September 11, 2008

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
June 24-25, 2008 Public Meeting
Docket Number: EPA-HQ-ORD-2008-0355
HSRB Web Site: http://www.epa.gov/osa/hsrb/

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

Dates and Times:	Tuesday, June 24, 2008, 8:30 AM – 5:15 PM Wednesday, June 25, 2008, 8:30 AM – 12:35 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. (via telephone)
	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 (via telephone) 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 Jerry A. Menikoff, M.D. Rebecca Parkin, Ph.D., MPH Sean Philpott, Ph.D., 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 June 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. She welcomed a new Board member, Dr. Ernest Prentice, Associate Vice Chancellor for Academic Affairs at the University of Nebraska Medical Center.

Welcoming Remarks

Dr. Elizabeth Lee Hofmann (Deputy Director, OSA, EPA) welcomed Board members, EPA staff, and the public to the meeting. Dr. Hofmann informed the Board that Dr. Pai-Yei Whung has recently joined EPA as the Agency's Chief Scientist in OSA. Dr. Hofmann conveyed EPA's appreciation for the Board members' work in preparing for and participating in the HSRB meetings on behalf of Drs. Whung and George Gray (EPA Science Advisor, EPA), who were unable to attend the meeting. She also thanked EPA staff for their efforts in preparing for this meeting.

Dr. Hofmann described the topics for this meeting. The Board will review a protocol from the Agricultural Handlers Exposure Task Force (AHETF) that will measure worker exposure to pesticides in a closed-cab airblast scenario. This review represents an important milestone for the Board. For the past 2 years, the HSRB has been reviewing the outline of this proposed research. The Board has reviewed proposed studies, scenario designs, and field study protocols for one mop and two wipe scenarios for the Antimicrobial Exposure Assessment Task Force (AEATF). Today, the Board will review research proposed by the AHETF to measure exposure to those who apply pesticides to orchards and trellis crops using airblast equipment drawn by vehicles with closed cabs. The Agency has provided governing documents and selected standard operating procedures (SOPs) from AHETF to assist with Board review of the protocol.

The Board also will review a completed insect repellent efficacy study from ICR, Inc. (ICR). The study evaluated the laboratory efficacy against mosquitoes of two registered products containing picaridin. At the October 2007 meeting, the Board favorably reviewed this proposed research.

The Board will provide final review and approval of their report from the April 2008 meeting. EPA appreciates the Board's efforts to make the draft of the report available for this meeting in such a short period of time.

Opening Remarks

Dr. Debbie Edwards (Director, OPP, EPA) welcomed Board members and acknowledged Dr. Prentice as a new member of the Board. She thanked the Board members for their efforts in preparing for HSRB meetings and for their thorough and thoughtful discussions of protocols and

reports. These meetings demonstrate that human research undergoes rigorous review both before and after it is conducted. Dr. Edwards thanked Dr. Lewis and his colleagues for managing the meetings and also thanked the public for its participation.

The Board will review a completed laboratory repellant efficacy study with *Culex* mosquitoes conducted by ICR. This is the first completed study report submitted by this organization for Board review. It reports execution of a protocol the Board reviewed favorably at a previous meeting. EPA's review has found the research to be scientifically sound, but some questions related to the ethical conduct of recruitment and slight changes to the protocol arose.

The Board also will review a protocol from the AHETF describing field research to measure worker exposure incurred when applying pesticides to orchard crops using an airblast applicator drawn by a vehicle with a closed cab. EPA requires this data to improve its estimates of handler exposure and risk. EPA has found the protocol to be acceptable, but believes that some changes, which the AHETF has agreed to make, would improve it.

The sampling design for these protocols has been discussed at several Board meetings. EPA considers the purposive diversity sampling (PDS) strategy proposed by AHETF as acceptable if the sampling strategy is fully documented, if random elements are incorporated whenever feasible, and an explanation is given when incorporation of random elements is not feasible. For this protocol, EPA believes that more random elements could have been included, and the lack of feasibility for incorporation of random elements at each level of the sampling strategy was not adequately justified; cost estimates alone are insufficient; however, EPA has deemed the proposed strategy acceptable for this protocol, but will expect a more thorough justification of sampling strategies in the future.

EPA's review of the protocol included consultation with outside statistical experts. In spring 2008, EPA asked Dr. Louise Ryan (Harvard School of Public Health) and Mr. Warren Strauss (Battelle Corporation) to review the AHETF protocols. The outcome of this review has been provided to the Board. Dr. Ryan and Mr. Strauss suggested replacement of the proposed sampling design with a probability-based random design. They suggested focusing on a larger geographical area and that the Task Force select states based on the amount of each crop type under cultivation.

EPA has declined to accept this recommendation because of the significant increase in costs associated with the probability-based approach. In addition, even if revised there will be significant limitations on the statistical inferences that can be drawn from the data because of logistical issues related to creating the sampling frame. EPA has decided that such revisions do not sufficiently justify the increase in costs.

EPA will use the data from this research to update its Pesticide Handler Exposure Database (PHED) and improve its risk assessment activities. The Board is asked to consider whether the proposed research will be conducted in an ethical manner, and if the data generated will be scientifically sound and sufficient for EPA's intended use. EPA has approved the protocols and wishes this research to go forward.

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. As the Designated Federal Official (DFO), Dr. Lewis serves as liaison between the HSRB and EPA and ensures that Federal Advisory Committee Act (FACA) requirements are met. As DFO, he 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.

EPA Follow-up on Pesticide-Specific HSRB Recommendations

Mr. William Jordan (OPP, EPA) reviewed the Agency's actions since the last HSRB meeting. Topics considered at the April 2008 meeting included the AEATF mop and wipe scenarios and protocols; ICR Protocol A382, a laboratory study of the efficacy of an insect repellent against stable flies; and completed studies SCI-001.4 and SCI-001.5 from Carroll-Loye Biological Research, which tested the efficacy of two repellents against mosquitoes.

The Board suggested several changes to the scientific design of the proposed AEATF mop and wipe scenarios related to the sampling design and the duration of study tasks. The Board agreed with the Agency that if the proposed mop and wipe scenario design, protocol, and supporting documentation are revised as suggested in EPA's review, the research would meet the applicable requirements of 40 Code of Federal Regulations (CFR) part 26, subparts K and L. In response to HSRB recommendations, EPA and the AEATF are developing revisions to the mop and wipe protocols to address EPA and HSRB comments and the AEATF expects to execute the research later in 2008.

The Board's concerns and recommendations for ICR Protocol A382 were mainly related to ICR's lack of recruitment of non-White subjects. If the protocol is amended consistent with the Board's concerns and recommendations, particularly regarding recruitment of under-represented minorities, this protocol would be sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of two formulations of picaridin against stable flies. The HSRB agreed with the initial assessment of the Agency that, if the protocol is revised as suggested by EPA and the HSRB, the study submitted for review would meet the applicable requirements of 40 CFR part 26, subparts K and L. In response to HSRB recommendations, ICR has consulted with EPA and revised the protocol and consent form to address EPA and HSRB comments. The revised proposal will be submitted in July 2008 for Institutional Review Board (IRB) review and ICR expects to execute the study in August 2008, and submit the completed study report for HSRB review in January 2009.

The HSRB agreed with the Agency that the completed studies SCI-001.4 and SCI-001.5 from Carroll-Loye Biological Research were sufficiently sound, from a scientific perspective, to be used to accurately calculate the complete protection time of the test materials for repelling

mosquitoes. The HSRB concurred with the initial assessment of the Agency that the study submitted for review by the Board meets the applicable requirements of 40 CFR part 26, subparts K and L; EPA will rely on data from studies SCI-001.4 and SCI-001.5.

