December 2, 2008

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
October 21-22, 2008 Public Meeting
Docket Number: EPA-HQ-ORD-2008-0629
HSRB Web Site: http://www.epa.gov/osa/hsrb/

Committee Members: (See HSRB Members list – Attachment A)

Dates and Times:	Tuesday, October 21, 2008, 8:30 AM – 6:00 PM Wednesday, October 22, 2008, 8:30 AM – 2:15 PM (See *Federal Register* Notice – Attachment B)	
Location:	EPA, One Potomac Yard (South Bldg.), 2777 S. Crystal Drive, Arlington, VA 22202	
Purpose:	The EPA Human Studies Review Board (HSRB or Board) provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Celia B. Fisher, Ph.D.
	Vice Chair:	William S. Brimijoin, Ph.D.
	Board Members:	Alicia Carriquiry, Ph.D. Gary L. Chadwick, PharmD, MPH, CIP Janice Chambers, Ph.D., D.A.B.T. Richard Fenske, Ph.D., MPH Susan S. Fish, PharmD, MPH Suzanne C. Fitzpatrick, Ph.D., D.A.B.T. Dallas E. Johnson, Ph.D. Kannan Krishnan, Ph.D. Michael D. Lebowitz, Ph.D., FCCP Lois D. Lehman-Mckeeman, Ph.D. Jerry A. Menikoff, M.D. Rebecca Parkin, Ph.D., MPH Sean Philpott, Ph.D., M.Bioethics Ernest D. Prentice, Ph.D. Linda J. Young, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the meeting agenda (Attachment C), unless noted otherwise in these minutes.	

Introduction and Identification of Board Members

Dr. Celia Fisher (Chair, HSRB) opened the meeting and welcomed Board members, U.S. Environmental Protection Agency (EPA or Agency) staff, and members of the public to the October 2008 HSRB meeting. She acknowledged the efforts of Dr. Paul Lewis (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA) and members of EPA's Office of Pesticide Programs (OPP) in planning and preparing for this meeting.

Meeting Administrative Procedures

Dr. Lewis welcomed Board members and thanked them and his EPA colleagues for their efforts in preparing for this meeting and also welcomed members of the public. Dr. Lewis also acknowledged the efforts of Mr. Hamaad Syed, Ms. Lashonia Richardson, and Mr. Bill Zerfas (all of OPP, EPA) for providing technical support and for their efforts in establishing a new Web portal system for the HSRB. He offered congratulations to Board Member Dr. Jerry Menikoff, who was recently named to lead the Office for Human Research Protections (OHRP) at the Department of Health and Human Services. Dr. Lewis noted that Dr. Kannan Krishnan's resignation from the HSRB becomes effective at the end of this meeting and thanked him for his service to the Board.

As DFO, Dr. Lewis serves as liaison between the HSRB and EPA and ensures that Federal Advisory Committee Act requirements—open meetings, timely announcements of meetings in the *Federal Register*, and meeting materials made available at a public docket—are met. As DFO, he also works with the appropriate officials to ensure that all applicable ethics regulations are satisfied. Each Board member has filed a standard government financial disclosure form that has been reviewed by Dr. Lewis and the OSA Deputy Ethics Officer in consultation with EPA's Office of General Counsel to ensure that all ethics disclosure requirements have been met. Dr. Lewis reminded participants that meeting times would be approximate and that public comments would be limited to 5 minutes.

Welcoming Remarks

Dr. George Gray (Science Advisor, OSA, EPA) welcomed Board members and the public and thanked them for their efforts in preparing for this meeting. He acknowledged the useful information the Board provides to EPA. Dr. Gray also thanked EPA colleagues, Mr. Syed, Ms. Richardson, and Mr. Zerfas for their assistance. Dr. Gray introduced Dr. Pai-Yei Whung, who has been named OSA Chief Scientist. Dr. Whung is responsible for assisting OSA in leading cross-agency scientific activities and ensuring that OSA relies on the best available science. Dr. Whung also provides oversight to the Board. Dr. Gray offered congratulations to Dr. Menikoff and thanked Dr. Krishnan for his services to the Board, particularly in matters related to toxicology. Dr. Gray presented Dr. Krishnan with a plaque recognizing his service to the Board.

Dr. Gray described topics to be discussed during this meeting. The Board will review and approve the June 2008 HSRB meeting report. This report includes Board review of a research proposal from the Agricultural Handlers Exposure Task Force (AHETF or Task Force) designed to assess exposure to pesticides of workers spraying orchards. This represents the first of many such proposals designed to aid the Agency's understanding of occupational exposure. The Board comments on these proposals will be informative for this proposal and future reviews as agricultural handlers studies move forward.

The Board will also review proposed AHETF protocols to test exposure of workers in closed-cab and open-cab airblast scenarios. The Board will review two completed studies that tested insect repellents containing picaridin; protocols for these studies were originally reviewed by the Board in June 2007. The EPA also will brief the Board on recommendations for the design and execution of intentional exposure studies to test pesticides designed to repel arthropods.

Dr. Whung expressed her appreciation for the opportunity to meet with the Board. She explained that her background is in climate change science and noted that she has previously worked with the National Oceanic and Atmospheric Administration and the U.S. Department of Agriculture (USDA). She said that she is looking forward to this opportunity to learn more about human subject research and protection from the Board.

Dr. Whung described her conversations with Dr. Fisher related to future direction for the Board. In discussions with Drs. Fisher and Gray regarding the importance of human subject protection, establishment of a program in human subject research ethics was proposed. This program will raise awareness of human subject research and how it serves the public. Dr. Whung asked Board members and the public to comment on this program.

Dr. Whung expressed thanks to Dr. Krishnan for his service to the Board and congratulated Dr. Menikoff on his new position.

Opening Remarks

Dr. Debbie Edwards (Director, OPP, EPA) welcomed Board members and the public. She noted that the Board's final report for the June 2008 meeting marks the 10th public meeting of the Board; during these meetings, dozens of proposed and conducted studies have been reviewed. Over this time period, a better understanding of the roles of the investigators, EPA science and ethics review staff, and HSRB members has developed. Investigators must clearly describe their research to facilitate thorough science and ethics reviews. Investigators also must be able to defend decisions made in the design of their protocols and help HSRB members understand how changes to the protocol would affect practical matters and the utility of the results. EPA staff must clearly describe the Agency's regulatory needs and perform thorough reviews of the science and ethics of proposed protocols for presentation to the Board. EPA staff also must decide how to respond to Board advice. The Board's role is to provide advice that will result in stronger protocols. The HSRB also assures the public that all intentional exposure research submitted to the Agency under the pesticide laws undergoes thorough review. These roles are complementary and interdependent and beneficial to all involved. Documentation of

research protocols by the investigators has improved over the years, as has the clarity and thoroughness of EPA reviews. HSRB advice has become more sophisticated and better targeted to meet the Agency's regulatory needs. At this meeting, new AHETF protocols will be reviewed and discussed by the Board. The Board also will review the results of protocols executed by Carroll-Loye Biological Research (CLBR) involving the testing of picaridin-containing insect repellents and new EPA guidelines for efficacy testing of skin-applied repellents.

Review of June 24-25, 2008 HSRB Meeting Report

Public Comments

Dr. Fisher invited oral public comment on the draft June 24-25, 2008 HSRB meeting report. No oral public comments were presented.

Board Discussion and Decision on Report

Dr. Fisher opened the Board discussion of the June 24-25, 2008 HSRB meeting report asking for discussion of the section on the AHETF Pesticide Handler Protocols: Closed-Cab Airblast Scenario on pages 12-13 regarding an alternative sampling design for selection of growers; the Board had deemed this a point for consideration but did not completely clarify the importance of such a change. Related to this matter, a clause on lines 37 to 41 on page 15 of the draft report stated, "including implementation of the Board's recommended alternative design" that raised concerns with EPA. Dr. Fisher asked the Board whether its intention was to indicate that inclusion of such a design would be more likely to generate scientifically valid findings and whether inclusion of this phrase emphasizes the importance of such a sampling design, but the Board's consensus was not that the investigators must adopt the design to have a valid study. Dr. Fisher recommended moving the proposed alternative sampling design to the appendix of the report to avoid the impression that use of such a strategy is required for acceptance of the study by the Board.

Dr. Alicia Carriquiry agreed with including the alternative design in the appendix and not requiring that this design strategy be used by the investigators. She asked that the discussion in the report state that investigators should seek to find a better common ground for designing sampling strategies. Dr. Richard Fenske agreed that the intention of the Board was not to claim that adoption of the specific alternative study design was a prerequisite for moving forward with the research.

Dr. Linda Young stated that her primary concern was sampling more than one worker from the same grower. This is a critical component that must be addressed to ensure a scientifically sound study. Dr. Carriquiry added that she had hoped the AHETF would change its sampling design somewhat to reflect Board recommendations. The inadvisability of drawing workers to observe (Monitoring Units [MUs]) from the same grower is critical and had not been included in the new protocols. Although changing this approach is not required to proceed with the research it may limit the usefulness of the data and it was somewhat disappointing that HSRB advice was not incorporated into the protocol. Dr. Fisher noted that the Board makes recommendations that may or may not be implemented by the Agency. The Board must be clear

about the urgency of its recommendations. Based on the minutes of the June 2008 meeting, it appeared that the Board had concluded that the study could proceed but the utility of the data was limited by a number of factors, including the lack of a requirement to gather data from only 1 MU per grower. At the last meeting, the Board noted that data collected from more than 1 MU per grower would provide categorical and descriptive information, but calculations such as mean and standard deviation could not be performed. The Board stated that if the study was performed as described, the study would be worthwhile, but the Board may not have been clear about the serious impact of the sampling design on the scientific value of the data in the draft report.

Dr. Carriquiry clarified that use of the alternative design was not required for the results of the study to be scientifically reliable; however, there are aspects of the design (as described by the investigators) that would result in questionable scientific validity, primarily the use of more than 1 MU per grower. Given the 5-MU scenario, all should be drawn from different growers, but the protocol states that no more than 2 MUs per grower will be sampled. This would result in insufficient numbers of independent observations. Dr. Dallas Johnson said that he disagreed slightly with this conclusion. Requiring the investigators to sample MUs from 25 different growers could increase costs sufficiently to discourage the AHETF from performing the research. He also suggested changing the word "implementation" to "consideration" on line 38, page 15 of the report. Dr. Fenske agreed with Dr. Carriquiry. His understanding of the Board's conclusion was that the current sample size justification was of limited utility since it was based on a different sampling plan than that presented in the protocol. The investigators did not appear to respond to Board recommendations and provided no explanation of why sampling more than one worker at a given site is acceptable, given that this approach differs from the original, hypothetical design presented by the AHETF. Sampling more than one worker per farm would be acceptable if the sample size was increased. Dr. Fenske added that this matter was distinct from the Board's proposed alternative sampling design.

Dr. Fisher agreed that the Board needed to make clear the distinction between the proposed alternative design and the issue of the acceptable number of MUs that can be drawn from a single grower. The alternative design may not need to be adopted in its entirety by the AHETF, but it should consider including some of the design's aspects to improve the proposed sampling design. Dr. Young noted that because the uniformity of conditions within a farm is greater than across farms, selecting each MU from a different farm is critical to obtaining a diverse data set. Dr. Carriquiry added that the increased cost of this approach is minimal compared to the entire cost of collecting data. Dr. Fisher clarified that if the Board asks for a change that improves the scientific soundness of a protocol, cost cannot be a determining factor to implementing such a change. The Board indicated that the sample size rationale that they reviewed was not appropriate for all planned calculations.

Dr. Michael Lebowitz noted that the Board must balance scientific criticism with its understanding and agreement that these studies should be performed. While the Board needs to clearly state how it believes a protocol should be implemented, it does not comment on cost issues. The Board can discuss why the AHETF may not execute an ideal protocol, but the final decision regarding how the protocol is executed rests with EPA and the AHETF. The Board must make clear how it believes the study should be designed, even if the AHETF is unable or unwilling to perform the research according to this design.

Dr. Janice Chambers agreed that the way the alternative design was proposed in the initial report did appear to be a mandate and agreed with Dr. Johnson's suggestion regarding the change of the word "implementation" to "consideration." She asked if Drs. Carriquiry and Young's concerns would be addressed if the 2 MUs at one farm used different equipment to apply the pesticide. Dr. Carriquiry answered that this would be insufficient because at one farm all the different equipment may be in equally poor condition, and also all trees on a particular farm may be exposed to the same wind characteristics (speed and direction). Regardless of the equipment used, all workers would be exposed to a wind speed and direction that may not be found at other farms. If two observations are correlated because of such farm-level effects, the observations contain less information than if they were obtained from different farms. The observations also would not be independent; thus choosing 2MUs from the same farm would seriously compromise the validity of the data.

Dr. Fisher noted that the Board must be clear regarding the seriousness of this recommendation. The HSRB does not dictate EPA decisions, but must make recommendations that maintain the Board's scientific integrity. She proposed considering three categories of recommendations for protocol improvement:

(a) modifications that would enhance a scientifically sound design and analysis;
(b) limitations that need to be considered in data analysis and interpretation of a scientifically sound design;
(c) modifications that are needed to ensure that the design and analyses are scientifically sound.

The issue regarding the number of MUs per grower appears to reach the level of a "c" recommendation. Dr. Fenske clarified that the proposed alternative sampling design would be an "a" level recommendation; truncating the range of exposures and variability would be a "b" recommendation; sample size would be a "c" issue; and recruitment procedures and understanding response rates would be a "b" recommendation.

Dr. Johnson stated that ensuring only 1 MU per grower might not be as critical as Drs. Young and Carriquiry suggest, although it would improve the data. Data including more than 1 MU per grower will provide a range of possible exposures; some statistical analyses could not be performed, but the AHETF did not plan to perform many of these in any case. Dr. Young clarified that if more than 1 MU is drawn from a single grower, there will not be 5 growers in the scenarios. Dr. Johnson agreed that in that case, it would be critical to draw only 1 MU from each grower.

Dr. Fisher asked how to frame the Board's comments that the study could be strengthened if the AHETF provided an improved sample size justification or an increase in sample size. Dr. Lebowitz suggested adding a statement asking the AHETF to ensure the independence of the samples. Dr. Carriquiry said that the Board should expect the protocol to be consistent with what was originally proposed in the sample design Governing Documents, which called for 5 independent observations per cluster; the submitted protocol was not consistent with this design. The validity of the results relied upon the assumption that this design would be used.

Dr. Fenske suggested editing the Board Consensus and Rationale on page 15, lines 38-42. The word "implementation" will be changed to "consideration" as suggested by Dr. Johnson. The alternative design plan for selection of growers will be moved to the appendix, where more detail can be provided than what is usually found in the final report. Dr. Fisher stated that she would change the verbiage in this section to indicate that the design plan had been moved to the appendix. The comments regarding the limited utility of the data if the sampling strategy does not conform to that described in the Governing Documents will remain.

Dr. Fisher requested comments on the Board Consensus and Rationale for ethics (page 17). No changes were suggested. No changes were made to the Consensus and Rationale for science (page 20) and ethics (page 23) for the ICR, Inc. (ICR) laboratory protocol A117. Regarding the Board criteria for analysis of completed studies in which planned protocol deviations were conducted, no changes were made.

Mr. Jordan asked to provide clarification to the Board regarding the AHETF protocols. He noted that the AHETF protocol did not specify that MUs would be drawn from only three growers, but asked instead for the flexibility to draw 2 MUs from a single grower if necessary; the AHETF agreed to strive for 1 MU per grower whenever possible. Mr. Jordan added that this would be further clarified when he presented information on recent AHETF field activities.

Mr. Jordan acknowledged Dr. Carriquiry's points concerning farm-level effects and agreed that the statistical rationale for the sample size was based on the assumption of 1 MU per grower and random selection of the MU and the grower. EPA's understanding of the sample size rationale was that it was a theoretical explanation rather than a scientific justification of the power of the sample size to calculate a particular mean or standard deviation. These additional limitations on the data set are similar to the farm-level correlation concerns raised by Dr. Carriquiry. It would be helpful to EPA if the Board would clarify the effect of using 3 growers versus 5 growers; 25 observations of workers will still be gathered, most from different farms. He asked if drawing MUs from 15 or 25 growers would change the ability to extrapolate statistical inferences from this group of workers to the larger population.

Mr. Jordan noted that differences in workers, equipment, and sites within the farm could mitigate the farm-levels effect. The time of year during which measurements are taken and the county in which the farm is located also could affect results. Given these issues, the AHETF expects to generate a range of exposures for a given scenario; EPA will use the data to analyze exposure for these scenarios. Dr. Lebowitz said that it might not be possible to recognize the extent of bias in a range of observations or determine different percentages of exposure. The data will be an improvement over currently available data, but will have some uncertainties that cannot be resolved. Dr. Carriquiry remarked that she does not believe any statistical analyses can be performed with these data. She asked the Board to develop a recommendation calling for the AHETF to use the 1 MU per grower design; such an approach will result in semi-independent observations and a diversity of observations. Three observations are insufficient for developing a good understanding of the range of possible exposures.

Dr. Fisher asked Board members to accept changes to the report as discussed during this session. All Board members agreed to the changes. Referring to a letter from the Agency to the Board detailing its decision to approve the implementation of the AHETF study prior to the Board's adoption of the final report, Dr. Fisher cautioned that the minutes of the meeting are not equivalent to the Board's final report. HSRB's By-Laws call for the Board to reach a consensus at its meetings. The meeting minutes are the Chair's minutes and impression of the meeting; these are not approved by nor do they speak for the Board. After the meeting report is drafted, the Board reviews public comments submitted on the report, conducts a final review and approval and approval of the report for subsequent release.

EPA Follow-up on HSRB Recommendations

Pesticide Specific HSRB Recommendations

Mr. Jordan described events taking place during the execution of the AHETF closed-cab airblast (CCAB) scenario for Georgia pecans and Florida citrus crops. The goal of this presentation was to provide a better understanding of how the EPA uses HSRB advice, how EPA works with investigators to improve protocols; and how EPA uses the results and experience of the investigators to inform future protocols. Efforts to execute the Georgia pecan protocol also have shaped EPA's presentations given at this meeting.

Topics considered at the June 2008 HSRB meeting included the ICR A-117 laboratory study of mosquito repellent efficacy, the AHETF CCAB scenario, and two protocols for this scenario: AHE55 (Florida citrus crops) and AHE56 (Georgia pecans).

According to Mr. Jordan, the HSRB concluded that the data from ICR A-117 were sufficiently scientifically sound to be used to assess the repellent efficacy of the tested formulations against *Culex* mosquitoes and that the study was conducted in substantial compliance with the applicable requirements of 40 Code of Federal Regulations (CFR) part 26, subparts K and L; therefore, EPA will rely on data from ICR A-117 to support label claims that the product tested will repel mosquitoes which may vector West Nile Virus (WNV).

The minutes from the June 2008 meeting and the draft HSRB report suggested a number of changes to improve the scientific design of the proposed CCAB scenario research; the Board also concluded that the proposed studies met the applicable requirements of 40 CFR part 26, subparts K and L. Based on this information, EPA and the AHETF developed a list of revisions required before implementation of the protocols. The AHETF revised the protocols consistent with EPA and HSRB comments, obtained Institutional Review Board (IRB) approval, and executed the field phase of the pecan protocol and initiated the citrus protocol. EPA has closely monitored AHETF implementation of the pecan study, particularly recruitment of participating growers.

EPA is eager to acquire the new AHETF data because it represents a significant improvement on existing data for pesticide handler exposure. In addition, unless the pecan and citrus protocols were initiated soon after the June 2008 HSRB meeting, the Task Force would miss the 2008 growing season. Given this urgency, EPA and the AHETF met to discuss the June

2008 HSRB meeting and identified a list of approximately 36 comments made during the meeting that both EPA and the AHETF believed should be considered. EPA and the Task Force decided how to address these issues, changed the proposals accordingly, and decided to proceed with implementation of the research. The Agency concluded that the Board's review of this proposed research was sufficiently favorable, that the AHETF had been responsive to Board comments and suggestions and substantially revised the protocols, and therefore the research could proceed.

Because of the Agency's impression of the Board's interest in having results from the pecan and citrus protocols to aid in review of subsequent protocols, field implementation of the pecan protocol will be described at this meeting by Mr. John Carley (OPP, EPA). EPA and the AHETF believe that this experience provided valuable lessons that would further improve the recruiting process and other aspects of future AHETF studies.

Dr. Fisher asked EPA to clarify whether the Board would be reviewing a completed protocol at this meeting and if review of new protocols in the future will clearly indicate implementation of lessons learned from previously conducted protocols. Mr. Carley responded that while the work for these CCAB protocols has not been completed, it can nonetheless provide valuable information to the Board, particularly regarding Board concerns raised at the June 2008 meeting. The changes will be systematically described and reflected in the new protocols. This material came to EPA after the Agency had reviewed the new proposals and reflects the experience of the AHETF, which will be incorporated into further revisions of existing and new protocols. EPA is not asking for recommendations on this material.

Dr. Fenske inquired if scientific reviews of new protocols will be presented before the Board discusses the protocols. Mr. Carley answered that recommendations for changes will be included in new protocols based on lessons learned as described in his presentation; however, the EPA science and ethics review of CCAB protocols at this meeting were completed before the new information was received. Dr. William Brimijoin noted that the presentation was designed to educate the Board and inform their understanding of the EPA changes recommended to the AHETF. He suggested that the Board confine itself to questions of clarification only.

EPA Overview of AHETF Research Progress since June 2008 HSRB Meeting

Mr. Carley introduced four topics to be addressed in this presentation: (1) identification of HSRB concerns; (2) addressing identified concerns; (3) field implementation of AHE56 in pecans; and (4) field implementation of AHE57 in citrus. EPA and the AHETF met after the HSRB meeting in June 2008 to revise the CCAB and open-cab airblast (OCAB) scenarios according to HSRB concerns raised at the meeting. The AHETF and EPA developed a list of issues to address and a timeframe for addressing them. The AHETF worked on revising the scenarios in June and July 2008, including obtaining IRB approval where required. In early July 2008, the AHETF revised the protocol and consent form for AHE56, which monitors exposure when spraying Georgia pecans. The end of the 2008 spraying season was quickly approaching and both EPA and the AHETF were eager to implement the research in 2008.

At the close of the June 2008 meeting, EPA believed that the Board review of the protocols had been generally favorable, with some concerns. EPA encouraged the AHETF to proceed with the research, with the caveat that the Agency and Board had raised a number of concerns that required attention. To identify and clarify Board concerns, the AHETF and EPA compiled notes from all staff who attended the June 2008 HSRB meeting. EPA and the AHETF then exchanged lists and developed a joint list of approximately 40 specific concerns raised by EPA and/or the HSRB.

EPA sorted the 40 identified concerns into 5 categories, depending on when and in what context they needed to be addressed. The 5 categories were: (1) address before executing AHE55 and AHE56 [10 concerns]; (2) address in new CCAB/OCAB submissions [4 concerns]; (3) incorporate in revised Standard Operating Procedures (SOPs) [14 concerns]; (4) address in future scenarios [6 concerns]; and (5) no immediate action required [6 concerns].

Issues to address before execution of the protocols included the following:

- disallowing participation by employees of the Local Site Coordinator (LSC)
- using bilingual researchers rather than interpreters
- explaining how the Study Director will determine understanding of subjects in consent interviews conducted in Spanish
- providing toll-free English and Spanish information telephone numbers
- capturing ethnicity and gender of participating workers
- clarifying the intended uses of photos/videos
- minimizing identifiable photos/videos of participants
- referring to “AHETF” consistently with regard to “AHETF” and “Sponsor”
- dropping the reference to “cognitively impaired” from the recruitment flyer
- changing “liquid pesticides” to “airblast application of liquid sprays.”

These changes were made and addressed satisfactorily in the amended protocols approved by the IRB on July 21, 2008, before protocol execution commenced.

Issues to address in new CCAB/OCAB submissions included the following:

- minimizing the paraphrasing of SOPs in protocols
- simplifying submissions
- explaining the voluntary nature of participation at the beginning of consent forms
- ensuring accurate Spanish translations.

The first two issues have been addressed; many of the paraphrases of the SOPs have been eliminated from the protocol, substantially reducing opportunities for disparity among related documents. This should help field investigators comply consistently with the SOPs governing their work. The submission structure also has been simplified. Volume I includes scenario design, summary of expert information, and surrogate labels and Material Safety Data Sheets (MSDS). Volume II comprises the protocol and supporting documents for the first field cluster along with the complete IRB correspondence for the first protocol. Volumes III, IV, and subsequent volumes will include protocols and supporting documents for subsequent field clusters along with complete IRB correspondence for the protocols in the clusters. Because there is significant duplication across the volumes containing the field study protocols within a scenario along with voluminous files of IRB correspondence, the AHETF has proposed streamlining future submissions by describing all field clusters in a single protocol, with only one record of IRB review, where possible. This is anticipated to reduce the bulk and internal redundancy of future AHETF submissions. This proposal has been approved by the Joint Regulatory Commission (JRC).

It was noted by the Board that the voluntary nature of participation in these protocols needs to be emphasized. The voluntary nature of participation is expressed very clearly in both the English and Spanish consent forms, but not until page 7 of the consent form. Addition of a sentence on the first page of the consent forms would be an easy and appropriate way to further emphasize the voluntary nature of participation; however, EPA does not judge this to be a critically needed change to the existing IRB-approved consent forms. EPA has concluded that the translations of the consent forms provided are not significantly inaccurate, but has identified four specific issues to address: (1) identifying and using a dialect appropriate to the likely subject population; (2) translating pesticide-specific terms accurately; (3) maintaining an appropriate tone in translations; and (4) ensuring a reading level in the translations appropriate to the likely subject population. These issues have not yet been resolved and EPA has agreed to advise the AHETF on best practices for the proposed revisions. EPA is particularly concerned about how to best ensure accurate translation of pesticide-specific or agricultural-specific terms, because such terms vary regionally as well as by language group. The California Department of Pesticide Research (CDPR) has a glossary of pesticide terms in both English and Spanish; this, along with the assistance of EPA staff with extensive experience translating worker training materials, will be used to guide translation.

