 2008 EPA Human Studies Review Board Meeting Report

Dear Dr. Gray:

The United States Environmental Protection Agency (EPA or Agency) requested the Human Studies Review Board (HSRB) to review scientific and ethical issues addressing: (1) Agricultural Handlers Exposure Task Force (AHETF) pesticide handler protocols: closed-cab airblast scenario and (2) completed Insect Control and Research (ICR) mosquito repellent efficacy study A117. The enclosed HSRB report provides the Board's response to EPA charge questions presented at the June 24-25, 2008 meeting. A summary of the Board's conclusions concerning these two topics is provided below.

AHETF Pesticide Handler Protocols: Closed-Cab Airblast Scenario

Science

The AHETF has provided the Agency with a well-documented approach to the assessment of worker exposures during closed-cab airblast applications. The Board considered the AHETF study designs and protocols to successfully address many scientific and logistical challenges. The Board appreciated particularly the clarity of the protocols and the extensive documentation associated with these materials. The Board concurred with the Agency that existing data on handler exposures during closed-cab airblast applications are inadequate and that the development of more accurate information is an appropriate goal. The Board also concurred with the Agency that there are only minimal risks associated with the procedures described in these protocols.

The Board strongly advised the Agency to require collection of information on growers who do not respond or who decline to participate, such that the representativeness of participating growers can be evaluated. The Board also recommended that Local Site Coordinators have demonstrable training and expertise in survey implementation so as to ensure optimal recruiting for these studies. The Board judged the current sample size justification to be of limited utility, since it was based on a hypothetical sampling plan that differs from the sampling plan presented for these protocols; i.e., the sample size calculation was based on sampling one worker from each of five growers, whereas the current protocols propose to sample five workers from three growers. The Board concluded that the protocol should be consistent with the governing document which required 5 independent growers and that the validity of the

study would be seriously compromised if data were collected on more than one worker per grower. If the approach presented in these protocols were adopted, then the sample size would need to be increased. The Board recommended that the Agency reconsider the design of the study, or develop an explicit statement of the limitations on the use of data that will be collected under the proposed design. The Board also noted that even with 5 independent growers the design limited analyses to a description of range of exposure and that data collected was not conducive to inference based on statistical analyses. An alternative design for the Agency's consideration is included in Appendix A.

The Board noted that many aspects of the proposed studies are likely to reduce the range of exposures that would be measured with applicators under real-world conditions. While a reduction in the range of exposures may be unavoidable due to practical considerations, it should be considered by the Agency when evaluating the usefulness of the data produced by these studies.

In conclusion, if the AHETF materials are revised in accordance with the Agency's suggestions and the Board's recommendations, several limitations with the proposed research will be alleviated and the research is more likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply liquid pesticides using airblast equipment drawn by vehicles with closed cabs.

Ethics

The Board concluded that the proposed studies meet the applicable requirements of 40 CRF Part 26, Subparts K and L.

Completed ICR Mosquito Repellent Efficacy Study A117

Science

The data of study ICR A117 are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes of the genus *Culex*.

Ethics

A majority of the Board concurred with the initial assessment of the Agency that the study submitted for review was conducted in substantial compliance with the applicable requirements of 40 CFR Part 26, Subparts K and L.

Other topics

The Board also provided comments concerning statistical analysis of arthropod repellency studies and revisited its criteria for analysis of completed studies in which planned protocol deviations were conducted.

Statistical analysis of arthropod repellency studies

In the review of the ICR mosquito repellent efficacy study, the Board continued to raise issues concerning statistical aspects of insect repellency studies. To improve the quality of the analyses of insect repellent studies, the EPA should be encouraged to provide better guidance in two areas, both of which would require some additional analyses. First, a meta-analysis, that includes more studies and uses more appropriate models of the relationship between standard deviation and mean time of protection, should be conducted. Second, the potential use of either maximum likelihood methods for estimation of the mean and variance in the presence of heavy censoring or estimation of the proportion of the population having protection times of at least a pre-specified number of hours should be considered as alternatives to those currently used to analyze the data.

Board criteria for analysis of completed studies in which planned protocol deviations were conducted

The Board revisited its criteria for analysis of completed studies in which planned protocol deviations were conducted: (1) prior to IRB review and (2) following HSRB review of the originally approved protocol. The need for such a reevaluation by the Board was informed by its analysis of the completed ICR mosquito repellent efficacy study A117. In the Board's report from its April 9-10, 2008 meeting, it advised the Agency regarding future review of a study with an originally approved protocol by the HSRB:

1.Any study executed prior to IRB approval of the Informed Consent Form and the protocol, or changed in ways that were not approved by the IRB will be judged by the Board as failing to meet the applicable requirements of §40 CFR 26, subparts K.

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

The Board has revised its recommendation as follows:

1. Execution of a study prior to IRB approval of the Informed Consent Form and the protocol, or changed in ways that were not approved by the IRB will be evaluated by the Board to determine whether such actions were or were not in substantial compliance with applicable requirements of §40 CFR 26, subparts K.

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

In conclusion, the EPA HSRB appreciated the opportunity to advise the Agency on the scientific and ethical aspects of human studies research and looks forward to future opportunities to continue advising the Agency in this endeavor.

Sincerely,

Celia Fisher, Ph.D., Chair
EPA Human Studies Review Board

NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use. Further information about the EPA Human Studies Review Board can be obtained from its website at http://www.epa.gov/osa/hsrb/. Interested persons are invited to contact Paul Lewis, Designated Federal Officer, via e-mail at lewis.paul@epa.gov.