The Board will review additional completed studies from Carroll-Loye Biological Research in the future. The HSRB reviewed the protocol for the laboratory tick repellent study SPC-002 in October 2007 and the data collection for this study was completed in March 2008. The HSRB reviewed the protocols for the field mosquito repellent studies SPC-001 and LNX-001 in October 2007 and June 2007, respectively, and data collection for these studies was completed in early June 2008. All three completed studies are expected to be reviewed by the HSRB in October 2008.

AHETF Pesticide Handler Protocols: Closed-Cab Airblast Scenario

Background, Scenario Definition, and Sample Selection

Mr. John Carley (OPP, EPA) presented background information on the AHETF closed-cab airblast scenario protocols. These represent two of five planned field study protocols for measurement of potential dermal and inhalation exposure during application of liquid pesticides to crops using conventional airblast sprayers drawn by vehicles with enclosed cabs. The AHETF submitted an IRB-approved scenario design of these two field study protocols for this scenario on April 7, 2008, along with extensive supporting documentation. EPA's Science and Ethics Reviews of May 27, 2008 were based on review of the April 2008 submission. The AHETF responded to EPA's review on June 13, 2008. The remaining three field study protocols associated with this scenario will be considered at the HSRB's October 2008 meeting.

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); therefore, 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 AHETF's April 7, 2008 submission included the following:

- documents describing the closed-cab airblast scenario design
- Florida citrus crop protocol AHE55
- Georgia pecan protocol AHE56
- AHETF governing documents
- governing documents with tracked changes
- referenced SOPs and other referenced materials
- AHE55 IRB materials
- AHE56 IRB materials

The AHETF governing documents and referenced SOPs were not discussed at this meeting.

Many elements of the two proposed protocols are the same. Both are field study protocols that address the same scenario and implement the same scenario design. The protocols

are identical in substance; the field phases differ only in location and crop. The analytical phases of the protocols are identical. This is the first scenario-specific design for agricultural handler exposure studies to be reviewed by the HSRB. These protocols represent the first responses from the AHETF to EPA's November 2007 decision to accept purposive sampling incorporating random elements whenever feasible, with explicit conditions. The April 7, 2008 protocol submissions contained all elements of documentation required by 40 CFR §26.1125. Although some refinement is needed to address the comments in EPA's Science and Ethics Review, EPA has considered these proposals to be ready for HSRB review.

The closed-cab airblast scenario is defined as application of liquid sprays by conventional airblast sprayers to actively growing, foliated orchard trees and trellis crops, using closed-cab tractors. It excludes mixing and loading for application, use of unconventional airblast sprayers (i.e., use of electrostatic technologies or other methods for minimizing non-target dispersion), airblast application with open-cab tractors, and application to dormant crops. The conventional airblast sprayer is composed of a tank carrying the pesticide mixed with water, comprising the one-third of the sprayer closest to the tractor, and a large fan, comprising the rear two-thirds of the sprayer. Nozzles that distribute an atomized spray can be found on either side of the sprayer and when both sets of nozzles are working, the sprayer and tractor can be enveloped by a cloud of atomized droplets.

The closed-cab airblast application scenario is one of 33 discrete pesticide mixing/loading or application scenarios defined by AHETF. This scenario includes five clusters, each of which is associated with a separate field study to be conducted in a different part of the country with a different crop. The two protocols reviewed during this meeting were the Florida citrus and Georgia pecan protocols. This application scenario differs from the mop and wipe studies reviewed by the HSRB at previous meetings. In contrast to the mop and wipe studies, in which a single study protocol could provide all the monitoring data needed to populate the scenario design because the research was conducted indoors, the monitoring data for the closed-cab airblast scenario will be collected in different parts of the country under five different field study protocols. Agricultural research must include the growers. To obtain realistic data, agricultural handler exposure studies require that agricultural pesticides be applied to appropriate crops using appropriate equipment, which can be accomplished only within the terms of registration of the pesticides and with the consent of the growers to whose crops pesticides are applied. A critical complication in the sampling design of these studies is the need to identify growers who are eligible and willing to cooperate in the research before recruitment of workers can begin.

No more than two monitoring units (MUs), or workers/applicators, can come from any one grower. As many as five growers may be selected for each cluster.

Initial purposive design choices include the following:

- selection of crops and states by choosing from states with the highest production of crops typically sprayed by airblast equipment
- selection of crop types by height and cultural practices
- exclusion of dormant application

- exclusion of hops and other unusual crops
- selection of no more than one crop type per state
- selection of no more than one state per agricultural region.

The first stage of diversity selection involves establishment of clusters. Crops for which airblast application is typical are identified; because airblast equipment is designed for use in orchard and on trellis crops, identifying the crops where it is likely to be used is straightforward. Next, the predominant states in which such crops are grown are identified using United States Department of Agriculture production statistics. States are grouped by agricultural region to incorporate diversity in conditions and agronomic practices; this is based on "agricultural regions" as defined by EPA when food residue or environmental data are needed from different parts of the country where different agricultural conditions and practices exist. One state for each crop type and one state in each agricultural region will be selected to maximize diversity with respect to region, climate, agricultural practices, and equipment. Although this approach increases diversity, it sacrifices representativeness. For example, although California has more than half the acreage in the United States in three of the identified crop types (nuts, stone fruits, and trellis crops), it is sampled only once. Next, a specific monitoring site (county or counties) within each selected state is chosen to minimize the costs of gathering needed monitoring data.

To conduct the study efficiently, a specific area within each selected state where growers and workers can be recruited is identified. Limiting the geographic area in which the protocols will be executed allows grower and MU identification and selection to be conducted efficiently from one local base. Collecting all MUs during a single visit to the study area minimizes researcher salaries, travel, food, lodging, and field fortification expenses. In its June 13, 2008 response to EPA, the AHETF argued that although two MUs can be collected from workers associated with a single grower in a single day, MUs from two different growers could not be collected on the same day.

The primary considerations for selection of study counties will be the availability of the target crop sprayed with airblast equipment; a large pool from which to recruit suitable growers who would be willing to use the AHETF surrogate compounds and participate in the study; and a Local Site Coordinator (LSC) with experience conducting similar studies and who is familiar with local agricultural practices. The likelihood that growers will agree to participate in an AHETF field study is influenced by how and by whom they are approached. Thus, a LSC who is familiar with both the research and the local growers will facilitate recruitment. EPA agrees that a locally knowledgeable LSC is important, but believes strongly that the LSC should not also be a participant in the research, either as a grower or employer of workers who will be monitored.

The second stage of diversity selection identifies MUs. This involves 1) defining practical strata for the amount of active ingredient handled (AaiH); 2) identification and recruitment of a pool of eligible growers with appropriate workers and equipment; 3) design of an array of MUs while considering the size of the equipment and area to be treated, AaiH, and other parameters; 4) approach and recruitment of eligible and interested workers to complement the MU design; and 5) repeating these steps as needed to complete the design.

Stratification by AaiH is achieved by defining five bands, in range from 5 pounds to 100 pounds AaiH per day. A minimum of 5 pounds AaiH per day will reduce non-detects to a minimum and 100 pounds AaiH per day is the practical maximum for a typical work day. In addition, EPA believes that it can extrapolate upwards from 100 pounds AaiH accurately enough for its risk assessment activities. One MU for each AaiH stratum will be identified.