A number of changes have been made to the SOPs, including the following:

- ensuring that all materials provided to candidates and label and MSDS summaries are approved by the IRB
- clarifying the role of the impartial witness in consent interviews with non-readers

- replacing references to the Western IRB with generic references
- accounting for the number of workers associated with each grower.

Other revisions to the SOPs include the following:

- standardizing forms and methods for recording field observations
- training observers to make/record field observations
- clarifying methods for observing workers when visibility is poor
- defining criteria for stopping observation of an MU because of worker behavior
- clarifying whether the questionnaire in SOP 11.B is an example or a standard.

Issues that remain to be addressed in the revised SOPs include the following:

- defining the processes for diversity selection of growers and construction of an efficient configuration of MUs
- increasing the number of growers and workers in the working pools to permit random selection of workers
- consideration of stratification of growers by farm size
- addressing the potential for non-response bias by characterizing non-respondents and those who decline to participate
- using professional local survey recruiters to identify growers and their characteristics.

The Task Force has decided to take more time to develop these SOPs to ensure that they reflect lessons learned from the pecan and citrus studies in the CCAB scenario. The AHETF has submitted a preliminary draft of a significantly revised SOP describing the compilation of Master Grower Lists (MGLs), grower interviews to establish grower qualification and interest, and compilation of a working pool of growers that incorporate lessons learned from the pecan and citrus studies, the recommendation of AHETF consultants, and many of the recommendations made by EPA and the HSRB. EPA expects this SOP to be completed in Fall 2008 and plans to present it to the HSRB in Spring 2009.

Issues to address in future scenarios include the following:

- better justification of decisions regarding the infeasibility of incorporating additional elements of random selection
- citation of sources of expert advice used in the scenario design
- a reconsideration of the recurring role of the LSC
- determining that interviewers are appropriately trained, culturally sensitive, and can evaluate participants' level of understanding
- simplification of consent forms to ensure the reading level is appropriate for the likely subject population
- consideration of the restriction to monitor no more than one worker per employer.

In August 2008, the AHETF submitted a more extensive cost analysis arguing for the infeasibility of using an overall probability-based sampling design for this monitoring program. EPA has asked the Task Force to provide scenario-specific cost analyses focused on the marginal cost to incorporate increments of randomness in subject selection and to justify their position that all feasible random elements were incorporated.

No immediate action was required on issues, including the following:

- definition of a time limit for analyzing samples (storage stability data show the samples are stable for at least 6 months)
- clarification of when workers receive a copy of the consent forms (sufficiently clear in the protocol)
- revision of the reference to reimbursement of uninsured costs of "reasonable and appropriate medical attention"
- consideration of offering risk consulting to pregnant women
- an explanation of how EPA will regulate if the results do not support the assumption of proportionality of exposure to amount of active ingredient handled (AaiH)
- an explanation of how data from studies with foliated trees can be extrapolated to estimate exposure when treating dormant trees or hops or specialty orchard crops.

Regarding the reference to reimbursement of uninsured medical costs, the AHETF's legal counsel has advised the Task Force not to change this language and the Independent Institutional Review Board, Inc. (IIRB) and EPA agreed with this recommendation. Upon discussion, EPA has determined that offering risk counseling to potential subjects with positive pregnancy tests would be inappropriate. EPA has also agreed that the Task Force does not need to respond to the last two issues. In EPA's judgment, the AHETF has responded appropriately to issues raised at the June 2008 HSRB meeting.

Proposed AHETF Research on Exposure of Subjects Applying Pesticide Sprays to Orchard and Trellis Crops Using Closed-Cab Airblast Equipment

Preliminary Results of Field Studies in Pecans and Citrus

Mr. Carley presented the preliminary results from the AHE56 and AHE57 field studies. The protocol, consent form, and flyer for these studies were revised in early July 2008 and IRB review and approval occurred in mid-July 2008. The MGL was compiled and revised in mid-to-late July 2008, and 21 qualified and willing growers were identified in late July and early August 2008. After visits with these growers, nine agreed to participate. Tropical Storm Fay (which occurred in August 2008) forced rescheduling of the studies. The MUs were reconfigured to include one new grower (located in an adjacent county and not on the MGL) and subjects were enrolled and data collected in late August 2008. Preliminary reports were delivered to EPA in October 2008.

The protocol identified seven potential sources for the MGL, including LSC, custom applicators, county extension offices, pesticide dealers, and growers' associations. The other two

sources—university researchers and crop consultants—were not consulted for this study. The LSC identified only a handful of growers. The extension service provided information about growers in five of the seven target counties, but could not screen growers by acreage to exclude those with less than 10 acres of pecans. The other sources (custom applicators, pesticide dealers, and growers' associations) did not contribute any growers to the MGL. To expand the MGL, other sources were used, including a local pecan packer and two commercial databases of farm directory information, denoted "Farm Progress" and "Farm Market ID." The local packer and Farm Progress did not provide any names, but the Farm Market ID provided 246 names. The Farm Market ID also provided information on acreage. After merging the lists and eliminating duplicates, the MGL was comprised of 238 names. This process took more time than expected and local sources were less productive than the Task Force had hoped; therefore, the AHETF plans to begin the process of identifying potential participating growers earlier in the process. Because this process does not depend on IRB approval, it can commence earlier without impacting the remainder of the study.

In the next stage of sample selection, growers were called in the order of the randomized MGL. The investigators made a total of 619 calls in attempting to reach all 238 growers on the MGL. Between one-third and half of all growers on the MGL could not be reached at all. Of the 135 growers that researchers were able to contact by phone, all but 4 agreed to the telephone interview. Of the 131 interviewed, only 77 were commercial pecan growers. Of the 77 commercial growers, 45 met all the qualification criteria and of these, 21 were willing to make their farm, crop, and workers available for participation in the research (working pool). Thus, 9 percent of the original 238 entries on the MGL agreed to participate. This experience revealed many opportunities for development of a better MGL and identification of more productive sources of grower information.

Of the 21 willing growers, 7 were unique to the Cooperative Extension list, 11 were unique to the Farm Market ID database, 1 grower was found on both the Cooperative Extension and Farm Market ID lists, and 2 growers were unique to the LSC. The working pool included small-, medium-, and large-scale growers. The average Georgia pecan grower cultivates approximately 35 acres of pecans. None of the 3 growers in the working pool with less than 10 acres were used in the study. The remaining 18 growers cultivated between 10 and 300 acres.

Site visits to growers in the working pool occurred during the second stage of grower selection. The goals of these visits were to confirm qualification, discuss the research, and provide a copy of the consent forms and a sample Product Risk Statement. Nine growers agreed to participate; 6 were scheduled to do so during the week of August 18, 2008. In all cases, the observed participants (MUs) were the growers themselves, rather than employees of the growers; this was more common than anticipated.

Tropical Storm Fay forced rescheduling of the field study. Because of this delay, 5 of the 9 growers declined to participate. Two new growers in an adjacent county were identified and 1 agreed to participate, resulting in a total of 5 growers for the 5 MUs planned. The MUs were reconfigured and monitoring rescheduled. The MUs were collected August 25–28, 2008. Each MU involved a different applicator using different application equipment to treat pecans on a different farm. Each MU also handled a different amount of the surrogate active ingredient (AI).

From this experience, the AHETF learned that specialized skills and knowledge are needed for the grower selection process. Thus, the AHETF has identified Mr. Randy Thompson, an agricultural market research expert, and Dr. Rich Honeycutt, an expert in grower interviewing, to assist with this process. The Task Force has also determined that careful coordination is needed to ensure efficient application of the qualification criteria and to account for all classes of response. The Task Force has learned that many local sources cannot reliably provide complete or usable grower lists; reliance on standardized sources in an appropriate logical sequence will reliably produce more complete grower lists. The AHETF has determined that developing the SOP for the grower selection process will be more difficult and will take longer than originally anticipated.

Mr. Carley described initial steps in the field implementation of the Florida citrus study, AHE55. The protocol, consent form, and flyer were revised in mid-July 2008, and IRB review and approval occurred shortly thereafter. MGL compilation began in mid-August 2008. This list was much larger than that for the pecan study—1,300 names versus 238. The citrus MGL was compiled primarily from records from the local "green tax" assessments on farmland; these records were complete and accurate. Telephone calls to the growers on the MGL began in early September 2008, and lasted for approximately 1 month. Although the results have not yet been compiled, there appears to be a lower percentage of list entries that were unreachable or not commercial growers. Because the "green tax" records were accurate, the MGL should contain approximately 75 percent of the growers of the target group in the target area based on the agricultural census. In contrast, the 238 growers on the pecan MGL probably represent less than 75 percent of growers in the target area.

In the Agency's assessment, field monitoring for the pecan study was conducted responsibly and well, given scheduling pressures and setbacks attributable to poor weather conditions. Given the circumstances of the pecan study, it was not feasible to incorporate more random elements in the sample selection. EPA commends the AHETF for its willingness and ability to adapt rapidly to suggested protocol changes and unexpected events and for their commitment to continuous improvement of the AHETF Monitoring Program

EPA Review of Three AHETF Field Study Protocols for the Closed-Cab Airblast Scenario

Ms. Kelly Sherman (OPP, EPA) opened the EPA science and ethics assessment of three AHETF field study protocols for the CCAB scenario. The HSRB reviewed the scenario design and two proposed field study protocols for this scenario at its June 2008 meeting. The AHETF submitted three additional IRB-approved proposed field study protocols for this scenario on August 14, 2008, and EPA's Science and Ethics Reviews on September 23, 2008 were based on this submission. Recent submissions have resulted in additional EPA comments which were not included in the September 23, 2008 reviews. Protocol AHE56 was executed in July/August 2008 and protocol AHE55 was initiated in September 2008.

The AHETF CCAB scenario submission dated August 14, 2008 includes the following materials: Volume I: Closed-Cab Airblast Scenario Design; Volume II: AHE57 – Michigan Stone Fruit; Volume III: AHE58 – California Grapes; and Volume IV: AHE59 – Washington Pome Fruit. These materials were provided to the Board.

The AHETF proposed including copper and sulfur in the CCAB scenario; both copper and sulfur are registered pesticides widely used on grapes. The Task Force received approval for this inclusion from the JRC on September 4, 2008. The AHETF informed EPA on October 7, 2008 of its wish to add these additional surrogates to both the CCAB and OCAB scenarios. Background information and sample product risk statements for copper and sulfur were submitted to EPA on October 10, 2008, and provided to the Board on October 17, 2008. EPA's September 23, 2008 reviews do not reflect the addition of copper and sulfur because EPA was not aware of their proposed addition until after these reviews were provided to the Board.

These are proposals for research involving intentional exposure of human subjects, with the intent to submit the resulting data to EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Thus the regulatory requirements 40 CFR §26.1125, which requires prior submission of the protocol and supporting documentation, and 40 CFR §26.1601, which requires review of the protocol by EPA and the HSRB, apply. The August 14, 2008 protocol submissions contained all elements of documentation required by 40 CFR §26.1125. Although further refinement is needed to address the comments in EPA's Science and Ethics Review and to reflect the lessons learned as a result of implementation of the two other CCAB studies (Georgia pecans and Florida citrus), EPA believes these proposals are ready for HSRB review.

EPA Science Assessment of Protocols AHE57, AHE58, and AHE59

Mr. Jeffrey Evans (OPP, EPA) presented the Agency's science review of the three proposed CCAB scenario protocols. Three substantive changes have been made to the protocols compared those presented at the June 2008 meeting, namely updating of the recruitment process, the addition of chlorothalonil as a surrogate pesticide in the August 2008 submissions, and the addition of copper and sulfur as surrogate pesticides in October 2008.

Chlorothalonil has a margin of exposure (MOE) of 2,745 with a target of 100 and is not of concern, except for a potential requirement for goggles and/or a respirator. No systemic toxicological endpoints of concern have been identified for copper, although goggles are required due to the potential for eye irritation and inclusion of copper will require an adjustment to the resulting face/neck exposure. Regarding sulfur, the AHETF cites a previous re-registration decision in 1991 that did not identify systemic toxicity concerns. A 2008 EPA review discusses inhalation incidents and the need for revised occupational assessment including inhalation toxicity. Chlorothalonil, copper, and sulfur all satisfy the criteria for AHETF surrogates. Because chlorothalonil is widely used on cherries, and copper and sulfur are widely used on grapes, inclusion of these surrogates will increase the potential pool of growers and workers. In addition, all three compounds have robust and sensitive analytical methodologies.

Based on its CCAB scenario review, EPA accepts the scenario objectives, diversity sampling design, and use of additional surrogates. The scenario and protocols should be revised to reflect the use of copper and sulfur, including analytical methodologies. The AHETF will also need to address exposure adjustment from the potential required use of respirators or goggles and make revisions to reflect updated recruitment methods for growers and workers.

The new field studies—AHE57 (Michigan cherries), AHE58 (California grapes), and AHE59 (Washington apples)—will employ exposure monitoring methods identical to previously reviewed CCAB protocols. The field study location for AHE57 is Leelanau and Grand Traverse, Michigan, and adjacent counties. The area contains approximately 6,500 acres bearing sweet cherries, representing 80 percent of Michigan production. The surrogate pesticides are widely used; 39 percent of the acres are treated with carbaryl, 71 percent with chlorothalonil, 69 percent with sulfur, and 11 percent with copper. The field study location for AHE58 is Fresno, California, and surrounding counties. The area contains approximately 420,000 acres bearing grapes and represents one of the top three grape growing regions in California. The surrogate pesticides are widely used; 89 percent of the grapes are treated with copper and 37 percent with sulfur. Carbaryl and malathion are not widely used for treating grapes. The field study location for AHE59 is in Kittitias, Yakima, and Benton Counties, Washington. The area contains approximately 50,000 acres bearing apples. Carbaryl is commonly used for thinning, but only during a 2-week window and at low application rates. Sulfur is used more frequently and at higher rates.

EPA has concluded that the AHETF must revise the protocols to reflect use of copper and sulfur, including analytical methodologies. The Task Force must also address exposure adjustment from the potential required use of respirators or goggles and revise the protocols to reflect updated methods for recruiting growers and workers. Given these revisions, the protocols adequately address the technical aspects of applicable exposure monitoring guidelines and are likely to produce scientifically valid and useful data.

Clarifying Questions

Dr. Fisher inquired if EPA has reviewed the details regarding the use of copper and sulfur in these protocols. Mr. Evans explained that EPA will review the details soon; use of chlorothalonil was reviewed the week of October 13, 2008. Dr. Fisher requested clarification of the Board's role in reviewing the use of these new surrogates and whether it was appropriate for the Board to review these protocols without information on the new surrogates. Dr. Lebowitz suggested that the Board could review the protocols because toxicology issues for the surrogates had been addressed. He noted that the systemic effects of copper and sulfur are based on application mode (whether they are applied as liquid or powder), particle size, and use of personal protective equipment (PPE). Dr. Lebowitz added that he had questions about the new exposure monitoring that will occur if these compounds are used, namely whether the size of inhaled particles and potential improper respirator use are monitored. This could have serious implications for the CCAB design. He inquired how the AHETF would perform inhalation exposure estimates and also asked about the methods for measuring eye exposure, given potential local toxic effects.

Mr. Carley agreed that Dr. Lebowitz's questions were important, but noted that EPA addresses many of these issues—PPE requirements and restrictions on particle size—in its registration requirement. Task Force use of these products in its research must be consistent with the use instructions specified on the registration labels; therefore, the specific effects of copper and sulfur do not need to be discussed further. Mr. Carley asked the Board to focus on the Task Force's argument that these are appropriate additions to its list of surrogates, given the

compounds' low toxicity, sound analytical methods, and other factors. The Board should not address registration issues. Dr. Lebowitz asked if other methods of measuring exposure, particularly for eye contact and inhalation exposure would be used for these surrogates. Mr. Carley responded that this was not the case; the same methods as are used for the other surrogates would be used.

In response to a question from Dr. Johnson, Mr. Carley explained that the scenario was the CCAB and the cluster would be CCAB application on cherries. Dr. Carriquiry asked if the MU consisted of the grower plus the equipment used, day of application, and other parameters. Mr. Carley responded that the MU represented an array of data collected for one worker using a particular equipment type, amount of AI handled, and so forth. Dr. Chambers inquired about the form of the copper used to treat crops. Mr. Carley answered that copper hydroxide and copper sulfate were the most common forms. Dr. Chambers questioned whether the AI strata for the copper and sulfur products would differ from the other surrogates. Mr. Carley replied that the strata would be based on the amount of AI, which is relatively high in the formulations (approximately 80 percent sulfur and 30 percent copper). Dr. Krishnan expressed concern about adding new compounds without a detailed assessment, particularly with regard to human health.

Dr. Fisher questioned how EPA could conclude that the protocols adequately address the technical aspects of applicable exposure monitoring guidelines and are likely to produce scientifically valid and useful data given the lack of information on the proposed surrogates. She noted that she was skeptical about whether the Board could confidently answer the charge question regarding scientific validity of the data without knowing more about the surrogates. She added that she did not want the Board to make recommendations that could be construed as approval for any decision to substitute new surrogates. Mr. Carley commented that the Board could answer the charge question and indicate that its response is limited only to the surrogates presented. The Board also could conclude that more information on copper and sulfur is needed before it makes its recommendations. He added that the protocols that include copper and sulfur have not yet been reviewed by the IRB.

Dr. Fisher clarified that the Board has not yet seen the protocol that includes copper and sulfur. She stated that the Board could discuss inclusion of these new chemicals but should be cautious to clearly state that the Board does not have sufficient information to make specific recommendations for this study. Dr. Fenske commented that the HSRB received the document requesting use of copper and sulfur in the protocols only a short time before this meeting and that EPA had not presented a review of this at the meeting; therefore, the Board can base its deliberations only on the comments EPA has made on this proposed substitution. He also asked that EPA provide Board members with the product labels for the surrogates listed in the protocol documents.

Dr. Fenske noted that non-volatile compounds were being substituted for semi-volatile compounds and expressed concern about how this would affect inhalation exposure estimates. Mr. Evans explained that the surrogates did not differ significantly with respect to inhalation, although the Task Force has not provided documentation of its assertion that substitution would have minimal or no effects on these estimates. Dr. Fenske remarked that using copper and sulfur meant substituting fungicides for pesticides and adding chlorothalonil adds a different functional

class of compound. Dr. Fenske noted that there are significant differences in application rates and percent AI in the new formulations compared to other pesticides in the Pesticide Handler Exposure Database (PHED). He asked if EPA believes that the data from these different surrogates can be merged and treated identically. Mr. Evans explained that EPA anticipates a wide range of AaiH which will help model potential exposure, based on the assumption that AaiH is proportional to exposure. Mr. Carley added that the PHED assumes that the identity of the AI is not critically important to modeling exposure; the equipment, the manner in which the compound is handled, and the amount of compound handled are more important. EPA would extrapolate data on fungicides to insecticide use if the products were used and handled in the same way and at the same concentration of AI. The use pattern is likely to have a more significant effect on exposure than compound identity.

Dr. Krishnan noted that discrepancies could arise if organic and inorganic substances are compared. Dr. Fenske asked if any tests had been conducted to demonstrate that dermal and inhalation measurement techniques for insecticides will work for these new compounds. Because the new compounds are used at higher concentrations, breakthrough and effects on hand wipes and face washes could be of concern. Mr. Evans answered that these issues would be addressed in the protocol amendment. Mr. Carley added that the compounds would not be applied at significantly higher doses because the amount of AI must fit into the AI strata designed for the scenario. The concentration of the AI in the original product is not applicable. Dr. Fenske countered that the concentration in the tank must remain at a certain level and the workers must spray for a given amount of time. The mass of sulfur a worker could be exposed to would be higher than the mass of malathion. Dr. Fisher reminded Board members that EPA has not yet received a specific protocol; therefore, much of this discussion is based on speculation. She cautioned EPA to avoid speculation regarding protocols it has not yet reviewed. Dr. Fenske noted that the protocols are established; the Task Force is requesting the ability to use different compounds in these protocols. Amendments will be made to the protocols, but new protocols will not be written. He asked if EPA has requested any tests regarding the validity of the sampling methods for the new compounds. Mr. Evans answered that this information has been requested and that the sampling methods were similar to those for the surrogates currently in use.

Dr. Fenske noted that copper and sulfur are considered "very safe chemicals" but the California Pesticide Illness Report of 2006 noted 14 probable or possible illnesses related to sulfur use and 6 for chlorothalonil. He asked if this raised concerns for EPA. Mr. Evans explained that this had been contemplated in EPA's assessment of the request to use copper and sulfur. He noted that EPA also considered whether the illnesses arose from typical or non-typical use. Mr. Carley added that this issue was addressed in the scoping documents for registration of fungicides containing sulfur and EPA did consider the accident history of sulfur.

Dr. Fenske noted that the AHETF documents indicated that the JRC does not approve of copper and sulfur for re-entry studies and asked EPA to clarify this point. Mr. Evans stated that these substances are not approved for such studies because of issues related to background levels in analysis. Dr. Fenske inquired why, if this is the case, the compounds were approved by the JRC for handler studies. Mr. Evans responded that exposure levels were expected to be significantly higher than background in the handler studies, thus allowing good quality analytical measurements. Mr. Matthew Crowley (OPP, EPA) added that analytical difficulties were related

to environmental measurements, not dosimetry sampling. Dr. Lebowitz noted that the sampling methods for these compounds are obviously different than those for the other surrogates. Copper and sulfur are inorganic compounds with different molecular weights and properties. Sampling for metals in the field is different than sampling volatile or semi-volatile compounds and the Board has no information concerning Task Force plans to account for these discrepancies. In response to a question from Dr. Suzanne Fitzpatrick, Mr. Evans explained that the copper- and sulfur-containing compounds are used more often on the types of crops studied in this scenario.

Dr. Fenske said that at the June 2008 meeting, the Board described approximately 40 issues that the Task Force needed to address. He asked Mr. Carley to explain to what degree these changes had been incorporated into the protocols under discussion today; these changes did not appear in any of the documents received by the Board or in EPA's science review. Mr. Carley replied that most of the issues pertained to ethical matters. All 10 science-related changes were made to the pecan and citrus protocols and are reflected in protocols AHE57, AHE58, and AHE59 as well. Referrals also were made to SOPs that had been changed. The use of chlorothalonil was incorporated into the protocols, although copper and sulfur were not. Dr. Fisher asked if the protocols would proceed if the Board decided that copper and sulfur should not be used. Mr. Carley answered that the Task Force would make that decision.

Dr. Fenske asked if the issues related to drawing MUs from the LSC, using no more than one worker per site as an MU, and extrapolation of data from foliated to defoliated trees had been addressed in the protocols the Board reviewed at this meeting. Mr. Carley explained that these changes would apply to future scenarios, i.e., those submitted after August 2008. Re-organization and collapse of the protocols was performed in a short time period. Because the basic airblast work had been performed, EPA believed the protocols could proceed. For the pecan study, EPA and the AHETF concluded that the role of the LSC should be reduced, particularly for creating the MGL; however, the role of the LSC in the research remains important because the LSC is likely to be the local good laboratory practices (GLP) research entity and can assist with ensuring that samples are collected and handled properly. The LSC will play a smaller role in the recruiting process.

Mr. Carley noted that the pecan study employed 5 MUs from 5 different growers, although use of 2 MUs from 1 grower was permitted. The Task Force would appreciate the flexibility to have 2 MUs per grower if the MUs will use different equipment at different times. If the Board concludes that correlation of observations is stronger than diversification of other factors, EPA will reconsider this approach.

Dr. Fenske noted that the Board specifically recommended employing a recruitment expert; collecting information on the characteristics of non-responders and non-participants; requiring each of the 5 MUs to be drawn from a different grower; and explaining the rationale for exclusion of certain application types (dormant versus non-dormant). None of these appeared to be addressed in the protocols presented at this meeting. Dr. Young agreed that EPA did not appear to strongly consider scientific issues and instead focused on ethical issues. Dr. Fisher noted that the discussion regarding sample selection rose to the level of a "c" recommendation; for the data to be scientifically sound, a scientific justification for the sampling method, or an increase in sample size, was needed. Mr. Carley stated that the message the EPA received in

June 2008 was that the Board was concerned about the sampling method. The pecan protocol used 5 MUs from 5 different growers; therefore, the record shows that EPA followed Board recommendations in this matter.

EPA Ethics Assessment of Protocols AHE57, AHE58, and AHE59

Ms. Sherman opened EPA's ethics review of protocols AHE57, AHE58, and AHE59. Since June 2008, chlorothalonil, copper, and sulfur have been added to the protocols. The protocols, informed consent document, recruitment flyer, and SOPs were revised.

Regarding value to society, exposure data for applicators using CCAB sprayers are needed to support EPA exposure assessments. EPA will use the results of these studies in conjunction with data from the two CCAB studies the Board reviewed in June 2008. The knowledge likely to be gained from this research will be used in exposure assessments for specific crop uses, the pesticides monitored, and for other crop uses and other pesticides applied using CCAB equipment.

Recruited subjects will be employed by eligible growers in the working pool (or by pesticide applicators used by eligible growers), or will themselves be eligible growers; have recent experience using the specific CCAB application equipment to be used in the study; and meet the subject eligibility requirements of the study. If more workers are available and interested than are needed, participants will be selected randomly. EPA believes that the proposed recruiting process is acceptable and that appropriate steps have been proposed to protect potential subjects from coercion or undue influence to participate.

EPA's overarching concerns in recruiting, screening, and obtaining consent fall into 4 categories: (1) equitable subject selection, (2) fully informed choice, (3) fully voluntary choice, and (4) respect for subjects.