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

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Human Studies Review Board Staff

Paul I. Lewis, Ph.D., Executive Director, Human Studies Review Board Staff, Office of the Science Advisor, United States Environmental Protection Agency, Washington, DC

* Not in attendance at the June 24-25, 2008 Public Meeting

INTRODUCTION

On June 24-25, 2008, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning: the Agricultural Handlers Exposure Task Force (AHETF) pesticide handler protocols: closed-cab airblast scenario and (2) completed Insect Control and Research (ICR) mosquito repellent efficacy study A117. Each of these topics is discussed more fully below.

1. AHETF Pesticide Handler Protocols: Closed-Cab Airblast Scenario

The HSRB has previously considered issues related to the design and conduct of research to measure the levels of exposure received by people when handling (i.e., mixing, loading, or applying) pesticides. The Agricultural Handlers Exposure Task Force (AHETF) has previously submitted materials for HSRB review. In response to concerns raised by the Board at its June 2006 meeting, EPA asked its FIFRA Scientific Advisory Panel (SAP), an advisory committee of independent expert scientific peer reviewers commenting on proposed pesticide regulatory decisions, to address a number of scientific issues surrounding handler exposure research at its January 2007 meeting. The Agency presented the results of the SAP review and additional issues at the April and June 2007 HSRB meetings. In response to the SAP and HSRB reviews, the Task Force reworked its research proposal.

At the April 2008 meeting and in earlier discussions with the HSRB, the design of the sampling strategies to be used by the AHETF and by the Antimicrobials Exposure Assessment Task Force II (AEATF), has drawn particular attention. As the Agency reported at the April 2008 meeting, after consulting with experts both within and outside EPA, and considering information presented by the Task Forces, EPA informed the HSRB that the Agency had decided to accept data developed through "hybrid" sampling strategies, i.e., strategies that use a purposive design but which incorporate random elements whenever feasible.

The AHETF has submitted two proposed protocols, each for a different field study involving pesticide application to orchard trees by airblast sprayers while the applicators are within a vehicle with a fully enclosed cab. Both field studies would provide monitoring data for the same scenario; the AHETF and EPA expect to present the protocols for the remaining three field studies associated with this scenario at a future HSRB meeting. When all five field studies have been conducted, data collection for this scenario will be complete.

EPA's regulation, 40 CFR §26.1125, requires a sponsor or investigator to submit to EPA, before conducting a study involving intentional exposure of human subjects, materials describing the proposed human research in order to allow EPA to conduct scientific and ethics reviews. In addition, EPA's regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the proposed research. Because the research proposed by the AEATF involves scripted exposure, it meets the regulatory definition of "research involving intentional exposure of a human subject" and thus these cited provisions of regulation apply to it.

EPA reviewed the AHETF proposals and concluded that, with a number of required revisions, they appear likely to generate scientifically sound, useful information and to meet the

applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L. Because the AHETF would like to conduct these field studies as soon as possible, and since EPA finds that the protocols can meet applicable scientific and ethical standards, EPA presented this protocol for review to the HSRB at its June 2008 meeting.

II.ICR Completed Mosquito Repellent Efficacy Study A117

In its October 2007 meeting the HSRB favorably reviewed protocol A117 from Insect Control & Research, Inc. (ICR) to evaluate the efficacy in the laboratory of two registered products containing picaridin against *Culex* mosquitoes.

Following that meeting, ICR revised the protocol to address EPA and HSRB comments and then submitted the revised protocol for IRB approval. ICR executed the research and submitted a report to EPA.

The Agency's regulation, 40 CFR §26.1602, requires EPA to seek HSRB review of an EPA decision to rely on the results of these studies. The sponsor has submitted these data to support applications for amended registration for the two test materials. EPA has reviewed the research, applying the standard in 40 CFR §26.1705, which states:

> **§26.1705 Prohibition on reliance on unethical research with non-pregnant, non-nursing adults conducted after April 7, 2006**
>
> Except as provided in §26.1706, in actions within the scope of §26.1701, EPA shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part . . . This prohibition is in addition to the prohibition in §26.1703.

EPA determined that the data are scientifically sound, and although there were some irregularities in the conduct of recruitment, that the study appeared to meet the standard of §26.1705. Unless the HSRB advises that the conduct of the study was not in substantial compliance with EPA's rules for the protection of human subjects of research, EPA proposes to rely on the results in considering the pending applications for amended registration.

REVIEW PROCESS

On June 24-25, 2008, the Board had a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the Federal Register "Human Studies Review Board: Notice of Public Meeting" (73 Federal Register 46, 12413). At the public meeting, following welcoming remarks from Agency officials the Board heard presentations from the Agency on the following topics: (1) Overview of EPA's assessment of AHETF pesticide handler protocols: closed-cab airblast scenario and (2) ICR completed mosquito repellent efficacy study A117.

Oral comments
The following oral comments were presented at the meeting:

(1) Overview of EPA's Assessment of AHETF Pesticide Handler Protocols: Closed-Cab Airblast Scenario

Victor Canez, Ph.D. of BASF on behalf of the AHETF
Richard Collier, Ph.D. of Landis International on behalf of the AHETF
Larry Holden, Ph.D. of Sielken and Associates on behalf of the AHETF
Mr. Curt Lunchick of Bayer Crop Science on behalf of the AHEATF

(2) ICR Completed Mosquito Repellent Efficacy Study A117
Mr. Niketas Spero on behalf of ICR,
Robin Todd, Ph.D. on behalf of ICR
Ralph Piedmont, Ph.D. of Loyola College of behalf of ICR, Inc.
Mr. Andrew Pechko of Avon

Written comments
Written comments were received by:

Richard Collier, Ph.D. on behalf of the AHETF
Mr. Micah Reynolds of behalf of ToXcel
B. Sachau, private citizen

For their deliberations, the Board considered the materials presented at the meeting, written public comments and Agency background documents (e.g., the published literature, Agency data evaluation record, weight of evidence review, ethics review, pesticide human study protocols and Agency evaluation of the protocol or study). For a comprehensive list of background documents visit the www.regulations.gov, or EPA's HSRB website at http://www.epa.gov/osa/hsrb/

CHARGE TO THE BOARD AND BOARD RESPONSE

Overview of Assessment of AHETF Pesticide Handler Protocols: Closed-Cab Airblast Scenario

If AHETF's proposed closed-cab airblast application scenario design, field study protocols AHE55 and AHE56, and supporting documentation are revised as suggested in EPA's reviews:

Science

Does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply liquid pesticides using airblast equipment drawn by vehicles with closed cabs?