At this point, all choices in the process (crop type, state/region, site/county, AaiH strata, etc.) have been purposive, but selection of cooperating growers will employ a random process. First, eligible growers will be identified by developing lists of local growers of the crop of interest based on information from knowledgeable local resources. Local resources are defined as LSCs, commercial applicator firms, university/county extension agents, crop consultants (e.g., pest control advisors or commercial applicators), agricultural researchers including LSCs, chemical dealers or sales representatives, and grower associations. All lists will be combined, duplicate entries suppressed, and the list randomized. Growers will be contacted in the order they appear on the randomized list to determine interest and apply eligibility factors. Willing and eligible growers will be placed in a "working pool" until sufficient numbers of growers have been identified. In its June 13, 2008 communication, the AHETF notes that the list of growers may not be complete, but that it should be "sufficiently complete for the purposes of this research." If the list is significantly incomplete, the resulting sample will be significantly non-random. EPA has recommended that the AHETF define SOPs for all steps within the sampling process; the AHETF has agreed to develop these SOPs.

Growers placed in the working pool must meet the following requirements:

- grow the target crop
- have sufficient acreage to support use of the minimum AaiH in a single day
- spray the crop with conventional airblast equipment drawn by vehicles with enclosed cabs
- have at least one worker experienced in using closed-cab airblast equipment
- be willing to cooperate in the research
- be willing to use at least one of the AHETF surrogate chemicals
- be willing to let the AHETF recruit workers without interference or influence.

The last three items are related to the growers' willingness to participate. Because neither the AHETF nor EPA can compel a response, it will not be possible to assess non-response bias by learning more about growers who are either uninterested or ineligible.

Data compiled from growers in the working pool will include the following:

- a list of crop(s) and acreage that might be treated
- specific location of crop(s)
- number, type, and size of airblast equipment available
- surrogate chemical(s) that might be used
- approximate timing of expected treatment
- number of experienced workers available

- the amount of active ingredient those workers might be able to handle in a day given equipment and acreage.

The amount of active ingredient (AI) potentially handled will be estimated by the investigators based on information provided by the grower about his spray equipment and acreage of the target crop.

The third step proposed in "2nd-stage diversity selection" is the design of what the AHETF calls an "efficient configuration" of MUs. The LSC and study director will define a group of MUs (i.e., growers, chemicals, workers, AaiH, timing) that would result in an efficient study. Such a configuration would include growers within a compact geographical area that expect to apply one of the surrogate pesticides at around the same time using airblast sprayers of differing size and type and who could together provide workers for all defined strata of AaiH. An efficient configuration must include more workers than the MUs required to satisfy the study design. EPA has questioned how many more workers than MUs are needed. If there were three or four qualified workers for each MU and if more than one of them were willing to volunteer, the individual worker to be monitored could be selected randomly. The AHETF agreed to define an efficient configuration with at least 3 or 4 potential workers for each defined MU, and to randomly select the workers to be monitored from among qualified volunteers.

To approach and recruit qualified workers, growers will be visited to confirm their eligibility and willingness to cooperate and to obtain a promise of non-coercion. Qualified workers employed by eligible, cooperating growers will be informed about the research and asked if they wish to participate. These actions will continue until the MU design is filled, with the following constraints: no worker is used for more than one MU; no airblast sprayer is used more than once; and no more than two MUs will come from any single grower. When multiple qualified and willing workers are employed by a single grower, participants will be selected randomly.

The third constraint (no more than two MUs from a single grower) was not explained in the AHETF proposal submitted on April 7, 2008. In its review EPA recommended this be changed to "no more than 1 MU from any one grower." In its response of June 13, 2008, the AHETF argued that to change from three to five growers would significantly increase the logistical effort and cost of the field study and is not necessary to ensure sufficient diversity of MUs to meet the goals of the research. The AHETF proposal lacks details about how the third constraint would be applied if workers are employed by a commercial spray service. Even if a service that works with several growers and has five qualified and experienced workers and five different airblast sprayers, all five MUs should not be drawn from the same employer.

The sampling design can be summarized as: 1) choose study crops, study areas, and AaiH strata; 2) identify growers of the target crop in the study area; 3) approach growers in random sequence; 4) compile data from eligible growers willing to cooperate; 5) design an efficient configuration of MUs; and 6) recruit a worker for each MU, selecting them randomly when multiple qualified workers are employed by the same grower. In its June 13, 2008 response to EPA, the AHETF has agreed to over-recruit workers for each MU to permit random selection of the worker to be monitored; however, the AHETF's goal of minimizing the number

of growers involved may compromise the randomness of worker selection. This part of the process needs to be specified in an appropriate SOP.

The AHETF has responded to EPA requests in its November 2007 decision to accept PDS for both the AEATF and AHETF exposure monitoring programs to describe in detail their sampling design for each scenario and incorporate random elements whenever it is feasible. The AHETF described in detail the sampling design for the closed-cab airblast scenario in its April 7, 2008 submission. The AHETF also agreed to over-recruit growers and workers to allow random selection of monitored workers. The AHETF was asked to document its rationale for using a particular approach, including all decisions regarding the feasibility of randomizing specific elements in the design. The AHETF has provided some documentation of its rationale, but provided only negligible cost data to document the feasibility or infeasibility of alternative designs.

In its first submission in response to EPA's November 2007 guidance, the AHETF has provided enough information to permit the Agency to conclude that the sample selection process proposed for this scenario design and these protocols is acceptable, with minor refinements. EPA expects to receive a more complete rationale for the sampling choices made in future AHETF scenario designs and protocols. The AHETF promised in its letter of June 13, 2008 both to make the refinements EPA requested from its review and to provide a more complete rationale for the sampling design and sample selection process in future submissions. EPA believes the proposed sample selection process, as altered consistent with the AHETF's June 13, 2008 response to EPA's review, is acceptable.

Clarifying Questions

Dr. Richard Fenske asked for clarification whether the charge to the Board asks it to assess exposure to handlers who apply liquid pesticides, but Mr. Carley's presentation indicates exposure to liquid sprays will be assessed. Mr. Carley clarified that liquid spray was the correct term. At least one of the seven products to be tested is a dry formulation in water soluble packets, but all products will be mixed with water to produce a spray. Because the scenario does not include exposure occurring during the mixing and handling processes, the original formulations of the pesticides are not relevant.

Dr. Michael Lebowitz said that he was impressed by the use of the existing databases to design the studies, but noted that in his own perusal of the data he did not find any evidence indicating a relationship that the AHETF could have used to determine the amount of AI needed to minimize non-detects in these applications. This is critical for the AaiH strata scheme, which is unevenly constructed. Dr. Lebowitz also expressed skepticism at EPA's claim to be able to extrapolate beyond 100 pounds of AaiH. He asked if EPA knew the levels of AaiH that produced non-detects. Mr. Carley answered that the AHETF would need to answer this question. Dr. Fisher inquired about the relationship between AaiH and pounds of AI, given the water-soluble nature of the products. Mr. Carley explained that regardless of initial physical form and concentration, the amount of AI sprayed can be determined based on the amount of product placed in the tanks and by calibration of the equipment and speed of the sprayer. The AaiH strata are based on the number of pounds of AI handled in a given monitoring event.

Dr. Alicia Carriquiry asked if stratification based on AaiH was based on what workers are anticipated to handle. Mr. Carley answered that the stratification is by range of AaiH, not precise amounts. The AHETF designed these strata to distribute the data points and improve the efficiency of the design. The amount of crop acreages, type of sprayer, volume of sprayer, and speed of sprayer through the crop are used to select growers. For example, a small grower expected to take three days to apply pesticide to his crop likely will fulfill the lowest band of AaiH. Because the tanks of the sprayers will be emptied, the amount of AI sprayed can be determined.

Dr. Lebowitz noted a lack of sufficient use of agricultural extension agents and their significant knowledge about local growers, types of crops, and characteristics of growers; extension agents also work independently of growers. Agricultural extension agents could help identify potential participating growers. He also asked about the lack of clarity in the SOP regarding exposure of the AI to the MU at the time of mixing and loading and if MUs will be near enough to the mixing and loading site to be exposed to the pesticide during these processes. Mr. Carley answered that the AHETF representatives would describe the location of the MUs during mixing and loading operations. He also explained that agricultural extension agents are on the list of local experts that the AHETF expects to consult. Dr. Lebowitz added that the agents could have information that would help determine why certain growers decline to participate.