Regarding equitable subject selection, the inclusion criteria (willing to participate and sign the informed consent form [ICF], handle pesticides as part of their job, trained in safe pesticide handling, experience within the past year using the equipment to be used in the study, at least 18-years old, in good general health, willing to follow all labeling and PPE requirements) and exclusion criteria (pregnant or nursing women, normally wear more PPE than required by the label, cannot understand English or Spanish, employed by a pesticide manufacturer or a contractor to the AHETF) are appropriate and acceptable. The general recruiting strategy is appropriate and acceptable. Although the sample will not be representative in a strict statistical sense, it is likely to include diverse characteristics expected to affect exposure, with minimal selection bias, and be useful for modeling future exposures. EPA believes that purposive elements in the sampling design have been thoughtfully selected and justified and that elements of random selection have been incorporated appropriately.

Regarding fully informed choice, the consent forms contain all required elements and the consent process is adequately described, with equivalent processes for Spanish and English speakers, and reliance on bilingual investigators. The communication of risks and benefits is acceptable. Use of "impartial witnesses" will ensure that non-readers are fully informed.

Confirming understanding is appropriately defined as a study director responsibility, with input from a bilingual researcher if the worker speaks Spanish.

Fully voluntary choice is ensured by management of dependent relationships to prevent coercion and undue influence. Cooperating growers must promise neutrality and employers are excluded from recruiting meetings. Employees of interested entities are excluded as subjects. The potential for peer pressure is minimized by holding private recruitment interviews. Real alternatives to participation are provided; if a worker declines to participate, the research will be conducted elsewhere, with another worker.

Regarding respect to subjects, payment to subjects has been deemed appropriate; candidates who attend the individual interview will be paid $20 and enrolled subjects who wear the whole body dosimeter (WBD) will receive $80. Subjects are free to withdraw at any time, for any reason. Individual results will be made available by request. Medical care for research-related injuries that are not covered by insurance will be provided at no cost to the subjects. Privacy and confidentiality of the subjects will be protected by appropriate and effective procedures. Thus, EPA has concluded that the processes for recruiting, informing, and obtaining consent from the worker-subjects of the proposed research fully address all of its overarching concerns.

The protocols and consent documents identify risks to subjects in 6 categories, and address the minimization of each class of risk. These risks are heat-related illness, exposure to surrogate chemicals, scripting of field activities, psychological risks associated with pregnancy testing or assisted dressing, exposure to detergents, and risk inherent to agricultural work. Regarding heat-related illness, unhealthy subjects are excluded, tractor cabs are air-conditioned, subjects are closely monitored by research staff trained to recognize signs and symptoms of heat-related illness and by onsite medical staff, and stopping rules based on subject activity and heat index have been established.

Risks associated with exposure to the surrogate chemicals will be minimized by reminding workers of safe handling practices and enforcing the use of required PPE during participation. Risks associated with scripting activities may occur if workers are asked to use larger tank sizes than they normally would or work for longer time periods. In such cases, researchers will vigilantly follow the guidance for minimizing risk of chemical exposure and heat-related illness. To minimize psychological risks, privacy and confidentiality for pregnancy testing is ensured and private dressing rooms and same-gender assistants will be available for workers wearing the WBD. The detergent solution used as a surfactant for face/neck wipes and hand washes causes mild skin/eye irritation in animal testing. Risk of irritation to subjects will be minimized by avoiding eye exposure and having an eye rinse station nearby. Historical data on use of this solution in exposure monitoring studies indicates the likelihood of skin or eye irritation is negligible. Because workers would be performing these applications in the course of their normal work activities regardless of whether the research occurs, the background risk of agricultural work was not considered part of the risk-benefit balance for this research.

This research poses no direct benefit to subjects, although subjects may realize indirect benefits from knowing their own exposure level and how it compares to that of other workers.

There is a societal benefit from improved data for risk assessment. Growers may benefit by being provided with free product, but this is countered by the costs of inconvenience and lost time caused by the research. The sponsors of this research benefit from the lower cost of shared surrogate data development. The risks posed by this research have been fully identified and effectively minimized and the residual risks to subjects will be low. The risks to subjects are reasonable given the potential societal benefits of obtaining reliable data on dermal and inhalation exposure while applying liquid pesticide sprays to crops with airblast sprayers drawn by vehicles with enclosed cabs.

IIRB reviewed and approved the protocol, the English and Spanish consent forms, and the product-specific supplements. IIRB is independent of the sponsors and investigators, is registered with OHRP, but is not accredited. IIRB procedures have been submitted directly to EPA under a claim of confidentiality; EPA has determined they meet regulatory standards. Because this is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws, the primary ethical standards 40 CFR part 26, subparts K and L apply to this research.

The same deficiencies were noted by EPA for all three protocols. Copper and sulfur should be added to the protocol and supporting documents. Due to current uncertainty about the potential for respiratory irritation, the protocols should emphasize that extra vigilance is necessary when observing workers using sulfur. Inclusion and exclusion criteria should be coordinated between the protocol and the ICF. All key members of the investigating team should be identified in the protocols. The possibility that monitored workers might be growers should be better handled. In the pecan study, all MUs were growers. The AHETF was asked to address the possibility that growers could be MUs in its recruitment script. This will be covered in the new SOP for developing the MGL and selecting growers.

Regarding compliance with ethical standards, all requirements of 40 CFR §26.1111, §26.1116, §26.1117, §26.1125, and §26.1203 are met. If all noted deficiencies and concerns are addressed, the AHETF CCAB Field Study Protocols AHE57, AHE58, and AHE59 meet the applicable requirements of 40 CFR part 26, subparts K and L.

Clarifying Questions

Dr. Fisher asked if the ethical conclusions include the use of copper and sulfur, given that EPA has not reviewed the protocol and there was no IRB review or approval for these compounds. She stated that the documents EPA has received and forwarded to the Board regarding the inclusion of copper and sulfur do not meet regulatory standards for ethics review by the HSRB.

The Board was asked to consider whether the proposed CCAB application field study protocols AHE57, AHE58, and AHE59, revised as suggested in EPA's reviews and performed as described are 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 and whether the research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L.

EPA Comments

Mr. Jordan presented EPA comments clarifying the addition of copper and sulfur to the list of surrogate compounds for the protocols. He added that Mr. Carley would address Dr. Fenske's questions concerning how the recommendations and advice put forward during the June 2008 HSRB meeting informed the protocols reviewed at this meeting.

EPA received a request from the Task Force to include copper and sulfur on the lists of surrogates. EPA considered scientific and ethical issues raised by these additions. The Agency concluded that adding copper and sulfur would be of value, as this addition would provide more information for evaluating the hypothesis that exposure is a consequence of the handling scenario and independent of AI type; exposure is assumed to be proportional to AaiH. Copper and sulfur also represent a large volume of pesticides applied by OCAB and CCAB application. Including these compounds will enable expansion of the pool of growers who may cooperate in the research because many growers use copper and sulfur on sites scheduled for future research; fewer growers use carbaryl and malathion.

EPA recognizes that timing issues have created problems for the Board and has decided that in the future, compounds will not be added to protocols after EPA has completed it review. The presentations given today also could have more clearly explained EPA's position.

Regarding the safety of copper and sulfur, EPA has examined these compounds in re-registration reviews; these are systematic reviews of previously approved pesticides designed to ensure that the pesticides are still acceptable for use based on current scientific and regulatory policy standards. Copper and sulfur were re-registered and the results of the extensive review associated with this procedure are documented and cited in Task Force materials. EPA extracted a brief summary from these materials; this summary was provided in Mr. Evan's presentation and indicated that the compounds are safe when used as specified by the labels. Generally, copper and sulfur are significantly less toxic than carbaryl and malathion, which are approved for this research, and therefore pose lower risk levels to participants; however, given the incident history regarding sulfur and respiratory issues, the Agency has recommended that the Task Force address this possibility directly in the medical monitoring plan for workers using sulfur. The incident history cited by Dr. Fenske may not provide the best basis for evaluating the relative safety of the compounds proposed for use in this research because extent or volume of use is a major risk factor. Higher levels of use lead to more exposure and greater opportunities for an incident to occur. Copper and sulfur are used more frequently than carbaryl or malathion, yet the relative incidences of problems are approximately the same. This suggests that incidents occur less frequently for copper and sulfur. Use also can play a role in the severity and type of adverse effects. In EPA's opinion, assuming that the copper and sulfur compounds are used according to label instructions and extra medical monitoring is added to the protocols, the inclusion of these compounds in the research is ethically acceptable.

The appropriateness of the sampling methods and monitoring equipment are standard parts of the protocol. Based on EPA understanding of copper and sulfur and potential exposure to these compounds, the trapping media in the air-cycling equipment may need to be changed, but the WBD and hand and face washes and wipes are acceptable for capturing residues of these compounds. In response to Dr. Lebowitz's comments that the analytical methods used to measure copper and sulfur compound residues differ from those used to measure carbaryl and malathion, data for carbaryl and malathion are available from previous exposure measuring experiments. Well-described analytical methods for whole body, air sampling, and face and hand wash that are robust and reproducible were given to the Board in June 2008 when addition of carbaryl and malathion were discussed; the Board approved of the use of these methods. The same information is available for chlorothalonil, although it was not presented at this Board meeting in the interest of time. These methods can be reviewed when the research reports are received by EPA and EPA will note any problems. Similar data on analytical methods are available for copper and sulfur; however, this information has not been reviewed in the context of these protocols and thus EPA cannot draw the same conclusions as it did for carbaryl, malathion, and chlorothalonil. EPA has decided that until it has reviewed such data on analytical methods for these compounds, the Task Force should not proceed with the use of copper and sulfur in its research. Assuming EPA has the data and reviewed the analytical methods for measuring residues and these methods are deemed appropriately sensitive and robust, the Agency believes that adding copper and sulfur to the research is acceptable and will provide scientifically useful and valid information.

In addition to the information presented by Ms. Sherman and Mr. Evans, EPA would require information to support the Task Force's contention that the proposed analytical methods are appropriate for the copper and sulfur compounds. Regarding ethics, the ICF would need to be altered to include copper and sulfur and product labels and MSDS would need to be included in the informed consent documents. If these conditions are met, EPA would consider the protocol to be scientifically and ethically acceptable.

Mr. Jordan proposed that the charge questions be revised for these protocols and that the Board consider whether it does or does not have sufficient information to deliberate on the ethical and scientific acceptability of the protocols.

Dr. Lebowitz stated that the measurement methods generally used to sample copper and sulfur are different from those used to sample pesticides in the field. He added that this issue may be more complicated than anticipated by EPA and considered that there was insufficient documentation for appropriate assessment of the protocols.

Mr. Carley described how information from the June 2008 HSRB meeting was used to inform the new protocols. He referred to slide 15 of his presentation, which described issues to address in future scenarios. The two airblast scenarios reflected similar designs and preliminary analyses. The AHETF did not believe it would be advisable for the OCAB scenario to differ significantly from the CCAB scenario; EPA agreed with this decision. The Board asked the AHETF to provide better justification of judgments related to the infeasibility of incorporating additional elements of random selection into the protocols. EPA expects that the Task Force will

improve its justifications and will in the future focus sharply on increased cost increments for including random elements in its purposive design.

The AHETF was also asked to reconsider the recruiting role of the LSC. EPA agreed that this needed to reflect the experiences gained in the course of implementing the Georgia pecan protocol. Substantial changes in recruitment were made because sufficient grower sites could not be obtained through the LSC; however, this occurred at too late a date to be included in the August 2008 submission; therefore, these adjustments were not described in the AHETF protocols reviewed at this meeting.

Regarding the use of trained interviewers, the AHETF has retained an interviewing specialist. There has not yet been an opportunity to assess cultural sensitivity and evaluate worker understanding, although EPA expects to see this in future protocols. The AHETF has simplified the ICF; further simplification is desirable, but the Task Force has made progress in this area. The AHETF and EPA have seriously considered the Board's recommendation for drawing no more than 1 MU from a single farm. The AHETF does not wish to perform studies using only 3 growers per cluster, but they would appreciate flexibility. The Task Force does not want to have to disqualify an entire study if they are unable to enroll all MUs from different growers. Discussions on this matter are ongoing; however, the Task Force's intention is to use only 1 MU per grower, and to date, they have achieved this goal.

Several Board recommendations were categorized by EPA as not requiring immediate action. The Board requested EPA explain how its regulatory activities will be affected if the results of Task Force research does not support the assumption of proportionality of exposure to AaiH. Past experience with similar exposure studies has shown consistent applicability of the proportionality assumption within the limits of the existing data. One goal of this research is to test this assumption more rigorously; EPA concedes that the assumption may not hold. This could occur if data from the airblast scenarios show that residues from the copper and sulfur formulations behave differently than residues from organic compounds; this will provide EPA with data to inform reconsideration of how to measure exposure. If the proportionality assumption does not hold, EPA will determine other ways to regulate exposure. The proportionality assumption will be examined for every scenario and the AHETF will focus on this issue in its analyses. At this time, it is difficult to speculate on how EPA will regulate exposure.

Determining the effects of the data on EPA regulatory activities and how results from studies of foliated trees can be extrapolated to estimate exposure when treating dormant trees, hops, or specialty orchard crops are the responsibility of the Agency and not the Task Force. Specialty crops include tropical fruits, hops, and similar tall trellis crops. These crops are grown only by a small number of growers; therefore, conducting studies using these crops would be logistically difficult. EPA is confident that these crops have canopies that fit within the range of foliage canopies of the crops used in AHETF research; therefore, EPA is confident that the data can be extrapolated.

EPA intended to use the data from foliated trees to determine exposure when treating dormant trees. Available data suggest that exposure is unlikely to be greater during treatment of

dormant trees because of increased drift away from the site. In addition, dormant application is performed in the winter and thus could not be included in the same cluster; data for dormant application would constitute its own cluster. In addition, because dormant application occurs in colder weather, workers are likely to wear more clothing than in warmer weather, which would affect exposure measured by the WBD. EPA agreed with the Task Force that dormant application was less appropriate for monitoring than non-dormant application.

Clarifying Questions

Dr. Fenske asked if the first review of airblast applications occurred at the June 2008 meeting. Mr. Carley confirmed that this was the case. Dr. Carriquiry inquired what the Task Force meant when it stated that 43 percent of growers on the MGL were "unreachable." Mr. Carley explained that the "unreachable" growers on the MGL were telephoned at least three times; some of the growers were deceased, some of the telephone numbers were incorrect, and in some cases there was no answer. It could be argued that relying on telephone interviews is unacceptable and that there may be a better way to recruit. EPA will monitor this situation because it affects the quality of the initial MGL. The number of "unreachable" growers is expected to be smaller for the citrus crop protocol. Pecan growers in Georgia do not receive subsidies; therefore, the Task Force was unable to obtain information on these growers through the USDA, which is usually a robust source of information. This situation complicated developing a MGL for the pecan protocol. Of those growers contacted, four refused to participate in the interview and only 13 percent of commercial pecan growers met the study qualifications. This meant that 9 percent of the initial pool was qualified and agreed to participate. Dr. Fisher questioned whether an adequate list of participants had been generated for the protocols presented at this meeting. Mr. Carley responded that the quality of the list could not be judged at this point.

Dr. Brimijoin commented on the assumption of proportionality of exposure to AaiH. He noted that the relationship probably would be linear, if not proportional. He asked if EPA could comment on whether it believes that the proportionality constant that may emerge from this work will be constant for all AIs. This will impact the validity of substituting different surrogates. Mr. Crowley answered that the proportionality constant likely will differ for each worker treated but not for each compound. Dr. Lebowitz inquired if proportionality would be the same for any organic or inorganic compound. Dr. Brimijoin asked why, if exposure is not related to the identity of the compound used, innocuous materials such as salts or food colorings could not be used in the place of pesticides. Dr. Fenske agreed, noting that the Board had previously suggested using a nontoxic surrogate compound, which would mitigate risk to workers. Mr. Carley explained that EPA does not consider it unacceptably risky for workers to apply registered pesticides consistent with label instructions. Dr. Fisher reminded Board members that the Task Force had speculated that it would be more difficult to convince growers to participate if salts or food colorings were used.

Public Comments

Dr. Victor M. Canez of BASF Corporation, on behalf of the AHETF

Dr. Victor Canez (Technical Chair, AHETF) opened his comments by reiterating that the goal of the Task Force is to gather exposure information for 5 MUs from 5 different growers. The Task Force is requesting flexibility for data to be acceptable if it is impossible to recruit 5 different growers. If 2 MUs from the same grower are monitored, each MU will use different equipment, work in a different field, and handle as different an AI stratum as possible. The Task Force will document reasons for any need to monitor more than 1 MU per grower. The AHETF will not permit use of the same mixer-loader by more than 1 MU. Drs. Fisher and Johnson encouraged the AHETF to add language describing this situation to the protocols.

Clarifying Questions

Dr. Carriquiry noted that she was encouraged by the use of the 5-by-5 monitoring strategy in the first protocol. She added that the AHETF must recognize that cost is not an adequate justification for decreasing the number of growers. The documentation for this research, as currently written, appears to indicate that the use of 3 growers is as acceptable as the use of 5; the AHETF must clearly state that this is not acceptable and would compromise the data. Dr. Canez noted that the chances of using more than 1 MU per grower decreases as the Task Force continues to improve its recruiting strategies. The MGL for the citrus protocol is significantly larger than that for the pecan protocol and triple the number of site visits is anticipated. The need to use more than 1 MU per grower will be rare. Dr. Young suggested that the inability to identify 5 different farms agreeing to participate in the research might suggest a flawed recruiting process. Dr. Carriquiry acknowledged the Task Force's effort to collect sound data. She suggested improving the creation of the MGL; a 43 percent unreachable rate is unacceptable, as is the lack of knowledge concerning the proportion of growers that the MGL represents.

Dr. Fenske asked why the pecan packers contacted were unable to provide information on growers. Dr. Canez responded that the packers refused to provide lists of the growers with whom they worked. Dr. Fenske noted that in most cases, it is possible to obtain lists of growers from an information clearinghouse and these lists are usually accurate. Dr. Fisher stated that this issue appeared to emphasize the need to employ experienced recruiters; failure to do so can have serious repercussions.

Dr. Fisher questioned whether the new protocols would be of value if the copper and sulfur formulations are not included. Dr. Canez replied that the studies would have value, but would be difficult to conduct. Other surrogates are rarely used in the areas being sampled. In response to a question from Dr. Fisher, Dr. Canez remarked that the other surrogates would yield generalizable data. Dr. Lebowitz noted that the AHETF had added other organophosphate compounds to its list. Mr. Carley cautioned Dr. Lebowitz not to confuse product with ingredient. The documents list products that contain one or more of the monitored AIs. There are three AIs, contained in 13 products. Sample labels for the copper and sulfur products were provided in the October 7, 2008 package.

Dr. Krishnan commented that it was surprising that the AHETF realized only relatively late in the process the need to include copper and sulfur in its protocols. He asked how similar situations would be avoided in the future. Dr. Canez explained that the need to use copper and sulfur arose during planning for a wettable powder scenario and the need to find surrogates for the mixing and loading of such products. The ability to use copper and sulfur will be important for future scenarios.

Dr. Fenske asked when the JRC informed the AHETF that use of copper and sulfur would be permissible, given that the Board received this information on October 17, 2008, only shortly before the meeting. Mr. Carley answered that the response had been received on September 4, 2008.

Board Discussion on the Inclusion of Copper and Sulfur in its Review of the AHETF Protocols

Dr. Fisher explained that during its administrative meeting to discuss procedural issues, the Board developed a statement with applicability to both current protocols. This statement indicates that the HSRB will only review protocols with sufficient information and documentation necessary for a responsible review. She asked the Board to consider whether sufficient information had been provided to review the protocols including copper and sulfur.

Dr. Lebowitz remarked that, in his opinion, there was insufficient information to consider inclusion of copper and sulfur to represent exposure to organic compounds. Dr. Brimijoin commented that he would agree to review the protocols with an amendment adding the two compounds if he were given specific reasons for believing the proportionality of exposure to AaiH was the same for these compounds as for the other surrogates. Dr. Brimijoin added that he expected that the proportionality constant would be different for each AI. The relationship between exposure and AaiH will be linear for each compound and thresholds and ceilings will apply; however, a worker handling a volatile liquid will not receive the same skin or inhalation exposure as if a salt, non-volatile or low- or high-solubility compound were handled. The relationship between exposure and AaiH will differ depending on the physical characteristics of the compound; therefore, he was not convinced that copper and sulfur are reasonable surrogates for organic compounds. Dr. Brimijoin agreed that the incremental risk of exposure to the copper and sulfur compounds was not significant, but if these do not constitute reasonable surrogates, their use in the protocols cannot be accepted.

Dr. Fenske suggested that it would be inappropriate for the Board to review these protocols at this meeting because the information prepared by the Task Force and received by EPA did not contain adequate information for responsible evaluation. The HSRB has not received formal EPA reviews of copper and sulfur in the read-ahead materials for this meeting. Many questions also have been raised by Drs. Lebowitz and Brimijoin regarding the physical characteristics of these compounds and the effects these characteristics may have on exposure. Dr. Lois Lehman-Mckeeman agreed with Dr. Fenske. The Board has established reasonable expectations regarding the nature of the protocols it will review and has held previous investigators to that standard. The protocols presented today are incomplete by those standards.

Dr. Krishnan agreed that Board review should be restricted to the information actually contained within the protocols. The information provided by Mr. Jordan was useful, but not complete. Dr. Krishnan added that he was troubled that IRB approval of the amendment was not brought to the Board. Dr. Sean Philpott noted that at previous meetings in which substitution of a test compound, characterized as a deviation from the protocol, was discussed, the Board would not consider an amendment that had not received IRB approval; therefore, the Board cannot review the inclusion of copper and sulfur formulations in these protocols.

Dr. Fisher summarized that the Board believes that insufficient rationale and documentation had been provided for the HSRB to responsibly review the inclusion of copper and sulfur in the protocols. The HSRB did not consider the addition of copper and sulfur to be an addendum but rather a unique and different protocol; therefore, if the HSRB reviews only the aspects of the protocol not including copper and sulfur, a study that went forward with these surrogates would comprise an intentional exposure study that had not been reviewed by the Board as required 40 CRF 26 (EPA's Human Studies Rule). Dr. Fisher informed Mr. Jordan and Mr. Carley that the Board will provide feedback on the protocols, but this should not be taken as Board review of any protocols that include copper and sulfur. The Board may be presented with information indicating that copper and sulfur are adequate surrogates in the future, but it does not have the information at this meeting. Mr. Jordan agreed that the Board's position is clear regarding the inclusion of copper and sulfur. He stated that the Task Force will move forward with the protocols that are restricted to the use of carbaryl, malathion, and chlorothalonil. He asked, on behalf of EPA, that the Board address the protocols that do not include copper and sulfur.

Board Discussion

Scientific Considerations – Protocols AHE57, AHE58, and AHE59

Dr. Fenske opened the science discussion by complementing the overview documents for the CCAB scenario and similar protocols. He stated that protocols AHE57, AHE58, and AHE59 would be reviewed as a single unit.

The protocols received by the Board are similar to those reviewed at the June 2008 HSRB meeting. EPA presented and the Board discussed key science issues raised in the draft June 2008 HSRB meeting report that were knowingly not incorporated into these protocols. EPA decided that the recommendations made in the June 2008 report would not apply to the CCAB scenario. Concerns from the June 2008 meeting remain. The low response rates achieved by the recruiting process are worrisome. The Board recommended that the AHETF employ specially trained recruiters and that the characteristics of non-responders and growers who declined to participate be documented to determine the reasons for non-response and/or non-participation. The protocols reviewed at this meeting do not address this issue. The issue regarding restricting monitoring to 1 MU per farm was raised in June 2008 because Board members believed that the proposal to allow 5 MUs to be drawn from as few as 3 farms violated the rationale given for sample size and also was not appropriate from a statistical perspective; this was not addressed in the proposals presented at this meeting. At this meeting, EPA provided justification of the exclusion of dormant spray applications (representing approximately 1 in 6 or

7 applications), but this was not addressed in the protocol. Logistical and cost reasons for excluding dormant applications were given, but not a scientific rationale. The Task Force is not required to include such applications in its research, but must provide a scientific rationale for doing so. Mr. Carley stated during this meeting that EPA has evidence that exposure during dormant application is unlikely to be higher than that occurring during application to foliated crops; this addresses risk assessment concerns, but this rationale was not documented for the Board.

Few changes have been made regarding the issues raised during the June 2008 HSRB meeting. The Board was provided with a protocol and asked for governing documents that would provide a context and enable the Board to determine whether the research was scientifically valid (if not, it cannot be ethically valid). In the October 6, 2008 EPA memorandum to the Board regarding the draft report for the June 2008 meeting, EPA states that the Task Force data will provide important exposure information and, when used with existing EPA data, will support regulatory activity at the high end of exposure; however, the Board has not assessed the existing data and therefore cannot determine if collection of additional data is worthwhile. Other science-related information is needed for these exposure estimates, but EPA has not provided this information.

Dr. Fenske noted the apparent misunderstanding by OPP regarding the authority of the meeting minutes compared to the Board's final report. In the minutes, the Board cautioned that it would be difficult to conclude that the data would be scientifically valid given the lack of replicate measures, but could be used to make qualitative assessments. Dr. Fisher clarified that the Board intended to state that the data could not be statistically analyzed. It could be used to analyze proportionality and determine if the results conformed to what EPA expected.

Dr. Fitzpatrick agreed that the issues raised during the June 2008 HSRB meeting had not been completely addressed in the protocols, but were addressed in Mr. Carley's presentation. She questioned with whether knowing how EPA will use the AHETF data in its regulatory decision making was part of the Board's charge.

Dr. Johnson stated that the protocol should include language indicating that the AHETF intends to monitor 1 MU per grower. He agreed with Dr. Fitzpatrick's distinction regarding Board approval of the protocol and how it is executed versus the ways in which EPA intends to use the results. He also noted that EPA's comments regarding the Board report were directed at the draft report, rather than the final report, which was finalized earlier in this meeting. Regarding the science charge question, Dr. Johnson stated, with slight reservation, that the protocols should provide information valid for assessing exposure.