Board Response to the Charge

General Comments

The AHETF has provided the Agency with a well-documented approach to the assessment of worker exposures during closed-cab airblast applications. The Board considered the AHETF study designs and protocols to successfully address many scientific and logistical challenges. The Board appreciated particularly the clarity of the protocols and the extensive documentation associated with these materials. The Board's concerns centered around study design issues and exposure variability constraints.

Study Design Issues

The designs proposed for the citrus (FL) and pecan (GA) studies have many positive aspects; however, two issues can significantly limit the utility of the data to be collected.

Low response rate

The AHETF anticipates a response rate by growers of about 5%. This extraordinarily low anticipated response rate has implications regarding the design of the study. Without information about important characteristics of the 95% of growers who are expected to refuse to participate in the study, the data obtained from the 5% who agree to participate cannot be considered a meaningful sample. It is not possible to determine whether the data collected from the responders can be considered in any way representative of the data that would have been obtained if the entire population of growers could have been observed unless: (1) it is possible to determine whether the 5% responders are a random sub-sample of the population of growers in the counties in the study; or (2) the missing data mechanism can be estimated from information collected from the non-responders. However, as currently written the AHETF study design provides no opportunity for collecting information from non-participating growers. Furthermore, no evidence is provided in the protocol regarding the expertise of the Local Site Coordinator (LSC) regarding his/her effectiveness as a recruiter of reluctant study participants. Given the generally unsuccessful prior experiences of AHETF with respect to the recruitment of participants for these types of exposure studies, reliance on a LSC without documented expertise in survey implementation appears to be a major shortcoming of the proposed approach.

Deviation from the design that served as the basis for sample size calculations

Earlier documentation provided by AHETF included extensive discussion and justification of a sample consisting of five monitoring units (MUs) in each "cluster", where cluster was defined as a combination of crop, state and location within state. In those calculations, each MU was assumed to be associated with a different operation (grower), and the ICC of 0.3 (rather low) was meant to account for correlations arising from applicators working in the same general geographic area, on the same crop, under similar climatic conditions, etc. The ICC did not include covariances that would arise within sub-clusters; i.e., applicators working for the same grower. Thus, the Board finds that it is problematic to now argue that the same sample

size of five MUs is still adequate when the five exposure measurements will be obtained from only three farms. If this is the new design, then the sample size needs to be re-calculated and would be expected to increase if the same estimation accuracy is to be met.

In light of these observations, several aspects in the proposed design of the citrus (FL) and pecan studies (GA) merit discussion as described below. In addition a few Board members proposed an alternative design for choice of growers in the study as described in Appendix A.

Number of Monitoring Units (MU) per grower

The Board recommended that no more than one MU be associated with a grower. If more than one MU is to be selected from a grower, then the AHETF should justify the sample size in light of the additional correlation that is expected to arise between applicators that work for the same grower.

Small Growers

The Board was concerned that the recruitment process will focus on growers with multiple workers. This may eliminate small growers who employ only a single pesticide handler. Yet these are often the workplaces in which the higher exposures occur due to fewer resources available for safety training, PPE, etc. The Board recommended that the AHETF better define the recruitment process in regard to local resources and how these local resources will be contacted. The AHETF is preparing to conduct studies in Florida citrus and in Georgia pecans. The Task Force should be able to identify for the Agency the individuals or organizations that will be contacted in these cases.

Applicator Behavior

The Board was concerned that the proposed studies will not capture the full exposure variability in this population, since applicators will not necessarily practice normal behavior while participating in these studies. For example, if another worker conducts all mixing and loading, then it seems likely that the applicators being studied will not exit their cabs as frequently as they might otherwise. The AHETF documents state that "AHETF suspects that exposure potential, especially dermal exposure, may be impacted by how often the applicator gets out of the closed cab." The Board agreed that this behavior is likely an important factor for applicator exposure in this scenario. Transitioning between tasks is usually an opportunity for exposure, but apparently this will not take place in these studies. The Board recommended that the Agency require the Task Force to record the number of times a worker exits the closed cab during the study period; these data can then be considered in evaluating the validity of the actual exposure scenarios that occur during the study.

If applicators do leave the cab they will need to wear all PPE required by the label and the EPA Worker Protection Standards (WPS). This makes sense, but will tend to underestimate actual exposures, since under normal working conditions many workers will not adhere to these procedures. For example, repair or adjustment of equipment is often hindered by chemical

protective gloves, and applicators often remove their gloves to perform these tasks. Such behavior will not be captured in these studies, leading to lower exposure values than might otherwise be seen.

An excerpt from the AHETF documents states that "workers will be allowed to follow their normal procedures as long as they fit the scenario definition and do not conflict with EPA's Worker Protection Standard. . . . Opening windows . . . therefore, will not be allowed." Again, this adherence to WPS is reasonable, but will not capture those exposures that occur when windows are open, which is not an uncommon occurrence.