Dr. Janice Chambers inquired whether the lowest AaiH stratum was expected to produce detectable residues. Mr. Carley responded that at the lowest threshold of 5 pounds AI, there likely will be detectable residues. Dr. Chambers asked if smaller growers would qualify for only the lower AaiH strata. Mr. Carley indicated that this was not clear. There is a relationship between AaiH strata and the capacity of the sprayer and size of the orchard that needs to be clarified by the AHETF. Dr. Chambers queried whether the AHETF believed it would be able to convince growers to use one of the two surrogate pesticides designated for use in the research protocols. Mr. Carley explained that the two surrogate compounds are registered and widely used. If a grower agrees to use one of these products, they can pick the product and physical form that best suits their equipment. These pesticides were chosen because there are robust analytical methods available for them and they are relatively non-toxic, requiring use of less personal protective equipment (PPE). Dr. Chambers inquired if participating growers would be required to spray their crops regardless of need. Mr. Carley replied that the AHETF intends to select growers who anticipate applying pesticide within a certain timeframe. Dr. Chambers questioned why the AHETF is asking the growers to buy the pesticide and be reimbursed, rather than having the Task Force purchase and supply the pesticide. Mr. Carley remarked that members of the Task Force would need to answer that question.

Dr. Dallas Johnson inquired about options if, as growers are randomized, there are insufficient workers among the three growers to obtain sufficient numbers of MUs. He asked if it would be possible to stratify based on the number of workers employed by each grower. Mr. Carley explained that to do this, the phase of the design and efficiency of the configuration must be considered. He added that it would not necessarily violate the random order of selection. Dr. Johnson asked about the impact of the first five growers on the random list having only one worker. Mr. Carley responded that there will be more than three growers in the

working pool, and emphasized EPA's recommendation that a SOP was needed to clarify this stage of the sampling process.

Dr. Fisher summarized the Board's questions for the AHETF. The Board asked to be informed about data that assures that lower levels of AaiH strata would have detectable residues, whether the workers would be exposed during the mixing and loading process, whether small growers would be restricted to the lower AaiH strata, whether pesticide would be applied even if it was not needed, and why growers will be asked to purchase the pesticides and then be reimbursed.

Sample Size, Sampling Design, and Cluster Configuration

Mr. Matthew Crowley (OPP, EPA) provided EPA's review of the closed-cab airblast scenario sampling size, sampling design, and cluster configuration; EPA's regulatory objective for this study is to obtain data that will enable the Agency to predict exposure for closed-cab airblast application of any pesticide AI. By estimating AaiH using application rates and acres treated, EPA believes it will be able to reasonably predict exposure to assess closed-cab airblast applicator risks. AHETF's primary objective is to provide a distribution of normalized unit exposures (e.g., milligrams (mg) AI per unit of AI handled) for workers applying pesticides with closed-cab airblast equipment. AHETF's secondary objective is to distinguish between complete proportionality and complete independence between closed-cab airblast application exposure and AaiH. If the analysis shows that use of the unit of exposure in the form of mg per AaiH is unreasonable for the purposes of risk assessment, an alternate normalization factor (or none at all) can be examined. Determining the extent of a particular factor's influence on exposure (such as crop type, wind speed, number of entrances or exits from the cab) would require different sampling designs and will not be assessed in this research.

The sampling design proposed by the AHETF is referred to as diversity selection. Its purpose is to obtain, given a small sample size, a diversity of conditions expected to directly or indirectly influence exposure. A MU is equivalent to a handler-day and involves one worker, one closed-cab airblast sprayer, one AaiH stratum, and one day's work (or application of at least three tank-loads of pesticide).

In its consideration of the sampling design, the EPA consultants Dr. Taps Maiti (Iowa State University), Dr. Ryan, and Mr. Strauss have all emphasized the relative desirability of a probability-based sampling design. Dr. Ryan and Mr. Strauss suggested an alternative using a probability-based random selection of the study areas and monitored workers. This design attempts to incorporate probability-based sampling for a sample of equivalent size to that proposed by the AHETF, without substantially altering the operational efficiency of the research; the alternative approach to selecting areas for monitoring calls for selecting two states per crop type to ensure diversity of geographic location. States and counties would be sampled with a probability proportional to the number of bearing acres. The approach mandates that a state with more than 50 percent of the bearing acres would always be selected as the 3-MU state, a state with 30 to 49 percent of the bearing acres would always be selected as the 2-MU state, and a state with less than 30 percent of the bearing acres would be selected with a probability proportional to its share of bearing acres. Once states are selected, counties within these states

would be chosen with a probability equal to the proportion of bearing acres of the target crop in each county of the state. Using this approach, Florida would have three MUs for citrus crops and California would have two. California would have three MUs for nut crops and Texas would have two. This approach results in over-representation of California.

After states and counties are selected, eligible within-county growers of the appropriate crop will be contacted to gather information about likely closed-cab airblast applications and AaiH within the target date range. Eligibility will be based on objective grower characteristics (e.g., sufficient acreage, at least one experienced closed-cab airblast application worker) rather than their willingness to participate. Unwillingness to participate should be treated as part of non-response and analyzed as such. Assuming all (or a high proportion of) eligible members of the sample provide information about their pesticide use, the highest stage sampling frame will be stratified (workers within geographic areas selected within the lower stages of the design) and a sample selected.

EPA's concerns regarding this proposed design and for probability-based sampling designs for agricultural pesticide handler monitoring in general are related to sampling frame, selection of field study locations, selection of growers and workers, and non-response bias. The ideal sampling frame would be based on a census of acre-treatments by closed-cab airblast equipment; unfortunately, this information is unavailable. Possible surrogates from which to generate a sampling frame include bearing acreage (e.g., 50 percent of nut tree acreage in the United States are in California); treated acres (e.g., 50 percent of nut tree acreage in California is treated at least once per season with pesticides); or acre-treatments (e.g., 50 percent of pesticide-treated nut tree acres in California are treated three times, 20 percent are treated twice, etc). Information on bearing acreage is easily available, but incomplete as not all bearing acres are treated, not all are treated using airblast sprayers, not all airblast sprayer treatments are delivered using closed-cab vehicles, and not all acres are treated the same number of times. Treated acres can usually be estimated with good confidence, but not all treated acres are treated the same number of times or with closed-cab airblast equipment. Basing the sampling frame on acre treatments is most nearly ideal, but would rely more on expert judgment. Many factors (including weather, pest pressure, equipment availability, etc.) can affect whether, how often, and with what pesticide a given acre is treated. Constructing an appropriate surrogate sampling frame is possible, but the more the sampling frame approaches the ideal, the more expensive it would be and the more it would depend on expert judgment. Additionally, use of a surrogate to generate a sampling frame would provide unknown inferential power. EPA considers the inability to construct an accurate sampling frame to be a fatal flaw for a probability-based design.

EPA also has concerns related to selection of field study locations. Several practical considerations indicate the need for purposive selection of field study locations. In order to contain costs, field study locations should be in contiguous, compact geographical areas where growers are likely to spray the target crop at approximately the same time. The selected counties also should have many potential cooperating growers of the target crop to allow diversification of equipment and other factors, and random selection of monitored workers. The number of field study locations is a major cost factor in this kind of research program. If a probability-based approach results in selection of geographically dispersed growers, the study would be significantly more expensive and less efficient. Monitoring in two states for each

crop-type would potentially double the number of field study locations for the closed-cab airblast scenario from 5 to 10, which EPA estimates would cost about $100,000 for each additional location.