Dr. Carriquiry commented that she could not imagine a case in which it would be appropriate for the AHETF to monitor MUs from only 3 growers. Efforts to improve the MGL will greatly improve the protocols. In response to the recommendations for future studies, these protocols have presented some improvement in the inclusion of random elements in the sampling design. Choosing crops, states, and counties purposively is appropriate. The Task Force could endeavor to make grower selection more random. EPA has recommended creation of larger MGLs, which is a sound recommendation. Creation of a larger MGL would satisfy and justify

the sampling design. Dr. Fisher noted that although the use of only 1 MU per grower is ideal, the Board should consider asking the Task Force to confirm that no fewer than 4 growers will be used. Dr. Young stated that no fewer than 5 growers should be used. In the case of the pecan scenario, the MGL had to be expanded because of foul weather. Because the data will be used for decades, 5 growers should be required. She agreed with Dr. Carriquiry that the Task Force's efforts to increase random elements in the sampling design were commendable.

Mr. Carley explained that the 5-by-5 sampling design for the pecan protocol was achieved by recruiting a grower from an additional county. This grower was not included in the original study area or MGL, which was a clear deviation from the recruitment protocol. When the pool was reduced to 4 growers, the AHETF had the option to use 2 MUs from a single grower. Dr. Lebowitz stated that having 5 growers was more important than recruiting from outside the counties defined in the protocol. Dr. Fenske agreed that the Task Force should be required to observe 5 MUs from 5 different farms; any deviations can be reported and will not invalidate the study. This is preferable to allowing observations to be made on only 3 farms to avoid recruiting outside the initially defined area. Dr. Young commented that the Board should be clear that it expects the AHETF to use 5 independent growers. Dr. Fenske inquired if this meant the Board would not approve a protocol that did not use 5 independent growers. Dr. Fisher clarified that the goal is to avoid a Board decision that a study does not have scientific value. If the 5-by-5 design is important, this should be made clear. It appears that the Task Force prefers to use the 5-by-5 design, and with the creation of better MGLs and Task Force experience, the AHETF probably will meet this expectation. To be clear, the Board should consider stating that use of less than 5 growers may result in the data being judged unreliable. The protocol also should be consistent with the Governing Documents regarding the use of 5 growers.

Dr. Young remarked that she considered use of the 5-by-5 design to be essential to ensure scientific validity of the data for use by EPA. Dr. Fisher noted that the Board has no role regarding EPA regulatory decisions; however, if the Board is advised that the usefulness of the data includes how it will be used in conjunction with data collected prior to the Rule, the HSRB will need to review the other data.

Dr. Fisher asked Mr. Carley to elaborate on the AHETF's efforts, or lack thereof, to collect information on growers who do not respond. Mr. Carley explained that collection of this data from growers who cannot be reached would be difficult. Depending on the source of grower information, different types of information will be available, such as acreage, number of employees, etc. For the pecan protocol, little information could be gleaned on the non-responders, but this will vary from cluster to cluster. In most situations, the AHETF should be able to analyze differences among qualified growers who agreed or declined to participate. Dr. Carriquiry interjected that studies performed in Iowa involving corn and soybean growers obtain information from national agricultural records. It is possible to determine the exact number of growers, operation size, use of conservation practices, and other characteristics. Mr. Carley explained that the recruitment methods that will be proposed by the Task Force for subsidized crops will rely on data from the USDA Subsidy Database that matches Agricultural Census data closely; however, many of the crops monitored in the airblast scenarios are not subsidized so the same resources and information are not available.

Dr. Fenske requested that EPA impress upon the AHETF the importance of gathering information about the sample, particularly with regard to characteristics of non-responders and those declining to participate. The current protocols lack statements indicating the AHETF's addressing this matter. Dr. Fisher acknowledged that Mr. Carley had explained that this sort of information for the types of crops used in the airblast scenarios may not be available. Dr. Young agreed with Dr. Fenske that the Task Force needs to indicate that it understands this information is valuable and could improve recruiting.

Mr. Carley explained that EPA and the AHETF agreed about the value of close attention to the creation and review of the MGL; however, the manner in which this information is gathered will be addressed in the recruiting SOP, rather than being detailed in each protocol. EPA will submit the amended SOP to the Board for review.

Dr. Fisher asked the Board to address the issue of the truncated range of exposures in these protocols. Dr. Fenske clarified that certain behavioral characteristics of the scripted activities in these protocols may lead to a truncated range of exposure. If the worker follows the label requirements and does not exit the cab during spraying, the data can only be adjusted at the EPA level. This should be explained in the completed study report.

Dr. Fisher asked if Board members had concerns about using growers as MUs. Mr. Carley noted that this situation was anticipated in the protocol, but occurred in the pecan protocol more often than expected. EPA has asked the AHETF to ensure that growers are treated as potential subjects from the time of first contact. IRB documents will be changed to reflect this.

The Board reached the consensus that the 5-by-5 design would be required for the data to be judged reliable and useful. The Board noted the enthusiasm of EPA and the AHETF for addressing MGL and other recruiting issues. It would be helpful to the Board if the final protocol report clearly stated any limitations of the data with respect to exposure and other matters.

Ethical Considerations – Protocols AHE57, AHE58, and AHE59

Dr. Susan Fish opened the ethics discussion by commending the AHETF for its responsiveness and the improvements in the protocol. She thanked the Task Force for its "redline" version that facilitated review of the protocol. She stated that all three protocols would be treated as a single unit for this review.

Regarding risk to subjects, Dr. Fish agreed that the risk inherent to agricultural work is unrelated to the risk posed by this research; therefore, this risk could be removed from the protocol. She asked that the phrase "reasonable and appropriate" medical attention be removed from the consent documents because it is likely to be unclear to the subject. Dr. Fish contended that it would not be possible for the consent process witness to attest to the subject's understanding of the research; only the subject can decide if he or she understands the research. Regarding the appropriateness of the Spanish translation, this series of protocols appears to

assume that Spanish-speakers will hale from different countries, but this is not clear. Dr. Fish requested assurance that Spanish-speaking staff are available at the toll-free telephone numbers provided to potential participants; Ms. Sherman assured Dr. Fish that this was the case. Dr. Fish agreed with Mr. Carley that the inclusion and exclusion criteria need to be synchronized between the protocol and the ICF. The issue of enrolling growers as MUs also needs to be more clearly addressed.

Dr. Fish addressed the matter of correspondence from the IRB, particularly the note to file from the principal investigator for AHE57. IIRB reviewed the application on July 29, 2008, and the study director received a call from IIRB indicating that review of the application was tabled until the next IRB meeting. This comment should have been provided in writing, indicated why the study had been tabled, and what issues prompted this action. Dr. Fish commented that this raised concerns about IIRB. In the IRB applications for AHE57, AHE58, and AHE59, the same racial distributions of subjects (90 percent white, 2 percent African American, and 6 percent Hispanic) were projected; this seems unlikely given the geographic disparities of the research sites. The Task Force should direct more attention to its IRB applications. Question 17 on the IRB applications for all three protocols (which addressed whether risk was greater than minimal risk) was not answered. If risk is considered to be higher than minimal, the IRB requires a Data and Safety Monitoring Plan, which was not presented to the Board. Although risks of agricultural work itself are not applicable, risk of heat exhaustion posed by use of the WBDs should be considered. Regarding the recruiting SOP, Dr. Fish noted that revisions have improved the SOP, but concerns remain about the discussion of illiterate subjects; the SOP calls for asking potential subjects to read part of the ICF. This is a potential source of embarrassment for subjects, many of whom may be reluctant to admit they cannot read. On page 275, mention is made of potential compensation for witnesses participating in the consent process. This was not addressed in the protocols and could lead to coercion. Dr. Fish concluded that none of her concerns rise to level "c," modifications needed to ensure that the design and analyses are scientifically and ethically sound.

Dr. Gary Chadwick focused his review on 40 CFR §26.111, subpart K. Criteria for the approval of intentional exposure research state that risks to subjects are minimized using procedures consistent with sound scientific design and do not unnecessarily expose the subjects to risk. By monitoring procedures that would be performed by subjects in the course of their normal work activities, this criterion is satisfied. Pesticides used according to label instructions do not pose undue risk; however, the question remains regarding whether non-toxic surrogates or food coloring could be used rather than pesticides. If EPA and the AHETF consider substituting inorganic chemicals for organic compounds to be acceptable, it is difficult to understand why non-toxic surrogates would be unacceptable. Mr. Evans explained that EPA was more comfortable adjusting for AI if pesticides and standard analytical methodologies are used. Use of fluorescent tracers has shown promise, but use of such substances would require protocol review by the Board and may be more difficult to adjust to AaiH. It also may be more difficult to convince growers to participate in research using these substances. The use of non-toxic salts or other tracers would open a new area of research. Dr. Chadwick inquired if EPA would apply a single set of applications to every product for licensing decisions. Mr. Crowley noted that EPA is not expecting this research to test differences between exposure to organic versus inorganic compounds, or even to determine if the proportionality constants for different pesticides are the

same. Dr. Chadwick noted that if the Food and Drug Administration wished to determine the size of a pill that could be swallowed comfortably, it would use a placebo rather than drugs, even regularly used, safe drugs. This is counter to what the AHETF proposes.

Dr. Fisher reminded Dr. Chadwick that exposure to the pesticides used in the research was not considered to be a risk attributable to participation in the research, because workers would use them during their normal work activities. The primary risk of the research is heat-related illnesses, which arises from wearing the WBD; whether pesticides or non-toxic surrogates will be used, workers will still need to wear the WBD. Thus, use of such surrogates does not minimize risks. Dr. Chadwick argued that it was unclear why the identity of the surrogate used was believed to be unrelated to exposure. Dr. Brimijoin agreed that the identity of the surrogate probably would affect exposure. If this is the case, EPA will need to analyze exposure by compound type, if not by each particular compound. He added that, in one sense, the risk-benefit ratio is more favorable for use of typical pesticides, because using a non-toxic surrogate would expose workers to the same risk of heat-related illness while spraying a substance they would not normally use.

Dr. Chadwick asked if the way EPA plans to use the exposure database is appropriate. Dr. Fisher clarified that for each protocol the Board reviews, they must determine whether or not the chemicals used are sufficient for that purpose. These are typically used chemicals and thus are appropriate for these exposure protocols. A different question is whether statistical analyses can be performed. The HSRB scientific experts have indicated that the substances are adequate for the research. Dr. Krishnan agreed that because these workers normally use the pesticides identified in the protocols, they are appropriate, assuming that they are used according to label directions. The MOE for the largest amount of AI used does not rise to the level of concern. The workers are unlikely to receive doses larger than threshold doses and are unlikely to suffer adverse health effects at these application rates. Dr. Chambers agreed that EPA has stated numerous times that the pesticides will be used according to label instructions. The plan to monitor 5 clusters of 5 different crops will test 5 different pesticides. If EPA finds that exposure varies by pesticide type, it must conclude that the data from different pesticides cannot be merged.

Dr. Fenske clarified the two primary concerns. First, the Board is concerned about the use of certain pesticides as surrogates for other compounds, and second, the Board is concerned about how EPA uses the exposure database to perform risk assessments for different types of compounds based on the assumption that the identity of the compound does not affect risk. Dr. Fenske stated that, in his opinion, this was a valid surrogate pesticide database and this approach was scientifically appropriate.

Another issue is minimizing worker risk. EPA claims to have performed risk assessments for these compounds and is not concerned about risk based on expected exposures. The Board has not heard a farm workers' representative agree with the claim that worker risk is identical whether the pesticides or non-toxic surrogates are used. Dr. Fenske concluded that, in his view, EPA's risk assessment at this point is hypothetical, but the Agency has adequately determined that no significant risk is raised by these experiments. Hypothetical risk assessment is not sufficient; recent tests in Washington State showed depressed cholinesterase activity in

20 percent of pesticide handlers. Dr. Brimijoin agreed that risk was not eliminated by using the pesticides at or below the levels required on the labels or at levels that produce an appropriate MOE. Working with pesticides is inherently hazardous. The Board needs to determine if the incremental risk posed to the handlers participating in these protocols is justified.

Dr. Chadwick stated that EPA has not yet addressed the assumption that one chemical can be used as a surrogate for others. Dr. Fisher noted that the Board has agreed that this approach is scientifically valid in its reviews of prior protocols. She agreed that testing occupational exposure differs from a clinical trial; the chemical itself does not confer risk. The proportionality theory is related to exposure rather than toxicity. In the protocols reviewed by the Board, there is some increase in risk caused by using the test surrogates compared to the workers' usual activities, but the primary risk of the research is heat-related illness.
Dr. Chadwick clarified that his concern was whether the data would be generalizable. If this research represents the first steps in developing a generalizable database, the risk of heat-related illness is acceptable. Dr. Fisher responded that this work does represent a first step. EPA has indicated that if the results are not what were expected, EPA will address this issue and make adjustments. Mr. Crowley reminded the Board that this research was not designed to test differences between AIs. Dr. Fisher concluded that at this point in time, the protocols do not appear to pose undue risk.

Dr. Menikoff noted that the Board had previously documented the possible use of non-toxic surrogates in its reports. If the Board is convinced that the workers would use the test compounds even if they were not participating in the research, the Board must conclude that the research does not increase worker risk due to exposure to the pesticides. He commented on the use of the phrase "reasonable and appropriate medical care," noting that this was phrased appropriately and was similar to language used in non-research settings.

Dr. Ernest Prentice complimented the AHETF for its responsiveness to Board concerns. He asked how the Task Force would determine that potential participants met the eligibility criterion that require experience within the last year working with the equipment to be used in the research and how the Task Force would determine if variability in exposure was associated with level of worker experience. In addition, inexperienced workers are more likely to be injured. Mr. Carley explained that the AHETF proposal stated that workers would not be asked to use unfamiliar equipment; the eligibility criterion requiring experience is based on this requirement. The criterion means that workers must have experience within the past year using the equipment they would use in the study. Similar reports over the years show a variety of years of experience when workers are asked how long it has been since they applied a certain pesticide. Such information will be collected, but not deliberately diversified; nonetheless, it will provide additional insight into the data.

Dr. Prentice noted a statement in the consent document indicating that a participant could refuse medical treatment, which is contradicted by a subsequent statement claiming that subjects cannot refuse medical treatment if they fall ill from exposure or because of heat. This needs to be clarified. He stated that he had no objections to the phrase "reasonable and appropriate medical care." He asked if deductibles were included in the costs of medical care not covered by a participants' medical insurance. He also asked who would determine whether an injury was

study related. Mr. Carley noted that this issue was not covered in the protocol. EPA's understanding is that the deductibles would be covered by the AHETF, but this would need to be confirmed by the Task Force.

Dr. Prentice requested clarification about subject compensation. The ICF claims a participant will receive $80 per day, and the protocol defines a day as lasting between 4 and 8 hours. He asked if participants would be involved in the study for more than a single day. Mr. Carley clarified that participants may be asked to don the WBD for more than 1 day if weather conditions change and prohibit pesticide application.

Dr. Prentice noted that the Task Force claims no risks of concern relative to pesticide exposure, yet subjects are required to sign product risk statements that state risks such as coma. If this is not a risk, it should not be included. If it is a reasonably foreseeable risk, there should be a reference to the probability of occurrence. Mr. Carley explained that a statement of degree of risk from the research should be in the materials, along with the risks associated with the pesticides. Dr. Prentice indicated that he could not find a reference to the probability of risk. Mr. Carley agreed to check on this.

Dr. Prentice concurred with Dr. Fish that it is not the witness' role to certify that the subject understands the research. He recommended rewording the statement regarding fully informed consent to indicate that the subject was informed about all the procedures, risks, benefits, and other aspects of the study to more clearly reflect that the individual has given full and voluntary consent to participate. Mr. Carley asked Dr. Prentice to provide advice on what would constitute an appropriate consent summary. Dr. Fisher explained that the Task Force should follow regulations to ensure that the subjects understand the meaning of informed consent. Dr. Prentice added that he was requesting a more comprehensive indication that the study had been fully explained to the subject. He noted the reference to the "short form" and asked if EPA had any data on the use of this form. Mr. Carley replied that EPA does not permit the use of the short form, although the Agency does allow verbal consent. EPA assumes that the entire form is described and all required signatures are obtained. Dr. Prentice inquired if all subjects have been able to read the consent forms. Mr. Carley responded that all subjects have been able to read the forms; typically, all or nearly all applicators are literate.

Dr. Philpott stated that his comments applied to all the protocols. He noted that Mr. Bruce's certification in human subject protection is more than 4-years old and that a refresher course may be needed. Dr. Philpott commented that language in both CCAB and OCAB documents stated that workers are expected to use PPE as required by the product labels, with the exception of a mask that blocks facial exposure; it would be inappropriate to pay a worker to use less PPE than usual. Mr. Carley explained that the eligibility criteria exclude workers if the research would require them to wear less PPE than normally used. Dr. Philpott responded that the documents must clearly state that workers are not influenced to use less PPE by the promise of payment. Although the ICF states that workers who use more PPE cannot participate, the potential of payment may induce workers to inaccurately report the PPE they use. The documents could be rephrased and workers tested to determine if they are familiar with the required PPE.

Dr. Philpott recommended that future designs give more consideration to consultation with farm workers unions; these organizations might serve as an important source of witnesses. Witnesses who are strong advocates for the workers would be acceptable. Dr. Philpott noted that the manner in which impartial and bilingual witnesses would be recruited was unclear. He added that he was pleased to see that the AHETF has considered providing individual exposure data to workers who request it; however, the Task Force must provide this information in a way that does not unduly alarm workers or give them a false sense of security regarding their exposure and work habits.

Dr. Carriquiry commented that the Spanish translation of the ICF is better than previous versions, but still not optimal. The statement about different Spanish dialects is incorrect; Latin Americans speak the same language with only a few different words. Just as the English version of the ICF is written in clear, concise, and simple English, the Spanish ICF also must be written clearly, concisely, and simply. The ICF is grammatically incorrect and there are no statements emphasizing that participation is voluntary until the end of the second paragraph. The verbiage at the beginning of this paragraph almost sounds as if participation is mandatory. Dr. Carriquiry offered to provide assistance with the Spanish translation of the ICF.

Dr. Fisher inquired if having a Data and Safety Monitoring Plan would be essential for this research. Dr. Fish responded that this did seem to be a requirement of IIRB based on the application form; however, this study does not have such a plan. Mr. Carley explained that the AHETF was considering developing an extended version of such a plan that would include heat exhaustion risk; the plan would be included in the appropriate SOP. Dr. Fish noted that the risks are minimized and the subjects are well monitored; however, IIRB's requirement for a Data and Safety Monitoring Plan was not fulfilled. Despite this, IIRB approved the protocol. Dr. Fisher remarked that this was an issue that pertained to the actions of IIRB. Dr. Philpott requested that verbiage regarding contacting the IRB should be changed to "during normal business hours" because the research study is conducted at sites in different time zones.

Dr. Fisher concluded that the recommendations made by the Board should be included in future protocols. She summarized that the risk inherent to agricultural work was not related to the risk of participating in the research. The phrase "reasonable and appropriate medical care" should be reconsidered, but is probably adequate. The AHETF needs to clarify the role of witnesses and their ability to assess subject understanding of the protocol and consent process. The voluntary nature of participation needs to be emphasized. Enrollment criteria need to be coordinated between the protocol and the consent documents. Members of the research team should be clearly identified. The lack of documentation from IIRB regarding why review of the study was tabled is troubling. The racial distribution appears to be incorrectly described. The way that subject literacy will be assessed should be reconsidered to minimize potential embarrassment of subjects. An explicit statement is needed to clarify witness compensation. The issues of subject experience with the pesticides to be used and anticipated exposure to injury needs to be clarified. Examples of information needed for a complete consent package should be provided to the AHETF. Most of the relevant AHETF staff members appear to have outdated human subject protection certification; this should be corrected. The Task Force should determine better ways to ask subjects about their familiarity with the required PPE. The Task Force also should provide better information on bilingual recruitment and how the data on

individual exposure will be communicated. The AHETF should develop a better Spanish translation of the relevant documents. Dr. Chadwick's concerns about minimizing risk by using non-toxic surrogate compounds also should be addressed.

Proposed AHETF Research on Exposure of Subjects Applying Pesticide Sprays to Orchard and Trellis Crops Using Open-Cab Airblast Equipment

Overview

Mr. Evans began EPA's review of the AHETF's proposed OCAB scenario. EPA reviewed the scenario design and three field study protocols for measuring potential dermal and inhalation exposure during application of liquid pesticides to crops using conventional airblast sprayers drawn by vehicles with open cabs.

The AHETF submitted an IRB-approved scenario design and three proposed field study protocols for this scenario on August 14, 2008. EPA's Science and Ethics Reviews on September 23, 2008 were based on review of this submission. The AHETF proposed and the JRC agreed on September 4, 2008, to add copper and sulfur to the scenario. Based on preliminary reports submitted in early October 2008, the AHETF will further amend these protocols to revise the methods for identifying and recruiting growers in the study areas. The OCAB scenario is similar to that of the CCAB scenario, with one significant difference: data collected under the three new studies proposed for the OCAB scenario will be combined with data collected in the AHETF's pre-rule OCAB study AHE07-A to comprise the full data set for the OCAB scenario. (Note: Pre-rule refers to the time before the Human Studies Rule became effective.)

These are proposals for research involving intentional exposure of human subjects, with the intent to submit the resulting data to EPA under FIFRA. Thus, 40 CFR §26.1125, which requires prior submission of the protocol and supporting documentation, and 40 CFR §26.1601, which requires review of the protocol by EPA and the HSRB, apply to this research.

The August 14, 2008 OCAB submission consisted of 4 volumes. Volume I described the OCAB scenario design. Volume II described protocol AHE62, which monitors exposure when spraying California grapes. Volume III describes protocol AHE63 (New York grapes) and Volume IV describes protocol AHE64 (Oklahoma pecans).

Common elements in the OCAB and CCAB scenarios were described. The same logic was used to select field study crops and locations and to identify cooperating growers (although methods may differ by cluster). The methods described in the August 2008 submission for identifying cooperating growers need to be revised to incorporate lessons learned from the CCAB studies involving pecans and citrus crops. Differences in clusters may arise because of the availability of different directory resources for creating the MGL for the different crops and states. The same range of surrogate pesticides are used, including newly added copper and sulfur compounds.

All three protocols address the same scenario, implement the same scenario design, and are identical in substance. The same study director directs AHE62 and AHE64; a different study director will be involved in AHE63. The analytical phases of the three protocols are identical. The field phases differ in location and crop and are likely to differ in Principal Field Investigator and/or LSC/Contract Research Officer (CRO). Only AHE62 cites CDPR requirements. Based on their work with the first two scenarios, EPA and the AHETF have agreed that a single protocol covering all proposed clusters will be prepared for future scenarios, which should reduce the bulk and review burden of future submissions. A novel element in this scenario is the proposal to combine existing pre-rule MUs with newly developed post-rule MUs to fulfill the scenario design.

The August 14, 2008 protocol submissions contained all elements of documentation required by 40 CFR §26.1125. Although further refinement is needed to address the comments in EPA's Science and Ethics Review and to reflect the lessons learned in early implementation of the CCAB studies, EPA believes these proposals are ready for HSRB review.

Scenario Definition and Site Selection

Mr. Carley presented the scenario definition and rationale for study site selection. The OCAB scenario is defined as the application of liquid sprays to orchard trees and trellis crops, using conventional airblast sprayers drawn by open-cab tractors. This scenario includes applications to actively growing, foliated crops using conventional airblast spray equipment; it excludes mixing and loading for application, use of unconventional airblast sprayers, and airblast application with closed-cab tractors.

The crops and states selected were among those with high production of crops typically sprayed with airblast equipment. No more than one crop type per state or more than one state per EPA growing region was selected. The selected states also differed from those used in the pre-rule OCAB study AHE07-A. Site selection was performed by first choosing a county or counties in each selected state where the study can be conducted efficiently. Primary considerations for selection of study counties included the following:

- presence of the target crop sprayed with airblast equipment
- an adequate pool from which to recruit suitable growers and workers
- proximity to a GLP-compliant CRO/LSC facility to handle materials and collected samples and field fortifications.

The sites selected for the new OCAB studies were Fresno County, California (AHE62), Erie and Chautauqua Counties, New York (AHE63), and Tulsa, Oklahoma, and surrounding counties (AHE64).

A conventional airblast sprayer directs the spray laterally from the radial nozzles on either side of the sprayer directly onto the vines and by the shrouds downward over the tops of the vines. The sprayer used to treat pecan trees sprays higher to accommodate the taller trees and sprays only to the left side of the rig.

Second-stage sample selection involved stratification of MUs by AaiH, compilation of the MGL, and screening the MGL in random sequence to identify a working pool of qualified and willing growers. An efficient configuration of MUs is designed, and one worker is recruited for each MU, selecting them randomly when it is feasible to do so.

The AHETF has recently developed a more standardized approach to compiling the MGL. Although the SOP defining the process is not yet complete, the general scheme was presented. The Farm Market ID database will be used to gather information on subsidized and California specialty crops. This database includes directories of all growers who received federal subsidies; typical crops in this database are corn, soybeans, and cotton. California collects detailed information on all pesticide use in the state and this information has been incorporated into the Farm Market ID database. This database will provide information that allows screening by acreage and other characteristics and should thus focus the MGL on qualified growers.

For specialty crops grown outside California, the potential primary sources of grower information include local "green tax" records, state crop/commodity commissions with unlimited membership, and grower associations with mandatory membership. Local "green tax" records were used successfully for the Florida citrus study. The other two sources are expected to provide good information, as long as membership is complete. The AHETF's goal is to identify growers who constitute at least 75 percent of the universe of growers of the target crop in the study area, as defined by the most recent Agricultural Census. The AHETF believes it can reach this goal through use of these resources, but may have to combine data from multiple sources. Potential supplemental sources include extension services (not personal lists from County Agents) and grower publication subscription lists. If the number of growers meeting the basic criteria is large and if the primary sources consulted include nearly all of them, the AHETF plans to build the MGL by randomly selecting 300 names if all growers' telephone numbers are available (more may be selected if all telephone numbers are not available).