Mixer/Loaders

The Board raised the question as to whether mixer/loaders should be considered to be participants in these studies, as they are being asked to perform certain tasks within the study, even though they are not being monitored for exposures. If so, these workers should provide informed consent.

Dormant Applications

AHETF has decided to exclude dormant applications for these studies. AHETF documents state that "dormant applications are estimated to account for 15% or less of all airblast applications." It was not clear to the Board why dormant sprays would be excluded, since they represent nearly one-sixth of the applications on these crops. It is very likely that exposures to applicators will differ between dormant and full-foliage spraying. Since the goal of these studies is to capture a representative sample of exposures, the Board considered that it would be reasonable to have approximately one-sixth of the applications in the study conducted under dormant conditions.

Exclusion of Tall Hops

The AHETF documents state that "trellis crops will be considered as a group with one exception – tall hops." The Task Force document did not provide a clear rationale for this exclusion. If exposures during applications to tall hops are different from other exposures, then the data generated by these studies may not capture the full range of applicator exposures.

Product and Packaging

The AHETF documents state that "the actual product and packaging type has no influence on the potential exposures to these applicators and is, therefore, not an important consideration for this scenario." The rationale for this statement was not provided. The Board raised the example of wettable powders and soluble packets that might clog spray nozzles, prompting the applicator to have direct contact with equipment, thereby increasing exposure potential.

HSRB Consensus and Rationale

The AHETF has provided the Agency with a well-documented approach to the assessment of worker exposures during closed-cab airblast applications. The Board considered the AHETF study designs and protocols to successfully address many scientific and logistical challenges. The Board appreciated particularly the clarity of the protocols and the extensive documentation associated with these materials. The Board concurred with the Agency that existing data on handler exposures during closed-cab airblast applications are inadequate and that the development of more accurate information is an appropriate goal. The Board also concurred with the Agency that there are only minimal risks associated with the procedures described in these protocols.

In regard to study design, the Board strongly advised the Agency to require collection of information on growers who do not respond or who decline to participate, such that the representativeness of participating growers can be evaluated. The Board also recommended that Local Site Coordinators have demonstrable training and expertise in survey implementation so as to ensure optimal recruiting for these studies. The Board judged the current sample size justification to be of limited utility, since it was based on a hypothetical sampling plan that differs from the sampling plan presented for these protocols; i.e., the sample size calculation was based on sampling one worker from each of five growers, whereas the current protocols propose to five workers from three growers. If the approach presented in these protocols were adopted, then the sample size would need to be increased. The Board also cautioned that even with 5 independent growers the design limited analyses to a description of range of exposure and data would not be conducive to inference based on statistical analyses In summary, the Board recommended that the Agency reconsider the design of the study, or develop an explicit statement of the limitations on the use of data that will be collected under the proposed design.

In regard to exposure variability, the Board noted that many aspects of the proposed studies are likely to reduce the range of exposures that would be measured in applicators under real-world conditions; dormant sprays and tall hops applications are excluded; applicators will not conduct their own mixing/loading; applicators may not exit the closed cab on a regular basis; applicators will be required to follow procedures consistent with the Worker Protection Standard. These constraints will likely truncate the high end of the exposure distribution. While this reduction in the range of exposures may be unavoidable due to practical considerations, it should be considered by the Agency when evaluating the data produced by these studies.

If the AHETF materials are revised in accordance with the Agency's suggestions and the Board's recommendations several limitations with the proposed research will be alleviated and the research is more likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply liquid pesticides using airblast equipment drawn by vehicles with closed cabs.

Ethics

Charge to the Board

Does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

The Board concurred with the strengths and weaknesses of the proposed research protocols, as detailed in the EPA's review (Carley 2008). Most of the risks of the study are consistent with the research subjects' daily work lives, or have been minimized as much as possible. In addition, the risks are justified by the potential benefits of eventually having a database of agricultural handlers' exposure to pesticides that EPA can use to make data-driven risk assessments.

The AHETF has addressed many of the major issues of concern raised at the Board's last reviews. There remain a number of additional issues to be addressed. Relating to the risks of the study, the agricultural work being done is not actually part of the study but rather the workers' daily job, and thus the risks of the agricultural work are not risks of the research, and should not be used when assessing the risk-benefit relationship. As there is a risk of fetal exposure to pesticides, all women will undergo a pregnancy test prior to enrollment and if pregnant, will not be enrolled in the study. The Board questions whether there will be any confidential risk counseling be offered to these women, whose daily jobs include handling these pesticides.

Although the AHETF has communicated to EPA that they will include a researcher who is bilingual in English and Spanish to enroll and work with Spanish-speaking subjects, there are a few remaining questions related to language and the consent process. All documents (SOPs and protocols) should be changed to remove reference to interpreters and witnesses, which are now unnecessary because of Spanish-speaking research staff. The protocols state that the expected population of potential research subjects is 90% Caucasian and 10% Hispanic in both Florida and Georgia. Members of the Board felt that this seemed quite low for proportion of Hispanic workers. The Board requested that the Agency confirm that these numbers are correct and are identical for the two states.

Reference is made to reading ability of the subjects, but there is no discussion of how this reading ability will be assessed, or whether it will be assessed in English or Spanish. In addition, the contact information for the researchers (Larry Smith and David Johnson of the AHETF) and Independent Institutional Review Board (IIRB) does not indicate whether or not there are Spanish-speakers available to answer questions by phone. In the description of the consent process, there is thorough discussion of the importance of understanding the information provided and a series of quiz questions is presented. However, there is no description of how this quiz will be used, whether it will be used on all subjects, and by whom. Finally there is no description of how interviewers will be trained to conduct the consent process and recognize whether or not potential subjects understand the information provided.