Another issue of concern for the probability-based sampling approach is selection of growers and workers. Gathering information on anticipated handler-days from growers within the selected counties as Dr. Ryan and Mr. Strauss suggested is likely to be very difficult. For this research, growers and workers are not independent populations; growers willing to cooperate must be identified before workers can be recruited or selected. In addition, although states maintain records of certified pesticide applicators, there is no registry of non-certified pesticide handlers, and neither the surrogate chemicals proposed nor many other pesticides applied by closed-cab airblast equipment are of sufficient toxicity to restrict their use to certified applicators. The information needed to develop a list of all possible or most pesticide handlers who might make closed-cab airblast applications is not available.

EPA also has concerns about the impact of non-response bias. Response rates are typically low in pesticide worker exposure research; only a small percentage of eligible growers are willing to provide information about pesticide use or to cooperate in the research. Neither EPA nor the AHETF can compel participation, which makes it difficult (or impossible) to assess non-response bias. In their proposal, Dr. Ryan and Mr. Strauss assumed that participation will be high and that the growers will readily supply information and participate in the research. However, this has not historically been the case. Dr. Ryan and Mr. Strauss suggested that unwillingness to participate should be treated as non-response and analyzed as such, but neither EPA nor the AHETF can obtain information about why a grower would or would not choose to participate.

EPA acknowledges the theoretical benefits of probability sampling but has concerns about the many practical barriers to a fully probability-based sampling design for the AHETF monitoring program. The Agency has concluded that diversity selection incorporating random elements whenever feasible is an acceptable compromise; however, for these protocols, EPA believes that the AHETF failed to adequately document the infeasibility of probability sampling.

Factors considered by the AHETF for the proposed sample size and cluster configuration for the closed-cab airblast scenario include a lack of usable existing closed-cab airblast applicator MUs; a target accuracy benchmark (or K-factor) in which selected log normal-based estimates are accurate to within 3-fold at least 95 percent of the time, of less than or equal to ($\leq$) 3; diversity of crop types treated with closed-cab airblast equipment; maximization of efficiency; and minimization of costs. Development of the K-factor of ≤ 3 relied on a reference model with the same two-stage nesting structure as the proposed sampling approach, but an assumption of simple random sampling at each stage. Thus, the reference model does not reflect the hybrid combination of purposive and random diversity selection proposed, but is nonetheless expected to be useful to help estimate an appropriate sample size. The reference model assumes that normalized unit exposure is log-normally distributed based on existing pesticide handler exposure data conducted before new EPA rules were implemented in 2006. Analysis of these completed AHETF studies found a geometric standard deviation (GSD) of approximately 4 and an intra-cluster correlation (ICC) of approximately 0.3.

The proposed sample size and cluster configuration for this research is five clusters of five MUs. This configuration achieves the target accuracy benchmark at the 95th percentile under the assumptions that GSD = 4 and ICC = 0.3. This approach reflects the diversity of the closed-cab airblast scenario; the five selected crop types represent approximately 95 percent of all acreage potentially treated by airblast equipment. The structure of one crop per state and one state per region helps to maximize efficiency and minimize costs. The 5x5 configuration will generate the data the AHETF needs when costs and benchmark accuracy targets are considered, but the configuration can be changed if another is found to be preferable. Other configurations that could achieve accuracy equivalent to the 5x5 configuration include 15 clusters of one MU. This is the smallest sample that achieves target accuracy and minimizes the ICC; however, gathering data from 15 different clusters would be prohibitively expensive. A configuration of four clusters of eight MUs would provide a larger total sample, although one less cluster, at comparable costs. However, this is inappropriate for the closed-cab airblast scenario because data would not be gathered for one of the five major crop types. Thus, EPA has concluded that the 5x5 configuration is acceptable for the closed-cab airblast application scenario. The resulting data will be of improved quality and quantity over existing data and the sample size exceeds the minimum called for in EPA and the Organization for Economic Co-operation and Development (OECD) Guidelines. The costs associated with including additional clusters could reduce AHETF's ability to monitor additional scenarios. In addition, if the benchmark accuracy target is not met, additional data collection will be considered.

The Agency has concluded that an overall probability-based random sampling design is technically and financially infeasible for this scenario; therefore, diversity selection incorporating random elements whenever feasible is an acceptable compromise. EPA recognizes that the resulting distribution will not be statistically representative but believes that the resulting data will improve risk assessment; however, EPA expects better cost analysis and justification for sampling design in future AHETF scenario designs.

Clarifying Questions

Dr. Carriquiry noted that it was not clear if the five MUs would be obtained from different growers. Choosing three growers and picking two workers from each of two growers could introduce an additional correlation not taken into account in the sample size calculations. If two workers are chosen from each of three growers, the sample size will need to be increased.

Dr. Fenske inquired about the basis for EPA's conclusion that response rates for participation in pesticide research are typically low. Mr. Crowley explained that this is a claim of the AHETF and it is supported by the Agency. Mr. Carley clarified that this information is contained in the background materials for this research and was used to inform EPA decisions regarding sampling in November 2007. Dr. Fenske asked why EPA believes that study investigators cannot assess reasons for grower non-participation. Mr. Crowley responded that if growers decline to participate because they are breaking laws regarding pesticide handling or other matters, EPA will not be able to learn this. It has not been possible to receive clear answers for reasons for non-participation. Dr. Fenske inquired if the investigators will ask growers who decline why they are declining. Mr. Carley explained that the concern is that

reasons for non-participation could be collected, but EPA is unclear about how these answers would influence the results. Dr. Lebowitz noted that in population sampling, it is often difficult to obtain sufficient information from non-participants, but investigators can compare characteristics of responders and non-responders.

Dr. Lebowitz commented on the issue of the different number of crops included in the closed-cab airblast scenarios. He said that it is understandable that there may be differences in exposure based on crop type, but the Board has seen no data for this. He stated that it was unclear why these five crop types were chosen and others were not, nor was it clear why it was necessary to include all five of these crop types. He also explained that good repetition of at least the 50th to the 99th percentile of exposures and small uncertainty factors are needed for risk assessment. Ensuring that data will be gathered for the top half of the distribution is critical, but does not seem to be addressed in the diversity sampling approach. Mr. Crowley remarked that the rationale for choosing five different crop types was based on the ICC and modeling used to develop the sample size and configuration. The argument for the ability of diversity selection to capture the upper half of the distribution can be found in the Task Force governing documents. Mr. Crowley added that he was unsure if this argument was accurate; capturing a wide variety of factors that may or may not influence the results and affect bias could result in over-estimation at the upper percentiles of exposure and under-estimation at the lower percentiles. Mr. Carley explained that there are important differences among the crop types; vines and trees on which these crops grow are of different heights and are spaced differently in the orchards. Different equipment is used to spray the crops, which are also grown in different parts of the country with different agronomic practices, ambient temperatures, and humidity. The AHETF picked the five crops for five clusters by observing that nearly all airblast applications are made to these five crops and they are grown in widely distributed geographical areas.

Dr. Prentice asked about the number of workers expected to agree to participate. Mr. Carley noted that this would be discussed in more detail in his ethics review of the protocol. Previous studies have not reported this information, but the Task Force plans to collect this data.

Dr. Kannan Krishnan noted that the most important factor affecting exposure would be the application rate. Given the different crop types, this is likely to vary substantially; PDS could be informative for this aspect of the study. If application rate also differs by type of pesticide, the data would be improved. He asked if the number of pounds AaiH reflected the number of acres treated. Mr. Carley replied that application rates vary based on equipment type and crop type. AaiH versus application rate per acre will be addressed in the science assessment of the protocol.