To process the MGL, the Task Force will merge lists from all sources, suppress duplicate entries, and sort the list into a random sequence. Growers will be contacted in sequence of the list to determine qualification factors and interest. Qualified, willing growers will be placed in the working pool and growers will continue to be contacted from the list until the working pool contains enough (a sufficient number of) growers. EPA has concerns about the vagueness of the target of "enough" growers and has asked that a specific target size for the working pool of growers be defined in each protocol. If a pool of the target size cannot be defined from the original MGL, then either another selection from the same sources (if they have not already been exhausted), consideration of additional sources, or geographic expansion of the study area will be needed to obtain additional grower names.

To qualify for the working pool, the grower must have sufficient acreage to support the minimum AaiH in a single day, spray the crop with conventional airblast equipment drawn by vehicles with open cabs, and have at least one worker with experience using OCAB equipment. The grower also must be willing to cooperate in the research, use at least one of the AHETF surrogate chemicals, and let the AHETF recruit among qualified workers without interference or influence.

Data compiled from growers in the working pool will include crop(s) and acreage that might be treated; specific location of crop(s); number, type, and size of available airblast sprayer(s); surrogate chemical(s) that might be used; approximate timing of expected treatment; number of experienced workers available; and AaiH those workers might be able to handle in a day given the equipment and acreage. This information also will help track and understand why some growers might not be eligible to participate.

To approach and recruit qualified growers, AHETF staff will visit growers to confirm their eligibility and willingness to cooperate, and to obtain a promise of non-coercion. They will approach qualified workers employed by eligible cooperating growers, inform them about the research, and seek their consent to participate. These activities will continue until the MU design is fulfilled, within constraints including no worker used for more than 1 MU, no airblast sprayer used more than once, and no more than 2 MUs from any single grower. When multiple qualified and willing workers are employed by a single grower, participants will be selected randomly.

Mr. Carley summarized the sampling design. The AHETF will choose the study crops, study areas, and AaiH strata. They will identify growers of the target crop in the study area and approach the growers in random sequence. The Task Force will compile data from eligible growers who are willing to cooperate. They will design an efficient configuration of MUs and then recruit a worker for each MU, selecting them randomly when multiple qualified workers are employed by the same grower.

EPA agreed to accept purposive diversity sampling for the AHETF and Antimicrobial Exposure Assessment Task Force (AEATF) handler exposure monitoring programs as a long as the Task Forces described in detail their sampling design for each scenario, incorporated random elements whenever feasible, and documented their rationale for using a particular approach, including all decisions regarding the feasibility of randomization of specific elements in the design. The AHETF has addressed the first two requirements. Better documentation of the rationale for their approach is needed; the AHETF was not asked to re-work its feasibility analysis, but is expected to improve this for future scenarios.

EPA has concluded that the AHETF has provided sufficient information to support the Agency's conclusion that the scenario definition, site selection, and sample selection process proposed for the OCAB scenario is acceptable, with minor refinements.

OCAB Scenario Review

Mr. Crowley reviewed the OCAB scenario. OCAB objectives and diversity sampling design are similar to those of the CCAB scenario. The OCAB scenario also includes the addition of copper and sulfur as surrogates. Differences include the use of open versus closed-cab tractors, merging of new OCAB data with OCAB MUs from an existing 2003 AHETF study, and the use of chemical-resistant headgear and head patches to monitor exposure in the OCAB scenario.

The existing OCAB MUs are from AHETF protocol AHE07-A, pre human studies rule research conducted in 2003. The study reported data on 25 MUs using carbaryl as a surrogate.

Exposure monitoring methods were consistent with those used in current AHETF protocols, including the use of chemical-resistant headgear and inner and outer head patches.

EPA conducted its science review of AHE07-A in 2006. The majority of exposure was to the head (greater than 50 percent). Without headgear, face/neck exposure accounted for less than 4 percent of exposure and hand exposure accounted for less than 6 percent. With headgear, face/neck exposure accounted for between 1 and 14 percent of exposure and hands accounted for between 6 and 53 percent. Exposure to feet is negligible (less than 1 percent). The study employed a limited range of AaiH. EPA found the work to be guideline acceptable and useful for risk assessment and is appropriate for use in the AHETF database.

EPA found that 10 MUs did not meet AHETF requirements for minimal PPE because they wore a chemical-resistant jacket with a hood; 15 MUs wore chemical-resistant headgear consistent with the requirement for minimal PPE. Five MUs were observed for treatment of Georgia peaches, 6 for Idaho apples, and 4 for Florida oranges.

To assess the feasibility of integrating old and new MUs, the AHETF considered the potential sample size for the OCAB scenario based on statistical characteristics of the data from AHE07-A. The geometric standard deviation (GSD) estimate was 2.9, the interclass correlation coefficient (ICC) estimate was 0, and the AaiH range was 24 to 90 pounds.

Simulations using AHETF standard GSD/ICC estimates of 4 and 0.3, respectively, and AHE07-A MU configuration produced results consistent with AHE07-A; there was no evidence to support a departure from standard GSD/ICC estimates. Two additional clusters of 5 MUs combined with the AHE07-A MUs would yield a configuration that would satisfy the target accuracy benchmark; however, the limited range of AaiH in AHE07-A presented problems for assessing the proportionality of exposure to AaiH. The actual range of AaiH in AHE07-A was 24 to 90 pounds, which satisfies only the 3 upper strata defined to diversify AaiH. Because 2 clusters of 5 MUs would not provide 80 percent power to assess the relationship between exposure and AaiH, the AHETF proposed 3 new clusters of 5 MUs each (for a total of 30 MUs).

EPA accepts the scenario objectives, diversity sampling design, and use of additional surrogates. The Agency also accepts the proposal for use of the AHE07-A MUs. Copper and sulfur must be added to the scenario design, including a discussion of the analytical methods required for these compounds. A discussion of the methods for adjusting the face wipe data when goggles are worn when applying copper also is needed. EPA also asked the AHETF to incorporate recently revised methods for recruiting growers and workers.

EPA Science Assessment of Field Study Protocols AHE62, AHE63, and AHE64

The OCAB protocols are similar to the CCAB scenario protocols. The methods described for these protocols are consistent with AHETF SOPs and generally acceptable to EPA. New elements in the OCAB scenario include the addition of copper and sulfur as surrogate pesticides and changes to the exposure monitoring methods to capture head exposure in the OCAB scenario. The new field study sites in California, New York, and Oklahoma, are not already used in AHE07-A.

The OCAB protocols will incorporate the use of chemical-resistant headgear. Head exposure will be measured by placing 50-square centimeter (cm^2) cotton patches inside and outside the headgear. The inner patches are positioned on the top of the head and secured by a tie under the chin. The outer patches are attached to the headgear with adhesive tape.

AHE62, which monitors exposure when spraying California grapes, will take place in Fresno County, which is one of the top 3 counties for grape production in the state. Copper and sulfur are widely used on this crop. AHE63 will monitor exposure when spraying New York grapes. This field study will be located in Erie and Chautauqua Counties, which contain approximately 63 percent of New York grape acreage. Fifty-eight percent of New York grapes are treated with carbaryl and 47 percent are treated with copper. AHE64 will monitor exposure when spraying Oklahoma pecans. This study will take place in Tulsa and surrounding counties where OCAB applications are common, according to an Oklahoma State University extension specialist. Use of carbaryl, malathion, and other chemicals is not in publicly available data; however, based on 2007 information, there does seem to be good use of those chemicals in Oklahoma.

EPA has concluded that the protocols adequately address the technical aspects of applicable monitoring guidelines and are likely to produce scientifically valid and useful data if several issues are addressed. The protocols should be revised to reflect the addition of copper and sulfur as potential surrogates and revised methods for recruiting growers and workers. The protocols also should address the adjustment of face wipe data when goggles are worn when applying copper.

Clarifying Questions

Dr. Fenske asked whether workers would be able to remove the chemical-resistant headgear at certain points in the study, such as during breaks or while mixing or loading the pesticide. Mr. Carley answered that this was unclear, but the workers are not supposed to remove the headgear. Dr. Fenske noted that this was a problem with scripted studies; workers often are asked to engage in behaviors they would not normally perform. He inquired if the reference to more than 50 percent exposure to the head was based on reading exposure from the inner or outer head patch. Mr. Crowley responded that this measured exposure as if the worker was not wearing a hat. Dr. Krishnan questioned if the raw data in the database had been analyzed to inform the value of each farm as an MU versus each application as an MU. Mr. Crowley answered that the data had not been analyzed to that extent. Dr. Young inquired if the data on the existing MUs was drawn from different farms than the new protocols. Mr. Carley replied that this was the case.

<u>EPA Ethics Assessment of Field Study Protocols AHE62, AHE63, and AHE 64</u>

Mr. Carley provided EPA's ethics review of protocols AHE62, AHE63, and AHE64. EPA reviewed the ethics of existing study AHE07-A, conducted by the AHETF before the effective date of the Human Studies Rule, and found that it meets the applicable standards of 40 CFR §26.1703 and §26.1704. Thus, there is no regulatory barrier to EPA's reliance on

AHE07-A. Because AHE07-A did not report toxic effects, HSRB review is not required by the regulations. The HSRB will see the data from AHE07-A when it reviews the OCAB scenario monograph.

AHETF protocols AHE62, AHE63, and AHE64 are expected to provide additional exposure data for applicators using OCAB sprayers that are needed to support EPA exposure assessments. Some existing data meet contemporary standards, but these data must be supplemented with additional studies to meet benchmark accuracy targets. The knowledge likely to be gained from the new research will be usable in exposure assessments for specific crop uses and pesticides monitored as well as for other crop uses and pesticides employing OCAB equipment.

Regarding proposed processes for recruiting, screening, and obtaining consent, EPA's concerns have been satisfactorily addressed by these three protocols. The AHETF has addressed EPA's concerns related to equitable subject selection, fully informed choice, fully voluntary choice, and respect for subjects. These processes do not differ from the five AHETF protocols previously reviewed by the HSRB.

Five risk classes and efforts to minimize these risks were documented. Appropriate steps have been taken to minimize the risk of heat-related illnesses. All AIs are fully tested and MOEs are high, minimizing the risk of exposure to surrogate pesticides. The limited scripting of field activities is unlikely to affect risk to subjects. The psychological risks of pregnancy testing and assisted dressing have been minimized, as have the risks of exposure to detergents. Based on the deliberations of the Board at the June 2008 HSRB meeting, the background risks of agricultural work are not risks of the research and were not considered in the risk-benefit assessment.

The research affords no direct benefit to subjects, but subjects may realize indirect benefits from knowing their own exposure and how it compares to those of other workers. The societal benefit from improved data for risk assessment is likely to be realized. Growers benefit from receiving free product, but also absorb costs of inconvenience and lost time associated with the research. The sponsors of this research benefit from the lower cost of shared surrogate data development.

EPA considers the risks to have been adequately characterized and effectively minimized; the residual risks to subjects will be low. The remaining risks to subjects are reasonable given the potential societal benefits of obtaining reliable data on dermal and inhalation exposure while applying pesticide sprays to crops with airblast sprayers drawn by vehicles with open cabs.

IIRB reviewed and unanimously approved the protocol and English and Spanish consent forms and the product risk statements supplementing the consent forms. IIRB has not approved product risk statements for copper and sulfur, but must do so. IIRB must also review and approve the revised recruiting procedure when protocols are amended; this revised procedure refers to the expected change to the process of compiling and screening the MGL.

This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the

pesticide laws. The primary ethical standards applicable to this research are 40 CFR part 26, subparts K and L.

Several deficiencies were noted by EPA. All key members of the investigating team should be identified in the protocols. All of the following should be recorded and reported:

- number of potentially eligible workers linked to each grower
- numbers of individuals attending initial group meetings and individual consent interviews
- numbers of individuals signing consent forms and subsequently withdrawing or being withdrawn
- number of individuals completing participation.

The AHETF also should coordinate the lists of eligibility factors in the protocol and the consent form. Additional EPA concerns include the need to incorporate the revised approach to compiling the MGL and identifying the grower working pool into the amended protocols. The AHETF should specify the target size of the grower working pool and the target number of potential worker volunteers in the efficient configuration. EPA requested the AHETF clarify how the subject recruiting process differs when the worker/applicator is the grower rather than an employee. The AHETF also will need to document the addition of copper and sulfur as surrogates.

The protocols meet all requirements of 40 CFR §26.1111, §26.1116, §26.1117, §26.1125, and §26.1203. If all noted deficiencies and concerns are addressed, and if field studies AHE62, AHE63, and AHE64 are conducted as described, the studies will likely meet the applicable requirements of 40 CFR part 26, subparts K and L.

The Board was asked to determine whether the proposed OCAB application field study protocols AHE62, AHE63, and AHE64 if revised as suggested in EPA's reviews and performed as described are likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply liquid pesticides using airblast equipment drawn by vehicles with open cabs and whether the research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L.

Board Discussion

Scientific Considerations – Protocols AHE62, AHE63, and AHE 64

Dr. Fenske opened the Board's science discussion of AHETF protocols AHE62, AHE63, and AHE64. He commented that it is important to be aware of how scripted activities can reduce exposure. It is unavoidable that the workers use PPE as indicated by label instructions; however, taking the chemical-resistant headgear off during breaks would be normal behavior, and he urged the Task Force to allow workers to behave normally.

Dr. Fenske considered the addition of head patches to monitor head exposure to be appropriate, as was the use of the pre-existing exposure data. He asked why the 15 new MUs

were allocated as 3 to each AI strata; this results in an unequal sample size. The design gives an expanded range of AaiH, but only a small number of samples are collected for the lower range of AaiH. The rationale for this design is unclear.

Dr. Lehman-Mckeeman remarked that she had no concerns about using the existing data at this time, but cautioned that greater error usually is found at the lower end of the analytical scale. This design collects only 3 MUs from the low end of AaiH and 10 MUs from the high end. She added that this would constitute a category "a" recommendation: modifications that would enhance a scientifically sound design and analysis.

Dr. Young emphasized the need for independent observations. She agreed with Dr. Lehman-Mckeeman's comments regarding collection of data from the low end of AaiH. Dr. Krishnan agreed with his colleagues' comments.

Dr. Carriquiry agreed that combining existing and new data was acceptable, but the process by which this would be accomplished required more thought. The justification for the design is based on simulated data using an ICC of 0.3 and a GSD of 4, consistent with the existing data; however, the existing data must be consistent with the new data; consistency with the simulated data is irrelevant. Typically decisions to combine data are made after the new data are collected. She suggested that the Task Force proceed as if the data will be consistent, but reassess the data after they are collected to determine if the 2 data sets can be combined. The Task Force also must determine if 15 new MUs are sufficient. Dr. Fisher asked Dr. Carriquiry if this suggestion of a midpoint analysis, before the data are combined, constituted a "c" recommendation (needed to ensure that the design and analyses are scientifically sound). She asked Board members to comment on the threshold for similarity. Dr. Young responded that because data already have been collected for the lower end of exposure, they will not be directly comparable with new data; however, if the methods used are similar, the additional diversity will not be detrimental. Dr. Fisher asked if Board members would recommend collecting data from the lower levels of exposure to determine if the new and old data are equivalent. Dr. Lebowitz replied that if the new study collects 9 observations from the same level of AaiH as the completed study, the data can be compared, but no statement about comparability at the lower levels can be made because there are insufficient numbers of samples taken at the low level of exposure. If the data are combined, there will be significant uncertainty at the lower levels of exposure because only 3 new samples at the lower levels are being collected. The Task Force may wish to consider collecting more samples from the lower strata of AaiH.

Dr. Johnson suggested that only the new data may be adequate for assessing proportionality. Dr. Carriquiry agreed that some similar levels of AaiH should be tested in the new protocols and that the Task Force should consider taking more observations at these lower levels, rather than using the 3 MUs per each of 3 AaiH strata as proposed. Dr. Fenske countered that analyzing 3 MUs across 5 AaiH categories would permit analysis of proportionality with the new data. Dr. Young stated that if the protocols are the same but extremely different results are obtained, it could be informative and warrants investigation. Dr. Fenske commented that the data probably will be similar; the Task Force has been performing this research for many years and evidence suggests that the data will be comparable. Dr. Carriquiry agreed, but stated that the Task Force needs to determine that this is the case and cannot assume, a priori, that the data can be combined.

Dr. Fisher asked if the old data could be included in the assessment of a proportional relationship between AaiH and exposure. Dr. Johnson answered that it could be included, but it will be difficult to do so. Dr. Fenske added that the AHETF had proposed no objective tests to determine if the data are comparable. Dr. Fisher clarified that there can be two ways in which the data may differ: the data gathered for mid-level AaiH may be different than what was expected based on observations made at high levels of AaiH, or the overlap between the 2 data sets at high levels of AaiH may be different. Dr. Carriquiry remarked that she would be suspicious if the estimated exposure at the low AaiH strata for the old data was higher than exposure observed at the high end for the new data. Dr. Fisher concluded that these points are important for data analysis. At this point, it is not possible to determine if the simulations are adequate for judging comparability of the data. The Board advised that during the analysis phase, the AHETF should be aware of any discrepancies and cognizant of the possible need to collect more data. Dr. Carriquiry added that the current design collects 3 samples at 5 levels of AaiH. She suggested that rather than equally distributing the observations over the 5 levels, more observations be made at the lower levels of AaiH for which there is no old data.
Dr. Johnson suggested a design in which 4 observations are collected for each of the 2 lowest strata, 3 for the middle strata, and 2 each for the 2 highest strata. Dr. Krishnan inquired if it would be logistically difficult to identify growers using the lower strata of AaiH and if this was the reason for few observations at that level. Mr. Carley explained that the lack of observations at the lower strata resulted from the old study's design and contributed to reasons why the EPA wanted new handler exposure studies. The old studies did not include an adequate range of AI; AHE07-A was performed during a transitional time, thus there was some improvement in the AI range, but not as much as EPA asks for at the present time. The AHETF does not expect difficulties identifying growers using the lower strata of AaiH.

Dr. Fisher questioned if the Board agreed to recommend the 4-4-3-2-2 design suggested by Dr. Johnson. Dr. Fenske explained that he was unsure whether the Board could make such a specific recommendation. Dr. Lebowitz suggested that the Board state that, if feasible, the Board would prefer the AHETF to consider a redistribution of MUs in AaiH strata such that more observations are made at the lower levels to compensate for the lack of such observations in the old data. Dr. Lehman-Mckeeman agreed that the Task Force should consider this approach. She added that the Board also should state that the AHETF cannot decide *a priori* that the old and new data will be consistent; an interim evaluation of the data will be needed. The Board also should express concern about the unbalanced subject distribution in the exposure ranges; however, this is only an "a" level comment.

Ethical Considerations – Protocols AHE62, AHE63, and AHE 64

Dr. Fish opened the ethics discussion by saying that her review would be similar to that for the CCAB scenario. She noted that the inclusion criteria stated that all potential subjects must be trained in pesticide handling or exempt from training and asked which subjects would be exempt. Mr. Carley noted that this statement is consistent with the worker protection rule. Workers who are employees must be trained, but farmers or employers who may also apply pesticides need not be trained. Thus, growers are not required to receive the standard training that employees are required to take. The point of the rule was to ensure that all employees are

adequately trained, but not to place onerous demands on family farm workers. Mr. Carley addressed Dr. Prentice's previous concerns about information on the pesticide labels. He explained that most of the effects that might occur are not anticipated with normal use of the pesticides. The paragraph about these possible effects specifically addresses the consequences of cholinesterase inhibition, and the Board should clarify whether this statement should be included in the ICF.

Dr. Prentice stated that the risks associated with participation in agricultural work should not be on the consent document. By the same logic, this applies to accidental spills, which would not be part of the research. He noted that he was not unduly concerned about the product risk statement, but acknowledged that the risk list could be clarified. Mr. Carley noted that there was no discussion of risk stemming from handling pesticides according to the label instructions in the core consent document; this discussion was found in the product risk statement included in the consent package. Mr. Carley commented that EPA would be interested in understanding whether in the case of minor differences in similar products, different product risk statements are needed from each product label, or if a simplified, streamlined, general-language document can be used to cover similar products. Such a statement would note that adverse events can arise from improper handling of the pesticides, list possible risks, and perhaps provide information on mechanisms of action, such as cholinesterase inhibition.

Dr. Philpott offered that such a product risk statement may provide too much information, particularly with regard to mechanism of action. It would be acceptable to list the symptoms of severe exposure. EPA and the AHETF should consider including information that the prudent participant would like to know, such as the signs of bad reactions to exposure. Dr. Fish noted that a better understanding of the handler population is needed before decisions concerning the amount of information provided can be made; it is unclear whether including statements about cholinesterase inhibition, for example, would be informative. She proposed that the signs and symptoms of overdose or exposure outside of typical conditions be included. In drug studies, participants are provided with information on risks that may be encountered at the dose the participants use, not risks associated with overdose. Using this analogy, references to overdose symptoms should be removed. Dr. Philpott cautioned against using a direct analogy such as this because of the risk of spills that may expose workers to larger than expected levels of pesticide. He agreed that information about the characteristics of the handler population would be helpful for generating an appropriate risk statement.

Dr. Fisher stated that the Board also must consider what handlers are typically told about the compounds they work with in order to separate risks associated with handling pesticides from risks associated with the research itself. Mr. Carley explained that the information was taken from the label, which describes extreme events. The label always is available to handlers, although it is doubtful that they read it every day. Dr. Philpott stated that if workers have the opportunity to examine the label, it is not necessary to reiterate the information on the label in the product risk statement. A more appropriate approach would be to explain signs and symptoms of adverse effects. Dr. Prentice agreed that protection should be confined to risks associated with participating in the research. He added that he was ambivalent about having participants sign the product risk statement because it focuses on risks associated with pesticide spills, which is not a part of the research. Dr. Philpott countered that workers participating in

scripted activities may use more product for longer time periods than they are accustomed to, and therefore could face greater exposure. They should be provided with information on risks of exposure to large amounts of pesticides, but this information must be presented in an understandable way.

Mr. Carley inquired if the HSRB would require a product risk statement tailored to each of the 13 products or 3 statements addressing each of the three AIs; 3 summary statements would be simpler for EPA to review and also would be easier for field investigators to use. The risks associated with scripted behavior fall under a different risk category than the risk of chemical exposure. Dr. Philpott responded that there is some overlap between these 2 risk categories. He added that a generic product risk statement would be acceptable as long as it covers the more likely and shared outcomes. Very rare outcomes could be omitted.

Dr. Philpott remarked that his ethics concerns were the same as those for the CCAB. He reemphasized Dr. Chadwick's point regarding the use of more PPE in the OCAB scenario and the increased likelihood of exposure and whether risk was minimized by using pesticides rather than non-toxic surrogates. Dr. Fisher advised the HSRB to ensure that its recommendations minimize risk.

Follow-up from Previous Day's Discussion

Mr. Jordan commented on Tuesday's discussion of the CCAB and OCAB scenarios with the goal of minimizing EPA's possible misunderstanding of Board recommendations, given that the AHETF would like to proceed with the research as soon as possible.

Regarding the addition of copper and sulfur to the list of surrogate compounds, EPA understands that these compounds were neither evaluated nor approved by the Board. If the Task Force wishes to use these compounds in its research, it must present proposals to do so to EPA for review, and EPA will assess the proposals and present its findings to the Board.

Mr. Jordan thanked Board members for acknowledging the changes made to the protocols based on Board comments made at the June 2008 HSRB meeting. EPA expects incorporation of Board recommendations to continue.

Regarding the issue of category "c" recommendations (i.e., critical changes to ensure scientific validity of the data), EPA understands that the Board wishes to see only 1 MU per grower and at least 5 MUs per cluster in the OCAB and CCAB scenarios. EPA will work with the AHETF to ensure that this strategy is followed.

Regarding Dr. Chadwick's concern related to the validity of the assumption of proportionality between AaiH and exposure, this conclusion was drawn after consultation with the Scientific Advisory Panel (SAP), based on 25 years of studies examining relationships that affect exposure. Dr. Chadwick had asked why innocuous substances could not be used in place of pesticides if the identity of the surrogate did not affect exposure. EPA agrees that risk could be reduced by using innocuous substances rather than pesticide AIs; however, the nature of the AI in the mix might influence the amount of exposure. For example, it is EPA's view that

volatile compounds behave differently than non-volatile compounds, with a greater potential for inhalation exposure. Therefore, EPA uses its generic database to evaluate dermal exposure for a group of compounds less likely to volatilize. When research is performed using more volatile compounds, EPA will require chemical-specific information. Other characteristics that influence exposure may exist; thus EPA must use AIs in its studies because the type of AI might influence exposure.

EPA has not had the opportunity to discuss this relationship extensively, but understands that the validity of the relationship is not entirely clear. EPA has insufficient information to define the relationship between AaiH and exposure with complete confidence. Available data suggest that there will be a strong relationship between AaiH and exposure in many cases; the relationship may not hold in closed systems, where exposure would be influenced by the number of times the system is connected to the container.

Based on this record, Mr. Jordan suggested proceeding with the research as proposed, using pesticide AIs that will provide EPA with a basis for drawing conclusions at least about the AIs used and to extend that to the data currently in the PHED. The research will aid EPA's understanding of cases in which AaiH is or is not a significant factor contributing to exposure.

Some Board members may question if the value of this research is adequate to warrant the associated risks. EPA has made a strong case that the risk of exposure to pesticides is low. Also, because this is essentially an observational study, the activities monitored in the research are similar to those performed by the participants during their normal work days. In addition, the calculated MOEs demonstrate that exposure, and hence the risks posed by the research, are low. The benefits of using AIs are real; use of AIs will be informative for these specific AIs and also about AIs in general; therefore, EPA will proceed on the assumption that it is acceptable to use AIs in the CCAB and OCAB scenarios.