The translation into Spanish of the consent form, the product risk statements, recruitment flyers and other documents was an area of concern for the Board. Many Board members felt that the IIRB should not provide the translations. Several Board members who are fluent in Spanish stated that the IRB-approved translations were not adequate. Both the English and Spanish consent forms were quite complex and needed simplification. The recruitment poster also was overly complex, using the term "cognitively impaired" for example. Simplification was needed for all documents so that understanding of the information by the potential subjects could be enhanced.

The Board was concerned about confidentiality and made a number of suggestions. While the consent form is clear concerning the use of photographs, the researchers should consider using black-out boxes to de-identify the photos and this should then be explained to subjects. The language in the consent form concerning the photographs may border on exculpatory, and the Board suggested that this section be revised to include a more complete discussion of why photos are being taken and that they will "only be used for purposes of this research." In addition, it seems as if the grower's identity does not appear among the data collected; this should be confirmed. The subject's identity should appear on the consent form, the product risk statement to be signed, and the form for the subject to request his/her own data. The data to be submitted to EPA with the study report should use the study ID number rather than subject name. However, EPA may see or view the identities of the subjects at the time of a quality assurance audit of study documents. This should be explained in the consent process and form.

The section of the consent form that discusses compensation for research-related injury states "AHETF will cover the cost of reasonable and appropriate medical attention that is not covered by our own insurance or insurance provided through your employer." The Board recommended removing the phrase "reasonable and appropriate" since that is something that the researchers or subjects cannot decide but rather is decided by the health care provider.

The Board agreed with EPA's suggestion to have standard procedures described in SOPs and remove them from the protocols, but rather refer to the appropriate SOP. The Adverse Event Reporting SOP refers to WIRB (presumably Western IRB) which is irrelevant for these protocols.

HSRB Consensus and Rationale

The Board concluded that if the AHETF follows the recommendations of EPA and the Board with respect to informed consent and confidentiality the proposed studies meet the applicable requirements of 40 CRF Part 26, Subparts K and L.

EPA Review of Completed ICR Mosquito Repellent Efficacy Study A117

Science

Charge to the Board

Is this study sufficiently sound, from a scientific perspective, to be used, in conjunction with other information, to assess the repellent efficacy of the formulations tested against mosquitoes of the genus *Culex*?

Board Response to the Charge

Overview of the Study

ICR A117 was a laboratory study of repellency to *Culex quinquefasciatus* mosquitoes of two registered products (lotion and spray) containing 10% picaridin; these two formulations are Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent (EPA Reg. No. 806-29) and Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent Spray (EPA Reg. No. 806-31). It was conducted by Insect Control & Research, Inc., of Baltimore, MD on March 4, 2008. The study was managed by toXcel, LLC of Gainesville, Virginia, and was sponsored by Avon Products, Inc. of Suffern, New York. The hypothesis provided by the sponsor was that protection (i.e., repellency) of 8 hours (h) would be demonstrated.

The study was required by EPA to support a proposed extension of label claims to include repellency of mosquitoes which can vector West Nile virus (WNV). Mosquitoes of the genus *Culex* are a major vector of WNV in the U.S. The test products had previously been shown to repel mosquitoes of other genera.

Cages were 2 x 2 x 2 feet; each cage was used simultaneously to test two subjects, each of whom was treated with the lotion repellent on one forearm and the spray on the other. A 250 cm^2 area of each arm was the tested region of skin, and the amount of repellent formulation applied to each arm was the amount (0.42 ml containing 417.5 mg of picaridin for a dosage of 1.67mg/$cm^{2)}$ that had been tested previously in support of the current label. Each cage contained 200 laboratory-reared, disease-free, young adult female mosquitoes which had never been provided a blood meal.

Thirteen adult subjects (7 male and 6 female; females neither pregnant nor nursing) were recruited from the ICR database of previous subjects. The ethnicity and age of study participants were not listed in the documents submitted to the Agency for review. One subject (male), selected by lot, served as an untreated control. After establishing the attractiveness of their untreated arms to the caged mosquitoes, the remaining 12 subjects were treated on each forearm with one of the test repellents, using the dose indicated above.

At thirty-minute intervals the untreated control subject confirmed aggressiveness of the mosquitoes in each of the 6 cages. If in any cage fewer than 5 mosquitoes landed on the forearm

of the untreated control subject within one minute, 200 additional mosquitoes were released into each cage. During the test this was necessary at 2.5 h post-treatment and 200 mosquitoes were added to each of the cages.

Treated subjects exposed their arms to the caged mosquitoes for 5 minutes at intervals of 30 minutes, for 10 hours (20 exposure periods) post-treatment or until failure of efficacy, whichever occurred first. Failure of efficacy was defined as a confirmed bite—i.e., a bite followed by another confirming bite on the same arm within the same or the subsequent 5-minute exposure period. Three subjects experienced efficacy failure on one arm; those arms were not tested further. No subjects experienced efficacy failure on both arms. All 12 treated subjects completed testing.

Over the ten-hour post-treatment duration of the test, one confirmed bite was observed for one of the test repellents and two confirmed bites were observed for the other. In addition, five unconfirmed bites were recorded—three for one repellent and two for the other.

Statistical analyses performed included Kaplan-Meier Product Limit analysis and descriptive statistics consisting of the mean, standard error, and 95% confidence intervals were provided. Medians were not calculated because less than half the sample experienced an efficacy failure. Mean "Complete Protection Time" (CPT) was about 9.5 h for each repellent. Based on power analyses contained in the protocol, it was concluded with 95% confidence that CPT was at least 8 h ± 2 h.