In response to a question from Dr. Fisher about the 5x5 design, Mr. Carley explained that the AaiH stratum would differ for each MU within the cluster. Each worker in the cluster will handle a different amount of pesticide. The strata for AaiH are defined the same way for all crops. When data are collected for the other three scenarios, five MUs per scenario in five different states will be collected. This will result in five data points for each AaiH strata, but the actual values of AaiH for the five MUs in a stratum will vary. For example, there will be 25 data points across five strata and five data points for application to pecans.

Dr. Fisher asked if, after completion of the five field studies in this scenario, the data within an AaiH stratum could be analyzed by combining data from the different crop types. Mr. Jordan explained that for each of the 5 MUs, unit exposure will be calculated for each MU adjusted for AaiH. This will result in 25 normalized unit exposure values. In the past, EPA determined the 50th percentile of exposure and the geometric mean for these data points. The unit exposure will vary from person to person based on work habits, so there will be a distribution of 25 data points. Based on the type of risk assessment activity EPA is performing, the Agency will use the most appropriate unit value of exposure based on duration of exposure. EPA probably will analyze the differences between crop types to determine if crop type has an effect on exposure, given the different types of equipment and sprayer behavior associated with each crop type. In general, EPA will use the central tendency value for multi-day exposure and the high end of exposure for a single day for risk assessment activities. Data points that generate central tendency values are normalized exposure values from all 25 subjects. Dr. Fisher noted that because there are no replicates, it will be impossible to determine if exposure differences are related to individual differences. She recalled previous Board objections to reliance on a single subject to represent all data points.

Dr. Carriquiry added that EPA's plans for using these data are correct. EPA is analyzing exposure of workers who apply pesticides using a certain piece of equipment for different types of crops under a variety of weather conditions. There will be 25 data points that refer to closed-cab airblast pesticide application for fruit crops. This can be thought of as drawn from a distribution of all closed-cab airblast workers. The data will give an idea of the distribution of exposures of these workers. Estimates of central tendency or means are appropriate, but exposure will be overestimated for the 95 percentile of exposure; this is acceptable because it is likely to result in more protective conclusions about exposure. The lower percentiles of exposures will be underestimated, but this is not a significant concern. EPA's approach for their intended use of this data is reasonable.

Dr. Fisher asked how dangerous exposure levels would be determined from this data. Mr. Jordan answered that this would be discussed in the science assessment of the protocol as well as how values derived from this data set fit into calculations of overall exposure. The unit exposure a worker receives when handling a pesticide is one component of exposure, and the Agency will explain an algorithm that it will use to determine upper-band estimates of high exposures. Toxicology data will be used to determine how exposure compares to levels that are not expected to have an adverse effect. Dr. Linda Young noted that proportionality of AaiH to exposure appears to be a key assumption for these activities and asked if this relationship had been validated. Mr. Jordan answered that EPA has a number of studies that permit examination of the relationship between AaiH and unit exposure. In some studies, there is strong support for a proportional relationship, but other studies are inconclusive and some show no proportional relationship. EPA is asking the AHETF to examine as a secondary objective the proportionality assumption for each scenario. Thus, they designed the study to incorporate stratification of AaiH. This will generate a data set with a useful spread of data points from which to examine proportionality. If the relationship is not proportional, EPA will attempt to determine factors that drive variability in unit exposure. Dr. Carriquiry stated that because EPA will have data on exposure and amount applied, they could determine distribution normalized in a different way if the proportionality assumption does not hold.

EPA Science Assessment of Field Study Protocols AHE55 and AHE56

Mr. Jeffrey Evans (OPP, EPA) presented EPA's science review of AHETF protocols AHE55 and AHE56. These protocols are designed to develop dermal and inhalation contact factors to assess potential exposure of individuals making airblast applications to orchards and trellis crops using enclosed cab vehicles. The results will be used to populate the closed-cab airblast scenario (a total of 25 monitoring units) in the PHED database. Protocol AHE55 will assess exposure occurring during application of pesticides to citrus crops (five MUs) and protocol AHE56 will assess exposure during application to pecan crops (five MUs). Citrus and pecans represent taller orchard canopy crops.

The sites selected for AHE55 are located in Polk and Hillsborough counties in central Florida. There are approximately 7,000 citrus farms in Florida and about 2,500 in Polk and Hillsborough counties. The local experts consulted suggested that enclosed cabs are widely used for pesticide application in these counties. The surrogate pesticides from which participating growers can choose are Carbaryl and Malathion; between 50,000 and 90,000 acres of Florida citrus are treated with one of these chemicals each year.

The sites selected for AHE56 are located in Tift County and surrounding counties in southern Georgia. Pecans are grown throughout Georgia on approximately 3,700 farms covering roughly 128,000 acres. Approximately 26,000 acres of pecans are grown in the study area. Experts consulted suggested that enclosed cabs are widely used in this area. As with AHE55, the surrogate pesticide options are Carbaryl and Malathion and 10,000 to 15,000 acres of Georgia pecans are treated with one of these chemicals each year.

Although there are only two surrogate AIs, they may occur in any of the following formulations:

- Carbaryl-containing products: Sevin® Brand XLR Plus Carbaryl Insecticide (EPA Reg No 264-333), Sevin® Brand 80WSP Carbaryl Insecticide (EPA Reg No 264-526), and Sevin® Brand 4F Carbaryl Insecticide (EPA Reg No 264-349).
- Malathion-containing products: Gowan Malathion 8 (EPA Reg No 10163-21), Malathion 8-E Insecticide (EPA Reg No 34704-452), Fyfanon® (EPA Reg No 5905-196), and Fyfanon® 8 lb. Emulsion (EPA Reg No 5905-250-ZA).

Each of the five MUs will apply a different amount of AI per monitoring event based on the following strata: 5 to 9 pounds, 10 to 17 pounds, 18 to 30 pounds, 31 to 55 pounds, and 56 to 100 pounds. EPA considers these strata to be appropriate for airblast application and are consistent with amounts used in studies to generate data for the PHED and with amounts used in EPA handler exposure assessments. The lower limit and minimum of three tank-loads are likely to result in measurable residues on all sample matrices, minimizing potential non-detects. Normalized data (mg exposure per pound AI handled) can be used to model longer work days or higher application rates than the proposed study durations (approximately 4 to 8 hours). EPA wished to obtain measurements on individuals performing these application activities; the data will then be used to assess exposure of people handling more or less pesticide. This relies on the

assumption of proportionality between mg exposure per pound AI handled. The protocols also will note how much product workers apply and their behaviors. Ultimately, there will be 25 unit exposure values for this scenario.

In estimating handler exposure, EPA assumes the maximum permissible application rate, the maximum practical acres treated per day, and a conservative estimate of dermal absorption. The dermal exposure algorithm will determine dose as a function of unit exposure times application rate times acres per day times percent dermal adsorption all divided by body weight. The margin of exposure (MOE) will be calculated as the no observable adverse effect level (NOAEL) (mg per kilograms per day (kg/day)) divided by the dose calculated as described above. Historically, a standardized body weight of 70 kg has been used in these calculations, but this value may be reconsidered. The value for percent dermal adsorption will be derived from animal studies and assumed to be the same for all workers. The goal is to achieve a MOE of 100.