Many other suggestions and recommendations for improvement were made by the Board in Tuesday's session, approximately 25 to 30 for ethics and a similar number for science. While most of these changes are not serious enough to derail the research, EPA understands the changes would improve the research and should be implemented when possible, given scheduling constraints. EPA will assess the Board report, meeting minutes, and staff notes to help the Task Force implement these changes. Mr. Jordan reiterated that EPA did not believe that any of the changes were significant enough to warrant bringing the revised protocols for a second Board review. EPA will work with the AHETF to revise the protocols and materials and to implement the OCAB and CCAB protocols using carbaryl, malathion, and chlorothalonil. The Task Force expects to implement these protocols in 2009, once IRB approval is received.

Dr. Fisher cautioned EPA that the impressions drawn from discussions taking place at the meeting do not represent a directive; the opinion of the Board is not official until the Board report has been finalized. If the studies are changed and proceed before the final report is issued, the studies risk being inconsistent with Board recommendations. The Board can clarify its recommendations between the meeting and the final report. The HSRB is sensitive to the AHETF's time constraints, but cautioned them against proceeding based on their impressions of Board recommendations. She advised that the AHETF wait until it receives the final and

approved Board report before changing and executing the protocols. She added that the meeting minutes are the Chair's minutes and do not represent the opinion of the Board.

Dr. Fisher commented that the use of the 1 MU per grower, 5 MUs per cluster design was considered by the Board to be critical. She stated that the Board's impression was that EPA will no longer assume universality of the ingredients serving as surrogates. When a new ingredient is introduced, EPA should not assume it is interchangeable with previously used AIs. EPA and the AHETF should include as much information as possible about new ingredients in their reports. Dr. Fisher noted that the Board wishes to review completed studies as soon as possible to help determine if the risk-benefit balance is appropriate. Once the Board has reviewed a completed study, there may be a shift in what the Board considers to be appropriate methodology for science and ethics.

EPA also should not assume that a given study is a precedent for the next study the Board reviews. The design of subsequent studies should not be based on a mistaken impression EPA may have of Board decisions. "Poor" studies should not serve as precedents and errors in the way a study was implemented also cannot serve as precedent.

EPA is correct regarding its impression of the meaning of a "c" recommendation; however, Dr. Fisher explained that her impression of the last two studies was that EPA decided which recommendations were or were not important and chose to ignore final Board recommendations and proceed with the research. For example, the recommendation to collect information on growers who do not respond and to identify a competent LSC should not have been ignored. In addition, it is unlikely that the Board assumed that the approximately 20 recommendations made for the science of the protocol were optional. It is important that EPA not ignore Board recommendations, because these recommendations will be considered when the Board evaluates the utility of a completed study. A "b" recommendation means that the Board may evaluate the data as having limited utility because of issues, such as representativeness of the sample.

The Board has continually asked EPA to explain how it will use the data as the Board discusses the charge question related to data utility. The HSRB does not wish to be involved in regulatory activities, but it is important that the Board understand the way in which EPA intends to use the data for its regulatory activities. This understanding will allow the Board to determine if the data has qualities that will support its use for the intended regulatory activities.

Dr. Fenske stated that he was concerned that EPA developed its list of issues to address based on the June 2008 meeting minutes and the impression it had of the meeting discussions. He also was surprised that the advice had been categorized as necessary or unnecessary to implement until the next set of studies was designed. He suggested that it might be useful to have Mr. Jordan share with the Board the list of items to address that EPA generated for this meeting. Dr. Fisher questioned the usefulness of such a list, stating that the accuracy of such Agency interpretations could not be confirmed prior to Board review and decision at a Board meeting.

With regard to incorporating copper and sulfur into the protocols, Dr. Fenske stated that he had reconsidered his earlier concerns. It is not clear whether EPA has a good scientific analysis discussing the boundaries of using generic compounds to make assumptions about other compounds. This has significant implications for developing risk assessment policies for workers. Copper and sulfur may be appropriate for use in these studies, but other compounds may not.

Dr. Lebowitz agreed that the Board should review EPA's list of issues to address from this meeting. Regarding the nature of the generic database, Dr. Lebowitz noted that EPA has the scientific expertise to address the impact of the chemicals' nature on the research. Further discussion of this matter would be appropriate to ensure that the HSRB and AHETF are aware of the boundaries and limits of the generic nature of the database and to permit EPA to receive advice pertinent to the uses of this database. He added that there is a significant amount of documentation within EPA on inhalation reference doses and other data on exposure factors that might be useful. When outside users evaluate the generic database, they will be familiar with these issues and may raise concern about the database. Dr. Lebowitz agreed that it was preferable to use the types of compounds that are normally used in the field and to use compounds with known courses of action. Physicochemical behavior may be different and may affect risk assessment analyses. Risk management based on the generic database also will be critical for farm workers and growers.

Dr. Lebowitz agreed that it would be preferable to employ surrogates normally used in the field in the research, particularly surrogates with known courses of action. Although the physicochemical behavior of the compounds may be different, the analyses for risk assessment based on the generic database will use bands of appropriate levels of pesticide to measure exposure. Therefore it is appropriate to use the surrogates, but descriptions of their properties and uses should be provided and the science and ethics pertaining to the use of each type of compound should be reviewed by the Board.

Dr. Brimijoin stated that he had been persuaded that using the actual compounds normally used by the workers is correct. The proprieties of many of these compounds are established and they pose only a very small, incremental risk to the workers. It would be impractical and expensive to require the Task Force to apply and measure exposure to different molecules. Dr. Brimijoin added that he believed EPA had made a good faith effort to understand the Board's deliberations regarding absolutely required changes versus recommended changes. The Board should be clearer about which recommendations must be implemented to support the finding that EPA will be able to rely on the data. EPA and the Board must communicate more effectively. He commended Mr. Jordan for the clarity of and insight provided by his summary.

Mr. Jordan thanked Drs. Fisher, Fenske, Lebowitz, and Brimijoin for their comments. With regard to providing a list of issues needing to be addressed that EPA gleaned from the meeting, Mr. Jordan stated that EPA would provide this list after the meeting; the list will be sent to Dr. Lewis. Mr. Jordan respectfully disagreed that EPA had ignored HSRB comments. EPA has seriously considered the Board's recommendation and the data and facts reflect this. EPA has addressed how it intends to use the data in several presentations but will do so again. EPA's risk assessment and exposure assessment algorithms have been included in past presentations

and EPA has explained the source of inputs to the algorithm, why they are conservative, and why these numbers represent the high end of exposure. Mr. Jordan explained that he provided his comments this morning to clarify EPA understanding of Board deliberations at this meeting. He stated that if this is not a reliable basis for understanding Board intentions, problems are created with respect to time-sensitive research. For example, had EPA waited until final approval of the Board's report for the June 2008 meeting before beginning the pecan and Florida citrus studies, the studies could not have been performed until 2009. EPA believes that its understanding of the report was accurate. One difference between discussions during the meeting compared to what was documented in the report relates to the use of the alternative sampling strategy. Based on the Board's discussion during the first morning session of this meeting, the Board and EPA are in agreement on this issue. Regarding the use of only 1 MU per grower, a shift in emphasis seems to have occurred between the June 2008 meeting and in the report, with the need for this worded less strongly in the report. EPA considered this to be a "c" level recommendation, but the recommendation did not appear to be as strong in the report.

EPA also wishes to stress that the public meeting serves as a venue at which the Board can communicate its thinking to the public, and that dramatic changes in Board consensus can undermine the utility of the public meeting. Any important points should be made during the meeting. If EPA should not allow research to move ahead until it has reviewed the final Board report, the reports will need to be completed more quickly. EPA must determine how best to accommodate implementation of Board decisions.

Dr. Fisher agreed that the Board could try to complete its report sooner, but disagreed that the public comments made at the meeting supersede those made in the report. EPA cannot say it has understood Board decisions until the report has been finalized. EPA needs to consider if it wishes to challenge the Board process. She disagreed with Mr. Jordan's assumption that there were dramatic differences between the report and discussions at the public meeting and that modifications to discussions made in the final report negate the utility of the meeting. Dr. Fisher also expressed concern about Agency requests to clarify Board decisions and recommendations discussed at this meeting; these cannot be verified until final Board review and discussion of the report. Similarly the HSRB cannot confirm that EPA's impressions of the outcome of meeting discussions are correct and that the research can proceed until final Board review of its report. . The HSRB will attempt to finalize its report quicker, but unless changes are made to the Board process, it is not valid for research to proceed based only on discussions at the meeting.

Dr. Brimijoin suggested that the Board might need to reconsider its process because EPA cannot wait 4 months to receive a finalized report. The Board should produce its draft quicker and hold teleconferences to finalize the report. In particular, the Board should be able to inform EPA within a month about serious issues that may compromise the validity of the research results. Dr. Krishnan agreed somewhat with Mr. Jordan's impression that EPA can choose to proceed based on deliberations at the public meeting. He suggested that Dr. Lewis could help produce a checklist of issues addressed by EPA, and why certain changes were or were not made; this could be appended to the report. Dr. Fisher inquired who would be responsible for confirming such a list. She also questioned whether the impression given by the Board at the end of the meeting was final, given that it can be difficult to create a clear and finalized consensus by the end of the meeting. She noted that her summaries of Board consensus during this and prior

meetings were always framed as the Chair's preliminary understanding and that there was always the expectation that the Chair's summary would be confirmed or modified when the Board wrote its final report. She reiterated that the meeting minutes are only the view of the Chair. Unless a different process is created, the Board can only agree to accelerate finalizing its report and have public meetings or teleconferences to discuss it. The Board should maintain its right to alter the language in the report if changes are needed to correct impressions or improve clarity. Dr. Lewis stated that minutes are required for this meeting, but they represent a summary of the discussion and not Board decisions. He agreed that the final report should be produced more quickly and that public meetings or teleconferences to finalize the report would be useful in this regard. Only the final report represents the Board's positions on matters discussed at the meetings.

Dr. Young commented that use of the "a," "b," and "c" categories for recommendations would help clarify HSRB decisions. Reducing the time between the meeting and production of the final report also should be helpful for EPA. Dr. Fenske agreed that adjusting the timeframe for producing the final report will help EPA communicate with the AHETF. He acknowledged the time pressure on Board members for review of documents for the meeting. For example, the Board received access to a Web portal with approximately 2,000 pages of documents relevant to the meeting only a month before the meeting. Board members also received an additional relevant document on the October 17, 2008. It may not be appropriate for EPA to ask HSRB members to make decisions on materials they have not had sufficient time to review.
Dr. Prentice suggested developing a brief list of recommendations to be presented during the meeting; more detail could be provided in the report. Dr. Fisher explained that this would represent a different Board process; currently, the Board's discussion and consensus are refined in the report. Another approach would be to rely only on the minutes and have them approved by the Board. Dr. Lebowitz agreed that the process of developing the report is necessary to ensure clarity of Board recommendations; however, it could be beneficial for EPA to provide its list of perceived recommendations to Board members, particularly the lead reviewers for science and ethics. Dr. Chambers agreed that Dr. Prentice's suggestion could be used if the recommendations were termed "tentative conclusions." Most of the AHETF protocols are seasonally dependent. HSRB reports have tended to include long descriptions of procedures that might not be necessary; if the Board agreed to produce a more concise report, it could be delivered to EPA in a timelier manner. Dr. Lehman-McKeeman agreed with Drs. Prentice and Chambers. She noted that she did not attend the June 2008 meeting and that upon first reading, the conclusions in the report were unclear. Categorization of the recommendations as "a," "b," or "c" recommendations will improve clarity. In addition, EPA should clearly inform the Board of time constraints associated with the protocols under review to allow the Board to be more responsive to EPA and AHETF needs.

Dr. Fisher discussed another misconception related to EPA's decision to execute the study based on statements heard at the meeting or written in the minutes, rather than waiting for the final Board report. EPA often makes comments on the final report that prompt the Board to make changes to the report because of misunderstandings. She added that the reports should place more attention on the "b" category of recommendations, which states that the study could be implemented, but the data would be of limited use; the Board should clarify the limitations of the data. Dr. Carriquiry stated that, in her opinion, Board recommendations are often equivocal,

particularly for science. From a scientific perspective, many of these studies would not be accepted by peer-reviewed publications. The Board accepts compromises in the interest of completing the research. She noted that although matters related to the completeness of the MGL were considered a "b" issue, these could rise to the level of a "c" issue for EPA when the Agency wishes to justify its regulatory process based on a sample that the Board cannot conclude is truly representative. The "a," "b," and "c" categories are relative to an endpoint that may change. Dr. Fisher stated that she intended the "b" category to serve as a signal that there would be critical limitations on the data when the Board was asked to review the completed study.

Dr. Fish suggested that the Board consider Dr. Prentice's suggestion for the next HSRB meeting. Having a work period during the meeting at which the Board could reach a consensus on the "c" issues could be useful. The primary and other reviewers could develop a slide describing their final recommendations to ensure that the Board, EPA, and the public understand the Board's positions on these issues. Dr. Fish added that streamlining the report to include bullet points outlining the recommendations might also be helpful. Dr. Brimijoin agreed that the report should begin with a list of recommendations, with the critical recommendations flagged. The body of the report should discuss how these conclusions were reached. Dr. Fenske also endorsed Dr. Fish's suggestions to add a list of the recommendations and then provide context. He also agreed with Dr. Carriquiry's comment regarding compromises made to ensure the research can be performed. For example, the protocol reviewed in June 2008 stated that dormant application would not be monitored because it represents only 15 percent of applications, but no scientific justification was given for this decision. A good scientific reason for this decision may exist, but was not presented to the Board. It appears that the AHETF is excluding an entire class of application because it is inconvenient to gather these data.

Regarding HSRB reports, Dr. Fenske noted that the Board is advisory to EPA and tries to assist in creating sound scientific and ethical research involving humans, but the HSRB also is a transparent public body that has the public trust. The report must be accessible to the public and understandable without the public needing to review the 2,000 pages of documentation provided to the Board. Justification of Board decisions must be understandable by lay people. Dr. Fisher noted that Drs. Carriquiry and Fenske have asked the Agency for justification of the sampling strategy if it deviates from the SOP; justification of the representativeness of the samples; and justification of the generalizability of the data for exposure in the protocols presented. In a completed study, the Board wishes to see discussions of adequacy and limitations of the conclusions that can be drawn as limited by the sampling strategy, representativeness of the sample, and generalizability. Because these limitations usually are not articulated to the Board, the Board is put in a difficult position of deciding how the data can be used. Dr. Lebowitz stated that, from a scientific standpoint, critical issues have been raised. Providing a list of suggestions to EPA and clarifying the utility of the data based on the protocols presented to the Board likely would be useful. The Board should provide detail in its report regarding when limitations may be of sufficient magnitude to affect use of the data.

Dr. Fisher summarized that in future meetings a list of recommendations will be developed and then finalized by the primary and secondary reviewers. The Board will attempt to identify its concerns as "a," "b," or "c" level issues and will clarify the meaning of the "b" level. This also is dependent on EPA including in future protocols justification for sampling strategy,

generalizability, and representativeness. EPA might also wish to refresh the Board on its risk algorithm and regulatory processes. To facilitate a rapid review, Dr. Fisher asked lead reviewers to provide a draft to Dr. Fisher within 2 weeks of the meeting, and Drs. Fisher and Lewis will draft the report within 1 week. The Board will strive to have a public teleconference to finalize the report will be held within 4 to 5 weeks of the meeting. Such a teleconference will be also be dependent on adequate time to announce the teleconference in the Federal Register and public access to the final draft report. Dr. Fisher reiterated that the final report is the Board's definitive statement. The public and EPA are free to comment on the draft report.

Dr. Lebowitz agreed that the format of the report should be changed. He added that EPA also should provide a timetable indicating when they and the sponsor need Board conclusions to be able to schedule the research. Dr. Fisher asked that, whenever possible, EPA present protocols far enough in advance to meet sponsors' needs, given the revisions to the Board's schedule for producing the final report. Dr. Lewis noted that the discussions at the meeting help EPA understand how best to operate with respect to the Board and how the Board can help present its recommendations. EPA also understands that recommendations presented during the meeting may be agreed on by the Board, but are not official until the report is finalized.

Dr. Fisher summarized that the report for the October 2008 meeting would contain a bulleted list of recommendations with a brief rationale and a description of the recommendation in terms of the "a," "b," or "c" levels. The ethics reviewers will need to determine their own system for categorizing recommendations. Dr. Philpott suggested establishing a working group to create a template for future Board reports, based on the outcome of the October 2008 report. Dr. Lebowitz suggested that the Board should review protocols at least 4 to 5 months before the AHETF wishes to execute them. Major changes to protocols and other supporting documentation should be provided to Board members well in advance of the meeting.

Mr. Carley asked how EPA should proceed on the protocols presented at this meeting. EPA strives to present its responsiveness to Board recommendations in all its presentations. Dr. Fisher agreed that the Board had a mistaken impression concerning changes that had been made or not made. She suggested that EPA e-mail a list of changes made or not made, along with rationales, a few days before the public meetings. Mr. Carley also agreed to send EPA presentations to the Board a few days before the meeting, with the caveat that small changes might be made in the interim. Dr. Fisher agreed that sending these the Friday before the meeting takes place would be helpful.

Dr. Fisher commended Mr. Carley for his presentations, acknowledging that the large amount of information presented may have resulted in some misinterpretations. Mr. Carley added that presentations would be sent to Board members in advance of the meetings; if Board members have any issues with the presentation, EPA staff can be contacted through Dr. Lewis. Dr. Carriquiry stated that the presentations were understandable; however, the Board did not expect that the pecan protocol would be changed because it was executed very shortly after the meeting. She stated that it was disappointing not to see Board suggestions incorporated into the other protocols. Dr. Fenske stated that this had been an unusual situation in part because it was the first time the Board had seen a presentation on a completed study. Providing advance material to Board members will help address this situation.

Completed Carroll-Loye Biological Research Field Study LNX-001

Background

Mr. Carley began EPA's review of the completed Carroll-Loye study LNX-001. This is a field test of mosquito repellency for two conditionally registered formulations containing 20 percent picaridin.

The protocol was submitted to EPA by Dr. Scott Carroll of Carroll-Loye Biological Research (CLBR) on April 10, 2007. The initial submission met the standard of completeness defined in 40 CFR §26.1125. EPA's Science and Ethics Review on May 24, 2007, was based on the initial protocol submission. Amendment 1 to the protocol and revised ICFs were approved by IIRB on June 12, 2007, and provided to the Board; the most significant change was to create separate consent forms for untreated "experienced" subjects and treated subjects. The HSRB reviewed protocol LNX-001 (as amended) favorably at its meeting on June 27, 2007. Amendment 2 corrected a typographic error in the protocol and was first submitted to IIRB on August 15, 2007.

The California Code of Regulations, Title 3, Section 6710 requires that an IRB-approved protocol and supporting materials be submitted for approval by the Director of the CDPR before a pesticide exposure study is conducted in California. On October 22, 2007, CLBR submitted revised Consent Forms and an Experimental Subjects' Bill of Rights to IIRB. On October 23, 2007, IIRB reviewed and approved these revisions. The CDPR approved the protocol as revised on January 25, 2008.

The original approval of LNX-001 by IIRB on April 5, 2007, was scheduled to expire on April 4, 2008. On March 18, 2008, IIRB reminded CLBR that this approval would expire. On March 23, 2008, CLBR submitted a Progress Report to IIRB, attaching two consent forms signed by subjects. On March 31, 2008, a deviation in the report—the investigator failed to sign one consent form—was noted. IIRB reviewed the progress report on April 1, 2008, noting the failure to sign the consent form, and extended approval of LNX-001 through March 31, 2009. On April 4, 2008, IIRB accepted the March 31, 2008 deviation report.

CLBR drafted Amendment 3, which clarified the methods of allocating treatment to subjects, bringing the protocol discussion of qualifications for service as an untreated control into accord with that in protocols recently reviewed by the HSRB. It also clarified when pregnancy tests would be administered to female candidates relative to other study events on March 27, 2008. This amendment was submitted to IIRB on April 25, 2008 and approved on April 28, 2008. Dose determination testing was conducted between May 14 and 23, 2008. Field testing was conducted on June 7 and 15, 2008. On July 6, 2008, CLRB filed a deviation report with IIRB regarding use of subject limb measurements from files of previous studies. On July 20, 2008, CLRB filed a deviation report to IIRB reporting failure to ensure approval of Amendment 2. On July 21, 2008, IIRB provided approval of Amendment 2 and acceptance of the deviation reports of July 6 and July 20, 2008.

An informal study submission was made to EPA on August 7, 2008. On August 8, 2008, EPA queried the time of treatment. The formal study submission was made to EPA on August 12, 2008; the formal study submission did not differ from the informal submission. On September 9, 2008, a deviation was reported related to the time of treatment reported to IIRB; IIRB accepted this deviation report on September 15, 2008. On September 23, 2008, EPA's ethics review noted gaps in the record of IIRB correspondence. Supplemental CLBR and IIRB correspondence was submitted to EPA on September 26, 2008.

EPA Science Assessment of Carroll-Loye Biological Research Field Study LNX-001

Mr. Kevin Sweeney (OPP, EPA) provided EPA's science review of LNX-001. The objectives of this research were to test the mosquito repellent efficacy of the test materials to satisfy a condition of registration imposed by EPA. The test materials were EPA Reg. Nos. 39967-50 (cream formulation) and 39967-53 (pump spray formulation). Both products contain 20 percent picaridin.

The study design of LNX-001 included a dosimetry phase with 10 subjects to establish the typical consumer dose of each formulation for use in efficacy testing. These subjects were trained in the laboratory to aspirate landing mosquitoes before they bite, using laboratory-reared, pathogen-free mosquitoes. Because cream and spray treatments are easily distinguishable, the study was not blinded. The 10 subjects treated with each formulation and the 2 untreated control subjects participated in each of the 2 field trials. Untreated subjects were used to monitor mosquito pressure; each subject was attended by 2 technicians to aspirate landing mosquitoes. Both treated and untreated subjects were exposed to mosquitoes for 1 minute at 15-minute intervals. Duration of efficacy was calculated as the mean time from treatment to "first confirmed landing with intent to bite" or "FCLibe."

The dosimetry results showed differences in dose between the cream and spray applications, and between legs and arms. More test material was used when the cream was applied compared to the spray, and more material was applied to the legs than the arms (1.18 grams (gm) cream versus 0.46 gm spray on the arms and 2.63 gm cream versus 0.90 gm spray on the legs).

Using the highest dose administered (526 milligrams (mg) cream on legs), the mean surface area of treated legs, an assumption of a 70 kilogram (kg) adult, and the limit dose for dermal toxicity in the rat of greater than 2,000 mg per kg, the calculated MOE for dermal toxicity is at least 266, and may be greater; the target MOE for this use is 100. Other MOEs calculated include cream on the arms (greater than or equal to (≥) 593), pump spray on the legs (≥ 778), and pump spray on the arms (≥ 1,527), all of which are greater than 266.

The field test sites were located in the California Central Valley. The two sites had similar, but not the same, mosquito populations. The Butte County (Site 1) habitat was a grassy lakeside with shrubs and the Glen County (Site 2) habitat was tall native forest understory. *Anopheles*, *Aedes*, and *Culex* species were present at both sites.

Field test results showed that the cream formulation out-performed the pump spray. At Site 1, there were no failures associated with the use of the cream formulation. Mean complete protection time (CPT) for the cream formulation was 14.0 ± 0.0 hours at Site 1 and 13.5 ± 1.1 hours at Site 2. Mean CPT for the pump spray formulation was 11.6 ± 1.8 hours at Site 1 and 11.6 ± 1.5 hours at Site 2.

Protocol deviations potentially relevant to the science review include the use of historical limb measurements from previous studies and reporting the estimated mean time of treatment for field testing at Site 1 on June 7, 2008. Reporting on June 15, 2008 was done in accordance with the protocol (testing began between 8:10 and 8:50 a.m.). The deviation in reporting on June 7, 2008, would have affected the CPT by at most 15 minutes.

Regarding the use of historical limb measurements, the protocol calls for measuring each subject's limbs to determine the area to be treated. Limb measurements recorded in earlier studies were used if they were less than 2-years old and the subject reported no significant change in weight or muscle mass. This was implemented on May 14, 2007 when previously recorded limb measurements were first used for subject #47; it was reported to IIRB as a deviation on July 6, 2008, after all testing was complete. This should have been handled as a protocol amendment and should not have been implemented before IIRB approval; however, because limb measurements are unlikely to change, the deviation was not of scientific significance.

Regarding the deviation in reporting, the protocol calls for recording the time of treatment of each treated subject in the field tests. Treatment of all subjects in the field on June 7, 2008 was reported as beginning at 8:00 a.m.; on June 15, 2008, the reported times of treatment differed for each subject, and varied over a span of 40 minutes. EPA noted this discrepancy, and CLBR explained that recording of the approximate mean time of treatment was a past practice inadvertently followed on June 7, 2008. At EPA's recommendation this was reported to IIRB as a deviation on September 9, 2008, and was accepted by IIRB on September 15, 2008. This deviation was of no scientific significance.

All previous EPA comments were satisfactorily addressed except that information was not provided on diagnostic statistical tests for normality, or on how non-normally distributed data would be analyzed. The study provides scientific results that meet EPA Guideline standards. The product EPA Reg. No. 39967-50 KBR 3023 All-Family Insect Repellent Cream (20 percent picaridin cream) provided a CPT of 14 hours; EPA Reg. No. 39967-53 KBR 3023 All-Family Insect Repellent Spray (20 percent picaridin pump-spray) provided a CPT of 12 hours.

Clarifying Questions

Dr. Krishnan asked if the MOE calculations were based on the no observable adverse effect level equivalents for toxicity rather than Lethal Dose 50 (LD50). Mr. Sweeney answered that the LD50 determination had not been used for these calculations.

<u>EPA Ethics Assessment of Carroll-Loye Biological Research Field Study LNX-001</u>

Mr. Carley provided EPA's ethics review of LNX-001. Documents considered in this review included Primary Study Report MRID 47506401, EPA Science and Ethics Review of Protocol, Report of the June 2007 HSRB meeting, and CLBR supplemental submissions (e-mail exchange during August and September 2008 regarding time of treatment and supplemental IIRB-to-CLBR correspondence).