Science Review

The study ICR A117 was carried out in accordance with the ICR protocol A117 which was favorably reviewed by the HSRB in October 2007 and which was revised in February 2008. There was no dosimetry phase to this study, consistent with the earlier studies on these products and consistent with the approved protocol. Also bites were used as the endpoint (except for the negative control which assessed landings) consistent with the earlier studies on these products and consistent with the approved protocol. The only deviation noted was the grouping of subjects in 2 groups of 6 subjects (for the sake of more orderly conduct of the study) instead of 6 groups of 2 subjects as was proposed in the protocol. This deviation related to grouping of subjects would not have affected the quality of the data.

The Board concurs with EPA's assessment of the scientific quality of the accumulated data, i.e., that the data were reliable. However, the Board expressed concern about the use of the Rutledge and Gupta (1999) method of calculating statistical power and also expressed concern about the validity of the mean and standard error calculated by the Kaplan-Meier analysis in light of the large amount of censored data resulting from the complete efficacy of both repellent formulations for the entire 10 h testing period for almost all subjects. An expanded discussion of these concerns and alternate statistical methods are presented in Appendix B of this report.

The Board remains unsure about the nature of the data and the type of statistical analysis that EPA requires for making its regulatory decisions regarding labeling arthropod repellency

products, and encourages EPA to provide more guidance to the Board on this matter in the future.

HSRB Consensus and Rationale

The data of study ICR A117 are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes of the genus *Culex*. Following the recommendations in Appendix B may help alleviate some of the limitations of the currently proposed statistical analysis.

Ethics

Charge to the Board

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

Board Response to the Charge

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Carley 2008). A majority of Board members also concluded that the completed research, as described in the documents submitted to the Agency for review (Reynolds and Kelly, 2008; Spero 2008), met the applicable requirement of 40 CFR Part 26, Subpart Q, namely that the study was in substantial compliance with 40 CFR Part 26, Subparts K and L.

The original protocol for this study (ICR A117) was reviewed at the October 2007 meeting of the HSRB, at which time the Board concluded that the study would meet the applicable requirements established in the Agency's final human studies rule (40 CFR Part 26) pending minor revisions (EPA HSRB 2007). The revisions suggested by the Agency and the HSRB at the October 2007 meeting were duly incorporated into the study protocol (Carley 2008; Reynolds and Kelly 2008; Spero 2008).

The submitted study documents (Reynolds and Kelly 2008; Spero 2008) assert compliance with the ethical and regulatory standards of 40 CFR Part 26, Subparts K and L, as well as the requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) §12(a)(2)(P), and the EPA's Good Laboratory Practice (GLP) Standards described at 40 CFR Part 160.

The study protocol was reviewed and approved by an independent human subjects review committee, Essex Investigational Review Board (EIRB), Inc., of Lebanon, New Jersey prior to submission to the Agency. In the documents submitted to the Agency for review (Spano 2008), EIRB Inc. is described as being accredited by the Partnership for Human Research Protections, Inc. (PHRP). PHRP was dissolved in late 2005, but the organization's website asserts that "the Accreditation status of [affiliated] organizations remain in effect and valid" (http://www.phrp.org; accessed 21 June 2008). The accreditation status of EIRB, Inc., however,

is not listed on the PHRP website. EIRB, Inc. is also described in the submitted documents as "being in the process of obtaining accreditation from AAHRPP (Association for the Accreditation of Human Research Protection Programs)" (Spano 2008, 17). Currently, EIRB, Inc. is not listed as an accredited organization on the AAHRPP website (http://www.aahrpp.org; accessed 21 June 2008). A description of EIRB procedures was previously provided to the EPA with a claim of confidentiality (EPA HSRB 2007), so they were not available for review by the HSRB. Agency staff, however, reviewed the documentation provided by EIRB, Inc., and previously determined these procedures and policies to be in compliance with the applicable standards of the Common Rule (45 CFR Part 46, Subpart A). It is not known, however, if these policies and procedures have changed since first reviewed by the Agency.

Overall, the risks to study participants were minimal and justified by the likely societal benefits, including the production of data on the efficacy of these picaridin-based formulations as a repellent for some of the key mosquito genera known to transmit WNV in the United States. A total of 13 'experienced' volunteers participated in the study – 12 treated subjects and one untreated control chosen at random. The study protocol justified the enrollment of twelve treated participants by stating that ten volunteers are needed to obtain statistical validity; an additional two participants will be enrolled as alternates to "allow for drop outs" (Spero 2008, 29).

The potential risks to study participants, adequately described in the protocol and informed consent document, were four-fold: 1) harms resulting from the physical requirements imposed upon volunteers; 2) reaction to test materials themselves; 3) exposure to biting arthropods; and 4) exposure to arthropod-borne diseases.

One potential risk of study participation was physical strain associated with the requirements imposed upon volunteers, particularly long-term exposure to the warm, humidified laboratory environment necessary to rear and maintain mosquito colonies. The risk of physical harm was minimized, however, by limiting each volunteer's exposure to this environment to five minutes every half-hour. A plan for medical monitoring and treatment of physical strains was also clearly articulated.

The risk that enrolled participants would experience adverse effects upon exposure to the test materials was also minimal. The active ingredient of these two repellent formulations is commercially available and is present at similar concentrations in other EPA-registered products; specifically, picaridin is registered and marketed as an insect repellent in the United States under the registered trade name Bayrepel™ and the brand name Autan®. In addition, picaridin is commercially available and has been used at higher doses as a repellent with little evidence of toxic effects. The inert ingredients are widely used in cosmetic and personal care products, and have previously been reviewed and approved by the Agency under FIFRA. Volunteers with known allergic reactions to insect repellents and common cosmetics were excluded from participating in this study, and the amount of skin treated with picaridin was limited. The study protocol also included clear stopping rules and plans for the medical management of any unanticipated side effects or adverse events associated with product exposure.