Dr. Carriquiry raised questions about the MOE calculation. She noted that the assumptions about dermal absorption and body weight, and that the acres treated per day are based on the number of acres a person and machine could cover in 8 hours of spraying and conversion of this amount to determine the amount of pesticide handled. She requested clarification of the MOE given that there will be 25 different values for exposure, based on MU use of different strata of AaiH. Mr. Evans explained that to estimate MOE, 25 unit exposures could be used, or EPA could perform a point estimate or select an arithmetic mean. If a probabilistic approach is used, each value could be a distribution from which EPA could select. Mr. Jordan explained that the application rate is a product-specific value that varies based on pesticide type. EPA likely will choose the highest allowed application rate for its risk assessment. Application rate and number of acres treated are the upper-bound values. Percent absorption is a conservative estimate. This will result in a high-end estimate of a worker's potential dose. Dr. Prentice inquired if EPA would measure variability in application rates across workers, or just assume a maximum rate. Mr. Jordan replied that EPA would assume a maximum application rate, although the Agency recognizes that less likely will be applied. EPA makes these assumptions to assure safe exposure at the high ends of application. Dr. Young asked if the difference between the high end and low end of unit exposure was based on having a higher concentration of pesticide in the sprayer tank or by spraying for longer time periods. Mr. Jordan responded that worker behavior, such as exiting the cab to unclog a spray nozzle, was more likely to affect exposure. Mr. Carley clarified that the differences in product handled with respect to the AaiH strata is primarily based on the size of the sprayer tank and the size of the orchard; concentrations of the pesticides are roughly consistent. The variables include the size of the tank, speed of the truck, and acreage; these variables are considered during the design phase when the growers and the strata for which they are candidates are selected.

Dr. Johnson asked about the relationship of the MOE to product registration, given the assumption that EPA will use the data for risk assessment activities to inform registration of products. Mr. Carley replied that the target MOE is at least 100. The predicted high end of exposure is based on the conservative assumption that it should be no more than 1/100th of the NOAEL. EPA also might use the data to inform calculations for open cab application. EPA would assume a MOE of only 25 for this type of application; if the exposure data supports this

MOE, EPA can require airblast use of these pesticides only when enclosed cabs are used. These data also only apply to spraying; data from other behaviors such as mixing and loading also will have to be considered in the risk assessment calculations. EPA also could require a specific, lower acceptable application rate. This research is based on the idea that exposure potential can be modeled using surrogate data, i.e., individual values for each of the 25 MUs. EPA hopes to be able to measure exposure for any pesticide and for any crop using this method. EPA would not usually use data from each participant separately, but is attempting to improve its deterministic assessment. Dr. Chambers inquired if the data would be used to predict individual exposure. Mr. Carley responded that the data would not be used for this purpose. The research models high ends of exposure to protect users while applying these pesticides using closed-cab airblast in orchards. EPA is attempting to determine the worst-case exposure possibilities and cap potential exposure using appropriate regulatory controls.

Mr. Evans continued his science review of AHE55 and AHE56. The AHETF will collect dermal and inhalation exposure measurements to develop unit exposure or other exposure metrics for both protocols. The Task Force recognizes that normalizing factors other than AaiH may be more appropriate for applicators using closed-cab vehicles. The resulting data can be used to estimate dermal and inhalation exposure to the monitored surrogate pesticides and to other pesticides registered for closed-cab airblast application to orchard or trellis crops. To determine inhalation exposure, airborne concentrations of the surrogate will be monitored in the subject's breathing zone using an Occupational Safety and Health Administration Versatile Sampler tube sample collector connected to a personal sampling pump. Particle size will not be measured; all residues will be assumed to be respirable. Dermal exposure will be measured by analyzing a 100-percent cotton whole body dosimeter (long underwear) worn beneath the subject's clothing. This will be performed in accordance with the draft EPA Series 875 Group A–Applicator Monitoring Test Guidelines. Measurements on the hands, face, and neck will be collected by rinse and wipe methods using 0.01 percent Aerosol OT solution according to OECD Applicator Guidelines. Foot exposure is expected to be insignificant, as determined by open cab data on foot exposure in PHED and thus socks will not be collected as dosimeters.

For hand wash and face/neck wipe samples, EPA proposes the following conditions:

1) if measured exposures from hands, face, and neck contribute less than 20 percent of total exposure, no action is required
2) if measured exposure contribution represents between 20 and 60 percent of total exposure, an automatic 50 percent adjustment will be made or the AHETF can submit a validation study
3) if measured exposure contribution is greater than 60 percent, a validation study is required.

Existing hand rinse data for Malathion exposure in field workers indicates 59 percent removal in the first rinse; combined with a second rinse, a mean of 85 percent removal would occur. These data are derived from validation studies involving intentional dosing of human subjects, and therefore require prior review by EPA and the HSRB.

These protocols address the technical aspects of applicable exposure monitoring guidelines. EPA Series 875 Group A–Applicator Monitoring Test Guidelines, OECD Applicator Guidelines, and Good Laboratory Practices [GLP] (40 CFR part 160) have been met. In its science review, EPA has concluded that while generally acceptable, the protocols could be improved slightly. As a contractor to the AHETF, the LSC is a member of the research team and therefore should not also serve as part of the study population, either as an expert or as a cooperating grower or commercial applicator. The processes of diversity selection of growers and construction of an efficient configuration of MUs should be fully documented in an appropriate SOP. Finally, the numbers of growers and workers in the working pool should be increased so that individual workers filling all MU slots can be selected randomly from among qualified, interested volunteers. In its communication to EPA dated June 13, 2008, the AHETF agreed to make these changes.

Clarifying Questions

Dr. Lebowitz requested clarification concerning how samples would be collected and stored, and asked about time to analysis and the methods of analysis. Mr. Evans answered that the governing documents discuss use of controls such as travel spikes and field fortifications, as well as quality assurance (QA)/quality control (QC) protocols and limits of detection. Field fortifications collected at the time of the studies and travel spikes will be used to control for pesticide degradation. The Task Force recognizes that potential degradation of pesticide residues is an important matter. The field fortifications will contain a known amount of pesticide; if decay is observed, the dosimeters can be adjusted to account for loss. In general, recovery from the dosimeters is efficient, the samples are stored on ice, and residues are successfully recovered.

Dr. Fenske noted that one point of the study was described as generating data that will allow MOE and exposure analysis of pesticides other than those used in this research; however, compounds of higher toxicity will have different NOAELs but the same dose and application rate, which would result in different MOEs. Protective clothing requirements vary according to the toxicity of the compound and this research uses lower toxicity pesticides. He asked how use of different types of PPE would be factored into the equation when the data are used to assess exposure to pesticides of higher toxicity. Mr. Evans explained that the cab is an engineering control; applicators wear what is required based for use of the pesticide outside of the cab. One issue that has arisen is whether respirators are required, because few manufacturers will certify that a cab is completely closed. Thus, regulations often indicate that respirators must be worn in the cab. An estimate of exposure in the cab when not wearing a respirator will be obtained from this research, and then a respirator protective factor can be applied. Dr. Fenske countered that a person performing airblast application from an air-conditioned cab likely will not exit the cab often, and thus it would be surprising if exposure is detected on the inner dosimeter garment. Outside of the cab, workers are supposed to wear protective clothing according to label requirements. If a worker is spraying a more toxic compound, he may be required to wear a coverall, which means that the NOAEL and PPE requirement are different. Mr. Evans explained that PPE requirements for pesticides generally are based on acute toxicity information. For risk assessment activities, EPA will examine data from a database of higher-toxicity compounds and evaluate if the PPE is sufficient. A protection factor for when a worker is wearing coveralls can be assumed. Dermal exposure measurements likely will be small; however, it is unclear if the

risk management decision to require coveralls is useful. Dr. Fenske stated that the dose value in the denominator of the equation calculating MOE (NOAEL/dose) will be the same, because it is based on workers wearing long-sleeved shirts and pants. If the same dose is used for higher toxicity compounds, the MOE will be lower but will have no value for chemical protection required by the label. Mr. Evans agreed, and noted that the data could be adjusted for wearing coveralls.