The study report MRID 47506401 was generally complete. Two deficiencies were noted, namely incomplete records of the October 7, 2007 IIRB review of revisions called for by CDPR and incomplete minutes of the IIRB meetings. These deficiencies were satisfactorily addressed in the supplemental submission of September 26, 2008 and did not compromise the review.

Reported protocol deviations include the failure of the researcher administering informed consent to sign one consent form submitted to IIRB with the renewal application and failure to ensure IIRB approval of Amendment 2 before initiating research. Two other protocol deviations, use of previously recorded limb measurements for some subjects, and the unreported deviation related to reporting of mean treatment time on June 7, 2008, were addressed in EPA's science review of this protocol.

The IIRB renewal reminder called for "a completed Progress Report with a copy of the most recently approved Informed Consent Form Completed by a subject." The investigator misunderstood this request to require submission of signed ICFs to qualify for renewal. Although at that point no subjects had been enrolled in the study, CLBR quickly enrolled 2 subjects in LNX-001 using ICFs approved by IIRB in October 2007, and attached the forms to their progress report and request for renewal. One of the forms was not signed by the researcher who conducted the consent interview; this error was immediately noted by IIRB. After several e-mail exchanges between CLBR and IIRB, the deviation was documented according to IIRB instructions. One of the two subjects involved never participated in the research and the other was reenrolled using the revised ICF approved April 28, 2008, before participating in the research. This deviation was clearly inadvertent and had no effect on the study.

Amendment 2 corrected a one-word typographic error in the protocol, which was of no consequence to the conduct of the research (the original protocol incorrectly stated that 20 percent picaridin was a lower concentration than previously tested picaridin repellents). The amendment was not received by IIRB at time of initial transmittal by CLBR on August 15, 2007. Neither IIRB nor CLBR noticed that the retransmitted amendment on August 17, 2007 was also not received by IIRB. CLBR noticed the error while preparing the study report, and reported it to IIRB as a deviation on July 20, 2008. IIRB accepted this deviation report on July 21, 2008.

All of EPA's substantive comments in the protocol review of May 24, 2007, were addressed in Amendment 1, and approved by IIRB before HSRB review of the protocol in June 2007. One typographical error remained, which was corrected by Amendment 2. In its report on the review of this protocol, the HSRB made no additional recommendations for refinements.

The applicable standards for this research are 40 CFR §26.1303, requiring documentation of the ethical conduct of the research; 40 CFR §26.1703, forbidding EPA to rely on data from

research involving intentional exposure of pregnant or nursing women or of children; and 40 CFR §26.1705, forbidding EPA to rely on data from research initiated after April 6, 2006 "unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." FIFRA §12(a)(2)(P), which defines as unlawful "for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed . . . and (ii) freely volunteer to participate in the test" also applies.

With the supplemental submission of September 26, 2008, the requirements of 40 CFR §26.1303 to document the ethical conduct of LNX-001 were satisfied. LNX-001 did not involve intentional exposure of pregnant or nursing women or of children less than 18 years of age. One of the four deviations should have been handled as an amendment, and should have been reported to and approved by IIRB before implementation. IIRB has procedures in place, as required by 40 CFR §26.1108(a)(3) & (4), but they did not prevent this deviation. CLBR incorporated all guidance received from EPA and CDPR, and consulted with IIRB, following all directions received.

EPA has concluded that all amendments to this protocol were initiated for the purpose of bringing the research into greater alignment with the developing guidance from EPA, the HSRB, and CDPR. None of the noted deviations from the protocol affected the rights or safety of the subjects, or compromised the informed consent process. Although minor exceptions were noted, the overall record shows that the investigators prepared for and conducted LNX-001 in substantial compliance with the requirements of 40 CFR part 26, subparts A-L. EPA found no barriers in law or regulation to EPA's reliance on LNX-001 in its actions under FIFRA or §408 of the Federal Food, Drug, and Cosmetic Act.

The Board was asked to determine if the CLBR study LNX-001 was sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the tested formulations against mosquitoes. The Board also was asked to decide whether the available information supports a determination that study LNX-001 was conducted in substantial compliance with 40 CFR part 26, subparts K and L.

Public Comments

Dr. Scott Carroll, on behalf of Carroll-Loye Biological Research

Dr. Carroll appreciated the HSRB's sensitivity to the challenges of timing these studies.. Although economic constraints can impact the quality of the science, Dr. Carroll disagreed with the Board that the studies could not be published in peer-reviewed journals. These studies are simple and less nuanced, but nonetheless of good quality. Dr. Carroll stated that CLBR has been making good faith efforts to incorporate the HSRB's comments and suggestions into its research.

Dr. Philpott asked Dr. Carroll to explain the failure to submit correct limb measurements. Dr. Carroll explained that after the HSRB meeting in which LNX-001 was reviewed, CLBR staff discussed reducing invasiveness to subjects by using previous limb measurements. Two years was deemed an appropriate timeframe for which previous measurements could be used. This

was meant to apply to future protocols; CLBR also decided that previous limb measurements could be used only if the subject reported no significant changes in weight or body mass. The Laboratory Manager misunderstood that use of previous limb measurements was to apply only to future protocols.

Board Discussion

Scientific Considerations – Study LNX-001

Dr. Chambers opened the science discussion by stating that the study would provide scientifically sound data to assess the repellency of the tested formulations. She commended Dr. Carroll for his improvements in reporting and EPA on the clarity of the presentations. She agreed that the deviations related to limb measurements and average start times did not affect the data. Dr. Lebowitz agreed with Dr. Chambers and also commended EPA on its review of the science. Dr. Brimijoin agreed with Drs. Chambers and Lebowitz.

Dr. Carriquiry complimented Dr. Carroll on his well-written report. She added that it remains important to consider the correct way to analyze the data. The data are collected appropriately, but Dr. Young previously presented guidelines for analysis of this data; these guidelines are not referred to in this report. This failure does not invalidate the scientific validity of these data, but does affect the validity of interpretations of the data. Therefore, Dr. Young's recommendations should be considered to be in the "c" category. Dr. Chambers reminded Dr. Carriquiry that the Board only approved the report with this recommendation at this meeting; thus it could not have been incorporated into LNX-001. Mr. Carley confirmed that this recommendation was made in the report sent to EPA on September 15, 2008, and LNX-001 was conducted in August 2008. Dr. Fisher stated that in the future, Dr. Young's recommendations should be considered. Dr. Young agreed that her recommendations should be considered. She also agreed with Dr. Carriquiry regarding the need to raise the level of statistical analyses performed in these types of studies. Dr. Fisher concluded that the Board had reached a consensus for approval of LNX-001 for scientific validity.

Ethical Considerations – Study LNX-001

Dr. Philpott noted that his previous comments regarding study design and risk minimization had been addressed well in LNX-001. The protocol displayed a clear recognition and minimization of the risks of the research by offering serological testing, alternative subjects in case of positive pregnancy tests, and clear stopping rules. The report for this protocol included mention of an adverse effect (skin irritation on the chin of one subject) that probably was not related to the test, but CLBR handled this situation appropriately.

Dr. Philpott agreed that the deviations were unlikely to increase risk or interfere with the informed consent process. Dr. Carroll has recognized the importance of making certain that his staff understands the process for ensuring adequate review of protocols. He commended Dr. Carroll on his decision to have his staff undergo CITI training. Dr. Philpott concluded that the protocol was in compliance with 40 CFR part 26, subparts K and L and commended

Dr. Carroll on the improvements in his studies. Drs. Fish and Menikoff agreed with Dr. Philpott's assessment.

Dr. Fisher commended Dr. Carroll for his efforts in improving these studies and his success with increasing subject protection. She agreed that the deviations were unlikely to increase subject risk or jeopardized informed consent. Dr. Chadwick corrected EPA's suggestion that the change in obtaining limb measurements be submitted as an amendment. Because previous limb measurements were mistakenly used, this could be reported as a deviation.

Guidelines for Product Performance Testing of Skin-Applied Insect Repellents

Background

Mr. Carley described EPA's efforts to improve its guidelines for insect repellent testing. Guidelines recommend appropriate testing methods to address EPA's data requirements; however, these guidelines are not mandatory and do not themselves define data requirements. Data requirements are defined by regulation and are interpreted and applied on a case-by-case basis. Data development guidelines are advisory rather than mandatory, but do indicate if a particular test is required. EPA has standard evaluation procedures that guide EPA's review of the data analysis reported for a completed study. These procedures include regulatory and policy standards for translating the results of repellent efficacy tests into label claims for repellent products. These standards are outside the scope of the guidelines.

Several assumptions underlie these guidelines. EPA will continue to require testing of repellent efficacy and both laboratory and field studies may be required. The guidelines should contain standard methods for commonly required types of repellent efficacy testing. The guidelines also should serve as a single source for all guidance directly relevant to sponsors and investigators conducting repellent efficacy tests. Examples of commonly required tests include field and laboratory tests for mosquitoes and biting flies; only laboratory tests are required for fleas and ticks.

The purpose for revising these guidelines included clarifying technical guidance, explaining the Human Studies Rule and what it requires, and informing investigators about what they need to know and do to prepare protocols and conduct studies likely to be reviewed favorably by EPA and the HSRB.

Sources considered for scientific aspects of these guidelines include the EPA guidelines of 1999 and comments of FIFRA SAP (2000), the draft revision of EPA guidelines (2006), and the draft World Health Organization guidelines (2008). Other references include *Insect Repellents: Principles, Methods, and Uses* (2007) by Debboun, M., Frances, S., and Strickman, D. EPA and HSRB reviews of repellent efficacy protocols and completed studies in 2006 to 2008 also were considered. Sources considered for ethics include EPA guidelines of 1999 and 2006, 40 CFR, part 26: Human Studies Rule, and HSRB reviews of repellent efficacy guidelines, protocols, and completed studies during 2006 to 2008.

Dr. Clara Fuentes (OPP, EPA) led the revision of the science guidance. Mr. Carley led the addition of new guidance concerning the Human Studies Rule. Multiple drafts were reviewed and refined by a broad-based workgroup that included all EPA entomologists who review repellent studies, EPA staff with regulatory interest in repellents, EPA staff from the repellent labeling project, and EPA's Office of General Counsel.

The guidelines include standard tests of repellents applied to human skin. They exclude, but do not preclude non-standard tests. Such tests can be proposed, but the investigator must provide compelling rationale for their use and EPA can agree or disagree with their use. The guidelines exclude repellent testing of repellent-impregnated fabrics and clothing and products intended to repel insects from indoor or outdoor spaces, such as pyrethrum coils and citronella candles.

In the future, EPA intends to publish the guidelines for topical repellents for immediate use. EPA also intends to further refine the guidelines for topical repellents in response to comments from the EPA Human Subjects Research Review Official (HSRRO), the HSRB, and the public. EPA will draft additional guidelines for repellency testing of impregnated fabrics and clothing and space repellents.

The guidelines are organized into six major divisions: (1) scope and purpose; (2) definitions: (3) guidance applying to all repellent studies; (4) guidance applying to specific types of repellent studies; (5) references; and (6) appendices. Mr. Carley focused on the third, fourth, and sixth divisions.

Guidance applicable to all studies includes development of repellent study protocols, review of repellent study protocols, changes to IRB-approved research before execution, execution of repellent studies, reporting of completed repellent studies, and records retention. Development of protocols includes scientific design of repellent studies, ethical justification for repellent studies, subject selection and informed consent, respect for subjects, data collection and reporting, and statistical analysis. New material concerning ethics and the Human Studies Rule has been included in this section. Science and ethics guidance were combined in one section of the guideline because science and ethics interact in the development and review of these protocols. Study-specific guidance discusses matters such as dose-determination studies, laboratory and field studies of mosquito repellency, laboratory studies of stable fly repellency, field studies of biting fly repellency, laboratory studies of flea repellency, and laboratory studies of tick and chigger repellency.

The guidelines contain three appendices, including Appendix A, Checklist of Elements Required by 40 CFR §26.1125; Appendix B, Framework for Science and Ethics Reviews of Proposed Human Research; and Appendix C, Checklist of Elements Required by 40 CFR §26.1303. Although the HSRB is familiar with these documents, which form the framework for EPA reviews and presentations, they are less well known among the investigators performing this research. EPA has provided these documents to registrants and investigators, but has decided to include them in the guideline itself so that they are more easily available to those who could benefit from a more complete understanding of EPA's process for assessment of these protocols.

New elements for science have been developed. These include the recommendation of landings with intent to bite (LIBes) as the endpoint for field studies; the option of either 1-in-15 or 5-in-30 minute intermittent exposure; expanded discussion of sample size; a call for MOE estimation in protocols; and expanded discussion of statistical analysis, especially of censored data. Mr. Carley noted that these elements do not reflect Dr. Young's comments made at the June 2008 HSRB meeting because these were unavailable at the time the guidelines were developed. EPA is considering including this information in the guidelines; an SOP regarding this topic may be created to avoid repetitiveness in the protocols.

New elements for ethics include examples of appropriate inclusion/exclusion factors; examples of classes of risks to subjects, linked to appropriate risk minimization methods; recommendation for post-study follow-up by the principal investigator to ensure subjects experience no delayed adverse effects; and recommendation of viral assays of field-collected insects. These are some of the many changes implemented and highlight EPA's responsiveness to HSRB advice.

The purpose of these repellency testing guidelines is to clarify technical guidance, explain the Human Studies Rule and what it requires, and also to inform investigators of matters that will assist them in the preparation of protocols and conduct of studies likely to be reviewed favorably by EPA and the HSRB. This document includes the first explanation of the Human Studies Rule as it applies to a specific class of studies. The document also serves as EPA's attempt to consolidate what the Agency has learned over the past 2 years of reviewing repellent studies and presenting them to the Board. EPA anticipates that the guidelines will be of particular use to investigators who have not yet submitted proposals after implementation of the Human Studies Rule.

The next steps in this process include publication of these guidelines for immediate use; solicitation of comments from EPA's HSRRO, the HSRB, and the public; and further refinement of these guidelines in response to the comments. The Board was not presented with charge questions for the guidelines, but was asked to provide recommendations for further improvement.

Board Discussion

Dr. Carriquiry commended EPA's update of the guidelines. She asked if a statistician had been involved in guideline development. Guidelines should propose best practices for the design and analysis of these studies. Toxicologists and entomologists may not be able to provide adequate input on statistical matters. She encouraged Mr. Carley to solicit comments from a statistician. Mr. Carley commented that EPA has not yet identified a statistician within its staff to assist with the guidelines, but they are working on incorporating Dr. Young's suggestions.

Dr. Philpott inquired if all formulations tested in this research would be cleared by EPA for use in repellency testing. Mr. Carley explained that only formulations previously reviewed by EPA, including additional known ingredients such as surfactants, can be included in the

proposed research. If the investigator wishes to include a new ingredient or formulation, sufficient information must be submitted to EPA so it can determine whether to use the product in testing.

Dr. Chadwick asked about the section on respect for subjects. Protocol reports typically address confidentiality of the data, subject protection and privacy, potential embarrassment of subjects, and the voluntary nature of the research. Assuming this language derives from the Belmont Report, this report emphasizes that respect for persons applies only to the ICF. He cautioned that if EPA places this language under the category of "respect for persons" it might be confusing for investigators who work with other agencies.

Dr. Krishnan questioned if the minimal required insect densities specified in the guidelines were based on historical data and if they were realistic. Mr. Carley explained that the numbers were generated based on conversion of data taken from studies performed in 2-by-2-by-2-foot cages. EPA is questioning whether the minimal required insect densities offer enough flexibility to the investigators. This is one reason why the guidelines are voluntary; EPA has not yet confirmed the range of acceptable cage sizes or densities.

Dr. Chambers noted that although the guidelines are voluntary, regulations carry a mandate. She asked if EPA specified to the registrant experimental details for performing laboratory or field tests. Mr. Carley responded that EPA does not prescribe experimental details; if EPA wished to define such details, a rule would need to be created, similar to the Food and Drug Administration protocol for sun protection factor testing. Investigators wishing to test a product usually participate in a pre-submission conference to discuss the types of data required. For example, in June 2008, EPA reviewed a request to expand label claims for protection against arthropods carrying WNV. EPA and the registrant agreed that a laboratory study using species that carry WNV would suffice, given that the results were similar to those obtained from field testing the product in the presence of different species.

Public Comments

Dr. Thomas G. Osimitz, Science Strategies, LLC, on behalf of the DEET Task Force

The DEET Task Force represents DEET manufacturers and marketers. The Task Force has assembled a database analysis team to lead its database effort; the goal of the database effort is to use data from the thousands of trials previously conducted on DEET repellents to determine the most effective and efficient ways to assess repellency in future trials. The DEET Task Force recognizes the significant biological variability in humans and insects and because of this variability encourages EPA and the HSRB to minimize human testing whenever possible.

The DEET laboratory database structure consists of 312 DEET studies encompassing 1,017 trials and 3,199 records. The term "replicates" is used to define distinct CPT tests (on the same or different subjects). The results from 4,461 replicates are represented in the database. The DEET field database structure has 19 studies encompassing 113 trials, for a total of 598 records. Results from 972 replicates of field data are represented in the database.

The DEET Task Force has evaluated the data quality and has developed a predictive model for laboratory data; development of a predictive model for field data is underway. The DEET Task Force also is examining the relationships between laboratory and field data. Analysis of 319 laboratory trials of products containing between 5- and 30-percent DEET found a relationship between mean time to first bite (TTFB) for each trial and DEET concentration; this relationship is curvilinear.

The DEET Task Force recommends that EPA should use the DEET database as a surrogate for additional human testing. The database contains over 4,000 replicates from more than 300 studies. The curvilinear model provides a high level of predictability for determination of CPT for common DEET formulations at concentrations of up to 30 percent. The predicted CPTs derived from the database appear to be more conservative than data from field studies. Additional laboratory testing can be used to substantiate claims of protection times that exceed those predicted by the database model.

The second recommendation of the DEET Task Force is that the laboratory bioassay becomes the standard product performance test for personal repellent registration. Testing in laboratory settings provides data that are less variable, and the variability of the biting insects and other environmental factors can be more readily controlled. The Task Force contends that harmonization of the existing protocols used by most product test laboratories would be simple, given the current similarities of the methods. Laboratory-generated data are significantly less variable than field data and are more easily modeled; the European Union (EU) is moving toward using laboratory data for regulatory purposes. Use of laboratory-raised arthropods essentially eliminates exposure to vector-borne diseases, thus reducing risk to human subjects. This approach also will allow harmonization of test methods with the EU.

The Task Force's third recommendation is to standardize product performance guidelines for a number of parameters. The most important parameter, with respect to scientific validity, is application method and dose per subject; the Task Force suggests 1 gm per 600 cm^2 of skin for all AIs. Other parameters to standardize include cage size and mosquito density; mosquito species; TTFB as the endpoint; exposure interval; number of test subjects; and minimum protection time for an effective repellent. Standardization should increase the predictability of the curvilinear model and provide improved experimental rigor for future analyses.

Base on their analyses, the Task Force contends that field testing should be necessary only to substantiate claims for miscellaneous biting insects that cannot be easily tested in the laboratory (e.g., black flies, deer flies, etc.) because of the difficulty of rearing these species in the laboratory. Other considerations for repellency testing involving human subjects are the importance of trained test subjects who are appropriately informed about proper protection, informed consent, and the voluntary nature of the research. Experienced subjects who have been trained in confirming a LIBes are preferable for these studies. Because protection time on the label drives reapplication intervals, repellency testing must be cautious about claiming overly conservative protection times that will encourage over-application with no additional protection.

The Task Force also recommends considering expedited reviews for future studies. The Task Force suggests that blanket approval and expedited reviews for standard protocols could be

developed, given HSRB comfort with this approach. Sufficient time also should be provided for stakeholder comment and EPA consideration of how the efforts of the DEET Task Force can inform EPA guidelines on repellency testing.

Clarifying Questions

Dr. Fisher asked Dr. Osimitz to describe the extent to which laboratory studies would be an adequate surrogate for field studies, particularly with respect to temperature, movement of subjects, and proximity to other subjects. Dr. Osimitz explained that the next step in the DEET Task Force's analysis will be to identify sets of studies performed in the laboratory that match, in product formulation, studies performed in the field. Variability in the field is equally attributable to human variability and field conditions. No matter how perfectly a protocol is designed and executed, intraperson variability affects the results. The Task Force's approach is to use controllable data to generalize results.

Dr. Brimijoin inquired if there were rigorous statistical reasons why the best fit line for comparison of DEET concentration to TTFB was curvilinear rather than a straight line. Dr. Osimitz replied that rigorous statistics had shown that a straight line with regression through the origin does not fit the data points. More details on this analysis will be provided in the Task Force's submission to EPA.

Dr. Brimijoin noted that fixed doses are used when testing DEET, but products will differ in efficacy. Dr. Osimitz explained that this work does not represent research on new products. Range-finding work will be performed, but most future repellency tests will be testing products containing previously tested concentrations of DEET to optimize new formulations.

Dr. Young stated that laboratory insects quickly evolve to differ from those found in the field and asked if this could be a major source of variability. Dr. Osimitz responded that the purpose of this research was to provide general guidelines for the consumer rather than trying to identify a precise dose of a pharmacologically active product with a narrow margin of safety and therapeutic efficacy. Variability between individuals will be a more significant factor in determining efficacy than the identity of the insects. For developing ranges of protection time, laboratory data are adequate. Dr. Young questioned if the Task Force was attempting to gather data on the variation among people and also among insects. Dr. Osimitz explained that this will be addressed during field test data analysis. Currently, it is not clear how field variability can be controlled. Larger studies could be performed, but because repellency testing is designed to determine a range of protection rather than a precise interval, the value of larger studies is questionable, given the cost, logistics, and impact on human subject protection.

Dr. Chambers asked if TTFB is also assessed as time to first confirmed bite. Dr. Osimitz answered that this was true, although there are fewer studies that use time to first confirmed bite.

Dr. Lebowitz noted that field studies have other sources of variability, such as the effects of temperature, humidity, wind speed, and so forth. These parameters have been largely ignored in field studies. He asked if any laboratory studies existed or were planned to determine the effects of these variables on protection time. Dr. Osimitz explained that the Task Force has not

yet found such data. He reminded the Board that labels on insect repellents only indicate whether a product provides more or less protection time than similar products. The ability to predict how protection would change depending on humidity or wind is not significant, given how the data will be used.

Dr. Johnson commented that the graph presented by Dr. Osimitz indicated a mean protection time of 5 hours at the highest DEET concentration. This appears to contradict many of the studies the Board has reviewed, in which protection times regularly exceeded 8 hours. He asked why laboratory tests seemed to indicate shorter protection times than field tests. Dr. Osimitz responded that many of the studies used to develop the graph were performed more than 5 years ago and used higher mosquito biting pressure than was found in the field. He suggested that these results could be considered as a starting point; sponsors wanting to extend protection time could do so by performing a laboratory study.

Dr. Krishnan questioned if the Task Force's analysis had included all of the data previously submitted to EPA. Dr. Osimitz replied that the data used were either published or came from industrial sources or other members of the Task Force. The Task Force did not have access to EPA data; however, the Task Force did evaluate the data for quality and completeness. Efforts to obtain data from the military were unsuccessful. Dr. Krishnan asked how protection time could be predicted for one product from another using laboratory studies for different products. Dr. Osimitz responded that the graph showed the results of this analysis. The Task Force does not yet have a quantitative breakdown of variability sources and their impact on the model, but this will be included in the final submission.

Dr. Lebowitz stated that in the laboratory setting, it is possible to determine the influence of protection in populations who are more susceptible to bites and asked if any of this work was included as part of the database. Dr. Osimitz remarked that this work answered questions of a more basic research nature and was not included in the database. The database includes data designed to help characterize products with intent to register the products.

Dr. Johnson suggested that confidence interval bars may not be the best way to show variability because they are based on the number of studies performed for a particular DEET concentration. Prediction intervals would better incorporate individual variability. Dr. Osimitz agreed with Dr. Johnson's suggestion. Dr. Fisher thanked Dr. Osimitz for his presentation and willingness to answer questions from the Board.

Mr. Carley commented that EPA has been working with the DEET Task Force for a number of years and is looking forward to receiving the results of this analysis; however, the draft guideline will be released for immediate use because EPA does not believe that the meta analysis of the old DEET data needs to be in hand before it provides the best practices guidance to investigators and sponsors wishing to conduct new studies on repellents. He also stated that many of the issues raised by the Task Force are outside the scope of the guidelines, for example, the type of studies that should be conducted and how completed studies will be interpreted. Another general question needing to be answered is whether EPA will be comfortable extrapolating from old data on old products to new and untested products. The Agency shares the Task Force's concerns regarding ways to responsibly minimize the requirements for new

testing, particularly involving human subjects, but EPA also must ensure that the way testing is conducted is rigorous, defensible, and appropriate from a regulatory perspective. Dr. Osimitz responded that the issues raised by the Task Force are relevant to the guidelines, particularly regarding alternatives to conducting guideline studies. Most of the formulations of repellents have not changed significantly in the past 20 years, and these changes are relatively small compared to the variability in results from tests using human subjects. The data are good and the scientific methodology is sound; these data are valuable for informing future directions in repellency testing. He acknowledged EPA's cooperation on these matters and offered to have members of the Task Force meet with EPA to discuss the data and its possible effect on the testing guidelines.

Dr. Scott Carroll, on behalf of Carroll-Loye Biological Research

Dr. Carroll expressed his appreciation for the work of the Task Force and also EPA in creating repellency testing guidelines. The simplest way to address variability is to recommend a larger number of subjects for repellency testing. The 1999 draft guidelines, which represented the industry standard prior to creation of the HSRB, describe specific details that arose in large part from protocols designed by Dr. Carroll. This likely has led to an imbalance in the nature of industry influence. The studies were designed to produce good science, but not necessarily to provide a broad foundation for repellency testing.