The endpoints of the study protocol require two or more mosquito bites to document breakdown of repellent effectiveness. A total of 11 mosquito bites occurred among the thirteen

study participants during the ten-hour observational period. Reactions to mosquito bites are usually mild and easily treated with over-the-counter steroidal creams; each participant receiving a bite was offered Caladryl® or Calamine® lotion to ease the associated discomfort. The study also excluded individuals with a history of severe skin reactions to further minimize the risk of a participant experiencing an extreme physical reaction to a mosquito bite. No study-related adverse events were reported by any of the volunteers during the two weeks following study participation.

The mosquitoes used for the study were bred and raised in a laboratory environment, and had never been fed a blood meal. The mosquitoes thus are likely to be pathogen-free, minimizing the risk of vector-borne disease.

Finally, the study protocol also included several mechanisms designed to minimize coercive recruitment and enrollment, and compensation was not considered to be so high as to unduly influence participation. As required by 40 CFR Part 26, Subpart L, minors and pregnant or lactating women were explicitly excluded from volunteering (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study). The potential stigmatization resulting from study exclusion was minimized by the enrollment of extra 'alternate' participants, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

Overall, the risks to study participants were minimal, but it is nevertheless important to note two significant deviations that occurred during the conduct of this study. First, although the HSRB-reviewed and EIRB-approved protocol states that participants will be treated with the test products and then exposed to mosquitoes in pairs, in reality six participants were treated and simultaneously exposed during each five-minute observation period. This protocol deviation was reported to the EIRB ten days after study completion. Federal regulations, however, state that the only acceptable deviations are those that are unanticipated and that are necessary to protect the safety of trial participants (45 CFR 46.103(b)(4)). In public comments to the HSRB, Dr. Nick Spero of ICR testified that the decision to change the protocol was made at an ICR staff meeting on March 3rd, 2008, one day prior to study initiation. He also testified that the change was made to "eliminate confusion among study participants about when to enter and leave the test area." Although the Board agreed with the Agency's assessment (Carley 2008) that this deviation was unlikely to have altered the risk-benefit ratio for the study participants, several members pointed out that planned protocol deviations are not allowed solely for expedience as appeared to be the case here.

Second, recruitment of study participants began prior to final approval of the informed consent documents by EIRB, Inc. As communicated verbally to ICR by the EIRB Office Manager, Karen Radcliffe, the revised protocol was approved on February 18, 2008. The revised informed consent document was conditionally approved on the same day, pending revision. This approval and conditional approval was also communicated to ICR via email on February 19, 2008. Recruitment of volunteers began on February 18th, with Dr. Spero identifying and calling potential participants to confirm their availability on March 4th, the planned study date.

According to documents submitted to the Agency, permission to begin participant recruitment prior to submission and approval of the revised consent document was given verbally by Ms. Radcliffe (Kelly 2008; Spero, personal testimony). However, the only written evidence of such permission to begin recruitment prior to final approval of the informed consent document was an email submitted to the Agency that was sent to ICR by EIRB, Inc. on February 19th but is dated June 3rd (Reynolds 2008, 3). Such permission also runs counter to formal written restrictions on study execution previously sent to ICR by EIRB, Inc. For example, in a letter sent to Dr. Spero dated August 2, 2007, Dr. Glenn Lambert, Chair of EIRB, Inc., wrote "**Please be reminded that the study may not commence <u>any</u> research activity (including scheduling) until formal, written approval and a stamped consent form is received by the research site**" (Spero 2008, 92; emphasis in original). The approved and stamped consent form was not received by ICR until February 26th, at which time potential study participants were again contacted and the consent document verbally conveyed to them. Copies of the consent document were then mailed and received by all but three of the study participants, and all volunteers were offered the opportunity to visit the ICR offices (without recompense) to discuss the document in greater detail. Although none of the study participants opted to do so, all volunteers were reportedly given ample opportunity to review the document on the morning of the study.

At the April 2008 meeting of the HSRB, the Board concluded that: "Any study executed prior to IRB approval of the Informed Consent Form and the protocol, or changed in ways that were not approved by the IRB will be judged by the Board as failing to meet the applicable requirements of 40 CFR Part 26, Subparts K and L" (EPA HSRB 2008, 35). However, the Board also noted that the actions in question occurred prior to the April 2008 meeting. In light of this and other considerations, some members of the Board felt that these two deviations, taken together, raised doubt about whether the study met the necessary standard of "substantial compliance" with the regulations promulgated in the Agency's Final Human Studies Rule (40 CFR 26.1706) . Other Board members, however, argued that it was unlikely that these deviations either put participants at increased risk or significantly impaired the informed consent process. (Note that the Board has revised this recommendation as described in this report).

<u>HSRB Consensus and Rationale</u>

A majority of the Board concurred with the initial assessment of the Agency that the study submitted for review was conducted in substantial compliance with the applicable requirements of 40 CFR Part 26, Subparts K and L.

Board criteria for analysis of completed studies in which planned protocol deviations were conducted

The Board revisited its criteria for analysis of completed studies in which planned protocol deviations were conducted: (1) prior to IRB review and (2) following HSRB review of the originally approved protocol. Such a reevaluation by the Board was informative based on its analysis of the completed ICR mosquito repellent efficacy study A117. In the Board's report from its April 9-10, 2008 meeting, it advised the Agency regarding future review of a study with an originally approved protocol by the HSRB:

1.Any study executed prior to IRB approval of the Informed Consent Form and the protocol, or changed in ways that were not approved by the IRB will be judged by the Board as failing to meet the applicable requirements of §40 CFR 26, subparts K.

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

The Board has revised its recommendation as follows:

1. Execution of a study prior to IRB approval of the Informed Consent Form and the protocol, or changed in ways that were not approved by the IRB will be evaluated by the Board to determine whether such actions were or were not in substantial compliance with applicable requirements of §40 CFR 26, subparts K.

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

Appendix A: Choice of growers for participation in the AHETF Study

This alternative study design focuses on two counties selected in Florida for illustration. There are approximately 2,500 citrus growers in the two counties under consideration. At a minimum, information on the size of the 2,500 farms is available from Federal or State records. The proposed method includes the following steps (where the actual numbers are hypothetical and used purely for illustration):

(1) stratify the 2,500 growers into three (or a different number) size strata. For the sake of discussion, let us suppose that about 20% of growers (500) can be considered to be "small", 45% (1,125) can be considered to be "medium" and 35% (875) can be considered to be "large";

(2) select, randomly, 2% of the growers from within each size stratum. This will result in a sample of 10 small, 22 medium and 18 large growers, for a total of 50 growers. These 50 growers form our new "sampling frame" and from this frame we will be drawing the sample for the study;

(3) contact each of these 50 growers by sending a letter that explains the purpose of the study, the importance of obtaining exposure information that can be considered representative, and assurance that grower participation and study information will remain confidential. The letter should come from an institution trusted by growers; e.g., county extension service or local land-grant university survey unit. In the letter, also explain to growers that someone from the survey unit will be contacting them by phone within the next two to three weeks;

(4) within the stated period, contact all 50 growers via phone. Interviews should be conducted by *experienced interviewers*, who can revisit issues associated with study goals and design, and can reinforce the importance of participation. Relevant information to be collected during this phone conversation includes: willingness to participate in the study, number of acres under crop, pesticide typically used for treatments, number of applicators employed by the grower and number of acres typically treated by each applicator, equipment (size, type, age) available for spraying liquid pesticide, etc;

(5) from among those growers who agree to participate in the study, select three, six and six at random from the small, medium and large size strata and for these fifteen growers, contact the actual applicators to obtain their consent (or not) for participating in the study. The final goal is to recruit one applicator from the small grower stratum and two applicators from each of the medium and large grower strata. Assuming that more than one applicator in more than the required number of growers in each stratum agree to participate, select purely at random the applicators (and thus the growers) who will ultimately participate in the exposure study;

(6) document the proportion (out of the 50 growers in the sample) who agree to participate and those who do not, and compare the characteristics of each of the two groups to determine whether non-response can be considered to be non-informative in further analyses.

Appendix B: Comments on Statistical Analysis of Arthropod Repellency Studies

Currently, the statistical foundation underlying most analyses in arthropod repellent studies is weak. Adopting the statistics proposed in the paper by Rutledge and Gupta (1999) can lead to flawed analyses. The relationship between standard deviation and mean, if any, is unlikely to be linear. Although it is reasonable to weight the analysis by sample size, the two large studies (from among about 20 studies included in the paper), each with 50 participants, had small means and standard deviations. The relationship tends to be easy to model when the means and standard deviations are small. The challenge arises when the means and standard deviations increase, and this is the region that it is most important to model well. The weighting by sample size had the unintended effect of putting less weight on samples in this region.

When the data are heavily censored, as is often the case in arthropod repellent studies, the use of the Kaplan-Meier method is problematic. If censored values are replaced by the time of censoring, the estimated mean is biased downward, and the standard deviation is under-estimated. The downward bias of the mean tends toward a more conservative result, but under-estimating the standard deviation may lead one to assume more confidence in the results than should be given. It is not appropriate to return to the power analysis conducted prior to the study as a foundation for drawing conclusions.

As an example, one can use the data reported in study ICR A117 in which a confirmed bite was observed at 3 hours with one participant while the other 11 participants did not have a confirmed bite when the study ended after 10 hours. In this case, it is not appropriate to say that the mean time of protection is 8 hours, plus or minus two hours. One can estimate the probability of protection lasting at least 8 hours to be 91.7%, and we are 95% confident that the true proportion of the sampled population having at least 8 hours of protection is between 61.5 and 99.8%. Another approach, which does not seem to have been explored in this setting, is to use maximum likelihood methods that account for the censoring of the values to obtain estimates for the mean and standard deviation.

To improve the quality of the analyses of arthropod repellent studies, EPA should be encouraged to provide better guidance in two areas, both of which would require some additional analyses. First, a meta-analysis, similar to that of Rutledge and Gupta, that includes more studies and uses more appropriate models of the relationship between standard deviation and mean time of protection, should be conducted. Second, the potential use of either maximum likelihood methods for estimation of the mean and variance in the presence of heavy censoring or estimation of the proportion of the population having protection times of at least a pre-specified number of hours should be considered as alternatives to those currently used to analyze the data.

All analyses have been based on the assumption that the population distribution of the protection time is normally distributed. Some evaluation of the appropriateness of this assumption should be conducted. A lognormal distribution is often more appropriate in studies similar to these. For the maximum likelihood approach, the E-M algorithm can be used to obtain the estimates. However, convergence may be an issue if the data are too heavily censored. Certainly, convergence will not be obtained if none of the study participants have a confirmed bite before the study's end. If one or two confirmed bites are obtained, convergence may be

obtained, but the estimates may still be unreliable. The challenges associated with estimation of the mean and standard deviation in the presence of heavy censoring lead one to consider other options. The proportion of the population having the specified protection time is one such alternative. Here, the proportion of the population that must have protection times at least as great as those considered would then be the criterion utilized.

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