Mr. Niketas Spero and Dr. Robin G. Todd, on behalf of ICR

Mr. Niketas Spero, on behalf of ICR, explained that ICR had concerns regarding local recruitment as it is required to recruit locally for field testing; the reliability of the test subjects is a concern. Safety also is a concern when unknown test subjects are involved in field testing, particularly for remote field studies. ICR believes it would be more reliable to use subjects who have participated in previous ICR studies and arrange their travel to the field study sites. Regarding possible coercion to avoid early withdrawal from testing at a field site, this situation has arose in the past and ICR does not consider it onerous to pay airfare home for withdrawing subjects.

The test area size defined as wrist to elbow or knee to ankle can be problematic because of differences in the body size and slippage of the bandage because it is placed on an area subject to movement. ICR prefers instead to define a 250 cm^2 area on the center of the arm or leg as the standard area for application.

Dr. Robin Todd, on behalf of ICR, noted that ICR agrees with most of the guidelines, but another concern is the use of subjects to collect their own data. In ICR's opinion, only GLP staff trained to recognize mosquito behavior should be used to collect data. Use of subjects to collect data also may pose a conflict of interest, if subjects have an incentive to confirm that they were bitten when they actually were not. Requiring subjects to collect data also limits the subject pool to people who are manually dexterous and have good eyesight. The registrant also is ill-served by using untrained participants to record that data; having trained staff record the data is preferable.

Dr. Carriquiry stated that she understood the preference for trained subjects, but given that this would result in a small subject pool participating in a number of studies, determining between-person variance could be affected. She suggested that a balance must be struck among measurement error, recording the data, and representativeness. Dr. Fisher countered that ICR's approach would increase representativeness because they are not using trained subjects and rather will rely on trained staff to collect data, which would result in a larger subject pool.

Board Discussion

Dr. Young commended EPA for producing a clear guideline document. She noted statistical issues that EPA should address. If the result of testing is CPT, the distribution is unlikely to be normal. Some parts of the document stress normality, but other parts claim that CPT may be exponential. CPT is more likely to be exponential; the document needs more consistency in the statistical assumptions of distribution. Transformations are suggested as a possibility for accounting for non-normality. Generalized linear mixed models also could apply in this setting and should be included as a potential analysis method.

A large proportion of the observations in these studies are censored, which makes the statistical analysis more challenging. Nonetheless, the guidelines should acknowledge that censoring needs to be treated appropriately. If mean protection time is reported without accounting for censoring, this value is biased. It is true that protection time would be biased downward, but the standard error would be similarly biased so confidence intervals do not make sense. Censoring must be accounted for, but this may not require a significant change in sample size.

On page 27, the guidelines state that field tests are to be performed in two habitats with different species. The guidelines then state that testing could be repeated at different sites in the same habitats on different days within the same study. This appears to be contradictory; two habitats are not the same as two sites in the same habitat.

Dr. Young noted that the round robin design suggested for testing more than one product may not be appropriate. She was concerned that use of this design would lead to testing of different products in a defined order, rather than in a randomized order. The randomized Latin Square can be used to randomize which subjects are treated with which product. She suggested removing the round robin design reference from the guidelines.

Dr. Young stated that it would be important for differences in location to be accounted for in the analysis, if not as a blocking variable then as a stratified variable. If the same subject is used in a different habitat, the appropriate blocking variable is the subject and then variability in dates and location can be accounted for. Because these studies test efficacy against more than one species, it is unclear if the tests define protection in general or is specific to each species. This should be clarified. Dr. Young commended the preference for continuous exposure, in contrast to one exposure in 15 minutes; continuous exposure more realistically mimics how the product will be used. Dr. Young expressed concern about testing using pairs of subjects in field studies who are performing normal activities, because she doubted that subjects could recognize bites while engaging in these activities. This does not appear to be a realistic design component.

She concluded that random number tables are not the best approach for randomizing; there are better, computer-based methods for randomization.

Dr. Fisher noted that the document inconsistently represented some issues regularly raised by the Board. On page 7, the guidelines explain that the endpoint of repellency should be selected to show failure, but the products do not fail in most of the protocols reviewed by the Board. The guidelines do not clarify this issue. If it is not possible to extend testing to reach failure, the analysis of the data must be changed. Most of the data the Board has reviewed is categorical, but the document suggests parametric analyses. Such analyses may be possible, but their use may still lead to data and analyses that the Board will question. The document does not provide a clear enough distinction between categorical, parametric, and linear data, and how to perform analyses.

Dr. Young commented that the mention of a Poisson distribution in relation to the number of bites is inaccurate; the number of bites is more likely to be a negative binomial and there are ways to analyze such data. Standard deviations and relative percent reduction will be inappropriate. More attention to this document from a statistical standpoint is needed. Some effort also should be given to the development of analysis guidance because the designs and analyses described are not appropriate. Dr. Fisher agreed that power analysis is described, but the subject sample size is always 6 or 10. The appropriateness of performing a power analysis on categorical or censored data is questionable. Dr. Young noted that there were ways to perform power analysis on nonparametric data, but these methods were not described in the guidelines. Dr. Fisher cautioned that sponsors may still be disappointed by HSRB review of their protocols if these issues are not addressed. Dr. Carriquiry speculated that, by suggesting power analyses, the Board may begin to see study designs involving other than 6 or 10 subjects once the guidelines are put into practice.

Mr. Carley explained that the 1999 guidelines specify a minimum sample size of 6 subjects. The last few protocols reviewed by the HSRB used 10 subjects. The Board has generally agreed with the sample size, but has concluded that the rationale for this sample size is weak. The goal of the guidelines is to improve the rationale for sample size. This guideline also will supersede the guideline specifying 6 subjects and instead will state that the investigator must provide a sound rationale for sample size.

Dr. Chambers stated that she appreciated the recommendation to use landings rather than bites to judge efficacy. She encouraged EPA to determine if field studies can provide information that laboratory studies cannot. The guidelines appear to state that the endpoint of testing is a confirmed bite or landing; this needs to be clarified. She stated that recommending an average consumer dose is appropriate. She speculated that a contributor to the problems with statistically analyzing the data is the long duration of product efficacy. If the goal is to develop labels that indicate a product will last 8 hours and the product lasts longer than 8 hours, it is questionable whether knowing the exact protection time past 8 hours is necessary. Mr. Carley agreed and stated that EPA is comfortable labeling products that last 14 hours in every case as lasting 8 hours. Dr. Young stated that if this is the goal, mean protection time is not needed. Instead, knowing the probability that a proportion of the population will be protected at least 8 hours would be more appropriate. A measure could be 95 percent certainty that 50 percent of

users will be protected for 8 hours; this could be tested using approximately 12 subjects. Dr. Fisher clarified that the Board is not concerned by censoring in itself, but rather by the attempt to develop a mean score using censored data.

Dr. Philpott reiterated Dr. Chadwick's comment regarding harmonization of language among different ethical standards. EPA may wish to restructure the ethics discussion in the guidelines to address this issue. He noted a problem on page 11, which appears to emphasize alternatives to research on human subjects. The guideline states that such research is not justifiable if it can be performed another way, but then states that in general, data on repellents is derived only from tests on human subjects. This sentence should be removed to avoid creating the impression that a human study is expected.

Dr. Philpott appreciated the distinction that guidelines, unlike regulations, are advisory, but noted that page 1 of the guidelines asks investigators to justify when submitted protocols deviate from the guidelines. When a list of ways to mitigate risk is offered, the need for justification of deviations should be emphasized. Dr. Philpott suggested including materials, such as recruitment scripts and proposed recruitment advertisements, in the list of information to submit to the IRB. EPA must be careful not to imply that the list in the guidelines is exhaustive; EPA either should provide a comprehensive list or a link to guidance that is more complete. Dr. Philpott commended the recommendation to use "landings with intent to bite" rather than bites. Any protocols that use actual bites should justify this decision. Dr. Philpott referred to a possible typographical error on page 13 regarding the heterogeneity of populations, with requests to make the study population as generalizable as possible to the population of repellent users. Protocols should include an explanation and justification if the subject pool does not include people with a diversity of ages, genders, and ethnic backgrounds. Recruitment problems are not a valid justification for a homogenous subject pool.

Regarding the use of trained subjects, Dr. Philpott suggested a hybrid approach in which the untreated controls might be experienced subjects but treated subjects could be inexperienced. He noted that Dr. Carroll had previously provided a good example of such an approach. Dr. Philpott requested EPA clarify its guidance regarding the coverage of uninsured costs of medical treatment. He also noted that pages 31 and 34 have discussions of field studies that include establishing subject attractiveness to mosquitoes by placing their forearms in test cages. This needs to be edited to more clearly indicate whether such tests will occur in the field or in the laboratory.

Mr. Carley commented on Dr. Philpott's proposal to use experienced subjects as untreated controls. Treated subjects participating in field trials are likely to receive few landings or bites, and therefore do not have to be as alert for mosquito landings. All protocols presented by EPA have specified that trained technicians verify these endpoints.

Dr. Chambers asked Dr. Philpott to clarify his statement regarding the necessity of using human subjects in this research. Dr. Philpott explained that EPA emphasizes considering alternative approaches, but that paragraph also presupposes that skin testing of repellents should be performed using human subjects. The guidelines on page 11, in Section 2, Subpart 1 under "Alternatives for Research with Human Subjects," include a presupposition that EPA expects

these tests to be performed with human subjects, but this section also asks investigators to consider other alternatives. Mr. Carley clarified that EPA was attempting to convey that it would be difficult to justify skin testing of insect repellents without using human subjects. He stated that EPA would clarify this section of the guidelines.

Dr. Johnson noted that on page 10, a discussion about the hypothesis to be tested includes a reference to an alternative hypothesis that is incorrect. The alternative should be that CPT is less than the hypothesized number of hours.

Dr. Fisher questioned if the Board would be asked to review these guidelines on another occasion. Mr. Carley explained that the guidelines are not complete and do not reflect recent statistical analysis suggestions. EPA would like to release the guidelines quickly, unless the Board believes they should not be released before making substantial changes. Although the guidelines will not solve all problems associated with repellent testing, they will be helpful for the investigators.

Dr. Lebowitz asked if 8 hours of protection was considered standard; if so, this has implications for the number of subjects needed for testing. Mr. Sweeney responded that label claims of 8 hours were based on previous data. Dr. Lebowitz questioned if labels could claim any duration of protection, as long as evidence to support this claim was provided. Mr. Sweeney agreed that the label could claim more than 8 hours of protection if the data indicated that this was the case.

Dr. Young noted significant flaws in the sections on statistical analyses that could be easily remedied by a statistician. She recommended that EPA obtain input from a statistician before releasing the document. If the label claims protection lasts up to 8 hours, reporting mean protection time is inappropriate. Reporting the proportion of the population experiencing that duration of protection would be more informative for the consumer. Mr. Carley agreed with Dr. Young, stating that this idea may help EPA work toward a better way to analyze repellent study data. EPA will work to correct the problems in the sections on statistical analysis.

Dr. Fisher stated that the Board disagreed with certain elements of the guidelines and found others confusing. She stated that if EPA wished to go forward without correcting the problems identified by the Board that the Agency should make clear that the HSRB does not support publication of the guidelines at this point. Dr. Fisher expressed concern that sponsors following the guidelines would erroneously assume the HSRB would recommend approval of designs submitted for review. EPA should avoid giving the sponsors expectations regarding HSRB review of their protocols based on the misimpression that the Board approved the guidelines.

Dr. Lebowitz stated that changes in how protection is conveyed in the label could affect study design, sample size, and data analysis methods. Dr. Fisher commented that it may not always be correct to use categorical, non-parametric data. Examples of when continuous data are important might be useful for users of the guidelines. Dr. Young suggested that it would not be difficult to develop sample size tables based on the proportion of subjects who are protected.

Dr. Fisher noted that because the Board was not asked to write or formally comment on the guidelines, it is not the Board's responsibility to address certain issues specifically.

Mr. Jordan commented that EPA understands that the guidelines can be improved. EPA will make changes to the guidelines before they are published and will provide the HSRB with the published version for its information. EPA will not claim that the Board approved the guidelines. Mr. Jordan thanked the Board for its efforts and stated that EPA will use the Board's comments to strengthen the science and protection of humans in this research.

Concluding Remarks

Ms. Sherman described the tentative agenda for the January 2009 HSRB meeting. The Board will address two completed reports from CLBR. These protocols were reviewed in October 2007 and test mosquito and tick repellency of picaridin-containing products. One new CLBR protocol will be reviewed, which tests three picaridin-containing products against biting flies. An ICR protocol testing a space repellent also will be presented. The AEATF protocol for an aerosol product will be reviewed. The Board also may be presented with data from toxicological studies for an old chemical currently under review by EPA.

Dr. Fisher thanked Board members, EPA, and the sponsors for their efforts and preparation for this meeting. She then adjourned the meeting.

Respectfully submitted:

Paul I. Lewis, Ph.D.
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

Celia Fisher, Ph.D.
Chair
Human Studies Review Board
United States Environmental Protection Agency

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Board members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice

from the Board members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final report prepared and transmitted to the EPA Science Advisor following the public meeting.

Attachments

Attachment A	List of HSRB Members
Attachment B	*Federal Register* Notice Announcing Meeting
Attachment C	Meeting Agenda

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

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Director, Center for Ethics Education
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Bronx, NY

Vice Chair

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Mayo Foundation
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Research Professor of Medicine
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Sean Philpott, Ph.D., M.Bioethics
Science and Ethics Officer
Global Campaign for Microbicides
PATH
Washington, DC

Ernest D. Prentice, Ph.D.
Associate Vice Chancellor for Academic Affairs
Professor of Genetics, Cell Biology and Anatomy
Professor of Preventive and Societal Medicine
University of Nebraska Medical Center
Omaha, NE

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Cleveland, OH

Linda J. Young, Ph.D.
Professor of Statistics
Department of Statistics
Institute of Food and Agricultural Sciences
University of Florida
Gainesville, FL

* Not in attendance

Attachment B
Federal Register Notice Announcing Meeting

Human Studies Review Board; Notice of Public Meeting

[Federal Register: September 16, 2008 (Volume 73, Number 180)]
[Notices]
[Page 53422-53424]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]

ENVIRONMENTAL PROTECTION AGENCY
[EPA–HQ–ORD–2008–0629; FRL–8716–5]

Human Studies Review Board; Notice of Public Meeting

AGENCY: Environmental Protection Agency (EPA).
ACTION: Notice.

SUMMARY: The U.S. Environmental Protection Agency's (EPA or Agency) Office of the Science Advisor (OSA) announces a public meeting of the Human Studies Review Board (HSRB) to advise the Agency on EPA's scientific and ethical review of human subjects research.

DATES: The public meeting will be held from October 21–22, 2008, from 8:30 a.m. to approximately 5:30 p.m., Eastern Standard Time (EST).

Location: Environmental Protection Agency, Conference Center—Lobby Level, One Potomac Yard (South Bldg.), 2777 S. Crystal Drive, Arlington, VA 22202.

Meeting Access: Seating at the meeting will be on a first-come basis. To request accommodation of a disability please contact the person listed under **FOR FURTHER INFORMATION CONTACT** at least 10 business days prior to the meeting, to allow EPA as much time as possible to process your request.

Procedures for Providing Public Input: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in Unit I.D. of this notice.

Addresses: Submit your written comments, identified by Docket ID No. EPA–HQ–ORD–2008–0629, by any of the following methods:

Internet: http://www.regulations.gov: Follow the on-line instructions for submitting comments.

E-mail: ORD.Docket@epa.gov.

USPS Mail: Environmental Protection Agency, EPA Docket Center (EPA/DC), ORD Docket, Mailcode: 28221T, 1200 Pennsylvania Ave., NW., Washington, DC 20460.

Hand or Courier Delivery: The EPA/ DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW., Washington, DC. The hours of operation are 8:30 a.m. to 4:30 p.m., EST, Monday through Friday, excluding Federal holidays. Please call (202) 566–1744 or e-mail

the ORD Docket at *ord.docket@epa.gov* for instructions. Updates to Public Reading Room access are available on the Web site (*http:// www.epa.gov/epahome/dockets.htm*).

Instructions: Direct your comments to Docket ID No. EPA–HQ–ORD–2008– 0629. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http:// www.regulations.gov,* including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information through *http://www.regulations.gov* or e-mail that you consider to be CBI or otherwise protected from disclosure. The *http:// www.regulations.gov* Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through *http:// www.regulations.gov,* your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD–ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes further information should contact Lu-Ann Kleibacker, EPA, Office of the Science Advisor (8105R), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; *telephone number:* (202) 564–7189; *fax:* (202) 564–2070; *e-mail addresses: kleibacker.lu-ann@epa.gov.*
General information concerning the EPA HSRB can be found on the EPA Web site at *http://www.epa.gov/osa/hsrb/.*

SUPPLEMENTARY INFORMATION:

I. Public Meeting

A. Does This Action Apply to Me?

This action is directed to the public in general. This action may, however, be of particular interest to persons who conduct or assess human studies, especially studies on substances regulated by EPA and to persons who may sponsor or conduct research with human subjects with the intention to submit it to EPA for consideration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) or section 408 under the Federal Food, Drug, and Cosmetic Act (FFDCA). Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under FOR **FURTHER INFORMATION CONTACT.**

B. How Can I Access Electronic Copies of This Document and Other Related Information?

You may access this **Federal Register** document electronically either through *http://www.regulations.gov* or through the EPA Web site under the **Federal Register** listings at *http://www.epa.gov/fedrgstr/.*

Docket: All documents in the docket are listed in the *http:// www.regulations.gov* index under the docket number. Even though it will be listed by title in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Copyright material will be publicly available only in hard copy. Publicly available docket materials are available either electronically in *http:// www.regulations.gov* or in hard copy at the ORD Docket, EPA/DC, Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW., Washington, DC. The hours of operation are 8:30 a.m. to 4:30 p.m. EST, Monday through Friday, excluding Federal holidays. Please call (202) 566–1744 or e-mail the ORD Docket at *ord.docket@epa.gov* for instructions. Updates to Public Reading Room access are available on the Web site (*http:// www.epa.gov/epahome/dockets.htm*). EPA's position paper(s), charge/ questions to the HSRB, and the meeting agenda are anticipated to be available by late September 2008, if not earlier. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov Web site and the HSRB Web site at *http://www.epa.gov/osa/hsrb/*. For questions on document availability or if you do not have access to the Internet, consult the person listed under **FOR FURTHER INFORMATION**.

C. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

a. Explain your views as clearly as possible.

b. Describe any assumptions that you used.

c. Provide copies of any technical information and/or data you used that support our views.

d. Provide specific examples to illustrate your concerns and suggest alternatives.

e. To ensure proper receipt by EPA, be sure to identify the docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

D. How May I Participate in This Meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA–HQ–ORD–2008– 0629 in the subject line on the first page of your request.

a. *Oral comments*. Requests to present oral comments will be accepted up to October 14, 2008. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to the person listed under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern time, October 14, 2008 in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Officer (DFO) to review the agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (e.g., overhead projector, LCD projector, chalkboard). Oral comments before the HSRB are limited to

five minutes per individual or organization. Please note that this limit applies to the cumulative time used by all individuals appearing either as part of, or on behalf of an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand these time limitations by having multiple individuals sign up separately to speak on their behalf. Each speaker should bring 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting. At the discretion of the Board Chair and DFO, public commenters, if present during the Board's discussion, may be asked to provide clarification of their comments to assist the Board in their discussion.

b. *Written comments*. Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, EST, October 14, 2008. You should submit your comments using the instructions in Unit I.C. of this notice. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to the person listed under **FOR FURTHER INFORMATION CONTACT**. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

A. Human Studies Review Board

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. App.2 section 9. The HSRB provides advice, information, and recommendations to EPA on issues related to scientific and ethical aspects of human subjects research. The major objectives of the HSRB are to provide advice and recommendations on: a. Research proposals and protocols; b. reports of completed research with human subjects; and c. how to strengthen EPA's programs for protection of human subjects of research. The HSRB reports to the EPA Administrator through EPA's Science Advisor.

The EPA will present for HSRB review scientific and ethical issues surrounding:

- The scenario design document and three associated protocols from the Agricultural Handlers Exposure Task Force (AHETF) for research to monitor the exposure of subjects in closed cabs who apply an agricultural pesticide using airblast equipment. The scenario design document is identical to the one that was reviewed by the HSRB in June 2008, except that chlorothalonil has been added to the list of test chemicals.
- The scenario design document and three associated protocols from the AHETF for research to monitor exposure of subjects in open cabs who apply an agricultural pesticide using airblast equipment.
- The report from a completed field study (LNX–001) by Carroll-Loye Biological Research of the mosquito repellent efficacy of two pesticide products containing picaridin. The HSRB previously reviewed the proposed study at its June 2007 meeting.

The Agency will brief the HSRB on its draft document, *Guideline for Efficacy Testing of Skin-Applied Repellents*. The guideline provides recommendations for the design and execution of studies to evaluate the performance of pesticide products intended to repel insects and other arthropods. In addition, the Board may be reviewing its draft meeting report from the June 24–25, 2008 HSRB meeting for subsequent Board approval. Finally, the HSRB may also discuss planning for future HSRB meetings.

B. Meeting Minutes and Reports

Minutes of the meeting, summarizing the matters discussed and recommendations, if any, made by the advisory committee regarding such matters will be released within 90 calendar days of the meeting. Such minutes will be available at *http://www.epa.gov/osa/hsrb/* and *http:// www.regulations.gov.* In addition, information concerning a Board meeting report, if applicable, can be found at *http://www.epa.gov/osa/hsrb/* or from the person listed under **FOR FURTHER INFORMATION**.

Dated: September 4, 2008.
George Gray,
Science Advisor.
[FR Doc. E8–21590 Filed 9–15–08; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
OCTOBER 21-22, 2008
PUBLIC MEETING

Tuesday, October 21, 2008
Environmental Protection Agency
Conference Center – Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive
Arlington, VA 22202

HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA-HQ-ORD-2008-0629

8:30 AM **Convene Meeting and Identification of Board Members** – Celia Fisher, Ph.D. (HSRB Chair)
8:40 AM **Meeting Administrative Procedures** – Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA)

Welcoming Remarks for October 2008 HSRB Meeting
8:45 AM **Welcome –** George Gray, Ph.D. (Science Advisor, OSA, EPA)
8:55 AM **Welcome –** Pai-Yei Whung, Ph.D. (Chief Scientist, OSA, EPA)
9:05 AM **Opening Remarks –** Debbie Edwards, Ph.D. (Director, Office of Pesticide Programs [OPP], EPA)

Review of June 24-25, 2008 HSRB Meeting Report

9:15 AM **Review Process –** Celia Fisher, Ph.D. (HSRB Chair)
9:20 AM **Public Comments**
9:30 AM **Board Discussion and Decision on Final Report of June 2008 HSRB Meeting –** Celia Fisher, Ph.D. (HSRB Chair)
10:45 AM **Break**

EPA Follow-up on HSRB Recommendations
11:00 AM **Pesticide Specific HSRB Recommendations –** Mr. William Jordan (OPP, EPA)
11:15 AM **AHETF Research Progress since June 2008 HSRB Meeting** – Mr. John Carley (OPP, EPA)
12:00 PM **Public Comments**
12:15 PM **Board Discussion**
12:45 PM **Lunch**

Proposed Agricultural Handlers Exposure Task Force (AHETF) Research on Exposure of Subjects Applying Pesticide Sprays to Orchard and Trellis Crops Using Closed-Cab Airblast Equipment

1:45 PM **EPA Science and Ethics Assessment of AHETF Protocols AHE57, AHE58 and AHE59 –** Mr. Jeffrey Evans (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
2:15 PM **Public Comments**
2:30 PM **Board Discussion**

If proposed closed-cab airblast application field study protocols AHE57, AHE58, and AHE59 are revised as suggested in EPA's reviews and if the research is performed as described:

(a) Is the research 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?

(b) Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

3:45 PM **Break**

Proposed Agricultural Handlers Exposure Task Force (AHETF) Research on Exposure of Subjects Applying Pesticide Sprays to Orchard and Trellis Crops Using Open-Cab Airblast Equipment

4:00 PM **EPA Science and Ethics Assessment of AHETF Protocols AHE62, AHE63 and AHE64** – Mr. Matthew Crowley (OPP, EPA), Mr. Jeffrey Evans (OPP, EPA) and Mr. John Carley (OPP, EPA)
4:30 PM **Public Comments**
4:45 PM **Board Discussion**

If proposed open-cab airblast application field study protocols AHE62, AHE63, and AHE64 are revised as suggested in EPA's reviews and if the research is performed as described:

(a) Is the research 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?

(b) Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

6:00 PM **Adjournment**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
OCTOBER 21-22, 2008 *
PUBLIC MEETING

Wednesday, October 22, 2008
Environmental Protection Agency
Conference Center – Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive
Arlington, VA 22202

8:30 AM **Convene Meeting** – Celia Fisher, Ph.D. (HSRB Chair)
8:35 AM **Follow-up From Previous Day's Discussion –** Mr. William Jordan (OPP, EPA)

Completed Carroll-Loye Biological Research Field Study LNX-001

8:45 AM **EPA Science and Ethics Assessment of Completed Carroll-Loye Biological Research Study LNX-001** – Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)

9:30 AM **Public Comments**
9:45 AM **Board Discussion**

(a) Is the Carroll-Loye Biological Research study LNX-001 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the tested formulations against mosquitoes?

(b) Does available information support a determination that study LNX-001 was conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

10:45 AM **Break**

Guidelines for Product Performance Testing of Skin-Applied Insect Repellents

11:00 AM **EPA Presentation** – Mr. John Carley (OPP, EPA)
11:45 AM **Public Comments**
12:00 PM **Lunch**
1:00 PM **Board Discussion**
2:00 PM **Concluding Remarks –** Mr. William Jordan (OPP, EPA)
2:15 PM **Adjournment –** Celia Fisher, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)

* Please be advised that agenda times are approximate and subject to change. For further information, please contact the Designated Federal Officer for this meeting, Paul Lewis, via telephone: (202) 564-8381 or email: lewis.paul@epa.gov.