Dr. Fenske inquired if dermal exposure as determined by hand and face/neck washes would be collected for each worker. Mr. Evans responded that these values would be collected for each MU. Dr. Carriquiry questioned whether dermal exposure measured for working in closed cabs was expected to be low, and if so, how this could be proportional to AaiH. Mr. Evans replied that one goal of the research was to assess this relationship. The researchers are aware that other behaviors may affect exposure. By analyzing measurements taken during the study along with existing data, it should be possible to characterize this relationship. Dr. Fenske noted that the probability that exposure will be based on AaiH and be consistent is fairly low. This will be a particular issue for this closed cab scenario. Mr. Evans agreed and noted that EPA has recognized this potential problem. Dr. Carriquiry inquired how the design would be affected if exposure is found to be independent of AaiH. Mr. Evans answered that EPA will need to determine whether it is still a reasonable assumption to assume a proportional relationship from a regulatory perspective. Other variables could be used to normalize exposure, but this will be difficult.

In response to Dr. Fisher's question about exposure occurring when the worker exits the cab, Mr. Evans explained that behaviors exhibited and time spent outside of the cab will be reported; however, there will be no controls for this aspect of the study. Dr. Fisher noted that because any differences in exposure will occur when the worker is outside of the cab, and because the design has no control for this, each data point will be "independent" and the usefulness of the data is questionable. Dr. Carriquiry commented that the policy regarding spraying three tanks of pesticide to determine the amount applied, and how this relates to the design and AaiH strata is unclear. It seems likely that a person applying 100 pounds of pesticide would exit the cab more frequently, which could cause confounding between the AaiH and the time to apply the AI. The time spent applying pesticide is more likely to be proportionally related to exposure than AaiH.

Dr. Susan Fish requested clarification of the utility of the data. It appears that this 5x5 configuration, with 25 different situations has a number of potential confounders, which may result in the data resembling a "case series" of 25 individuals, i.e., a qualitative study of each particular MU. This data would be qualitatively useful, but not quantitatively useful, and impossible to statistically manipulate. Dr. Fenske explained that, in EPA's view, the research will generate 25 high-quality measurements of a time period of exposure under the general condition of closed-cab airblast application. There are thousands of worker-days for application of pesticides using this method per season; if 1,000 workers were sampled, the same level of diversity would be observed as with the 25 workers. The hope is that these 25 workers will be a sample of total worker-days that will allow EPA to calculate the upper bound, 95th percentile of the distribution of exposure. The data likely will be better than existing data used for risk assessment activities.

Dr. Fisher noted that although the MOE calculation is understandable, it is difficult to understand how data generated for each of the MUs can be analyzed statistically in any way, given the high degree of variability. Unless there is an assumption that different AaiH will be applied across the five scenarios, there will be 25 different data points. Given the costs of this research, it is difficult to understand the advantage of maximizing variability across five scenarios versus replicability in fewer scenarios. She also asked if there is a need for five participants per AaiH strata, because the relevance of measurements taken at lower dosage is questionable. Another alternative would be to include replicability to control for individual error, which may be more important than variability across different crop types. This may also permit a stratum to be removed and thus costs would be the same, but a better control for error would be possible. Mr. Evans explained that driving tractors through orchards is a basic activity. Obtaining measurements from many different people participating in many different activities related to pesticide handling is important for assessing exposure. The available data show that measurements can be made and the issue of non-detects can be resolved. EPA needs to address the issue of magnitude of exposure for workers using closed cab tractors. Mr. Crowley agreed that replicability would be desirable, but it would lead to an exponential increase in the number of samples needed to capture variability. It is unclear, from a regulatory perspective, if a limited data set with smaller error would be better than the current approach, or if data from a limited set (i.e., single crop type) could be extrapolated to other scenarios.

Dr. Fish noted that there are many unknowns for this research. She asked if it would be possible for the HSRB to review data from a completed portion of the research and, based on the results, require the AHETF to perform the research using additional AaiHs, scenarios, or replicates. Dr. Fisher noted that the AEATF used three replicates and the HSRB had concerns about this, although the Board understood the need for this number of replicates. The Board stated that its approval of the protocol at the time it was presented did not guarantee that the data will be acceptable once the protocol has been executed. The Board's interest is in ensuring that the research does not generate un-interpretable data.

Dr. Young inquired if time spent outside the cab will be tracked. Mr. Carley replied that complete observations of activities, such as the time it takes to spray the orchard, distance the worker is from mixing and loading activities, and other parameters, would be made; however, the activity of the workers in this research is not tightly scripted because the goal is to incorporate "natural" variability that occurs in the world of applicator days. The variability observed among the 25 MUs is likely to be representative of the variability in the agricultural world. Applying pesticides is a highly variable activity, and each application can be viewed as its own "story." The idea of developing a schematic in which points of replicability can be chosen is not possible, because some behaviors cannot be replicated. The research will generate data for a number of scenarios; EPA will analyze the data and present it to the HSRB. After this, EPA will determine if a scenario has been sufficiently explicated to allow the Agency to assess future closed-cab airblast applications. Until the data are generated, it is not known what the data will show.

Dr. Carriquiry agreed with Mr. Carley, but asked why, given that the proportionality assumption had not been proven, a pilot study with one grower and five MUs had not been

proposed. Mr. Carley explained that EPA has data from approximately 15 studies, several of which were performed using open cab airblast application and modern dosimetry. Based on this existing research, the AHETF is reasonably sure that measurable residues will be detected. If no relationship between AaiH and exposure is found for the closed cab application, but is found for the open cab application, these results are nonetheless informative, from a regulatory perspective, about the ability of a closed cab to mitigate risk. If the research shows that exposure occurs when the worker exits the cab, EPA will use that information to develop strategies to reduce risk. A strong correlation between AaiH and exposure in the open cab scenario is expected, which would speak to the ability of a closed cab to effectively protect against exposure. The amount of pesticide that deposits on the outside of the cab also might impact exposure.

Dr. Fisher asked when data from this protocol would be available. Mr. Carley responded that the Board will see the data when the entire scenario is populated with all five studies, the timing of which depends on whether the other three scenarios are ready in time for the October 2008 HSRB meeting. If the Board finds the protocols presented at this meeting to be acceptable, AHE56 will be executed in August 2008, and AHE55 (and other protocols, if found acceptable) will be executed in spring or summer of 2009. Dr. Fisher asked that the Board be provided with the prior open cab studies for informational purposes. Mr. Carley explained that EPA will meet with the AHETF shortly after this meeting for further discussion. The AHETF has sent preliminary documents for the next round of studies that will complete both the open and closed cab airblast application scenarios. EPA hopes to bring these protocols to the Board's October 2008 meeting.

EPA Ethics Assessment of Field Study Protocols AHE55 and AHE56

Mr. Carley presented EPA's ethics review of AHE55 and AHE56. Assessment of the value of this data to society is based on the need for exposure data for applicators using closed-cab airblast sprayers to support EPA exposure assessments. Few data currently exist, and these data do not meet contemporary standards. The knowledge likely to be gained from this research will be usable in exposure assessments for the specific crop uses and pesticides monitored as well as for other crop uses and pesticides employing closed-cab airblast equipment.

The AHETF proposes to recruit subjects for these protocols from among the employees of eligible growers in the "working pool." Screening of growers will continue until the working pool includes growers with a total of at least 10 workers who may potentially volunteer for the study, and at least two workers for each defined AaiH stratum. The pool will include more growers and more workers than are ultimately needed for the study. In its letter to EPA dated June 13, 2008, the AHETF agreed to "over-recruit" growers to provide at least three or four potential workers who meet the criteria for each needed MU. Subjects will be recruited from among workers who are employed by eligible growers in the working pool (or by pesticide application service companies used by eligible growers in the working pool), have recent experience using the specific closed-cab airblast 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, subjects will be selected randomly.

EPA has determined that the inclusion factors are appropriate. Exclusion factors also are appropriate, except for the exemption of employees of the LSC from the exclusion that applies to employees of all other AHETF contractors. Appropriate steps have been proposed to protect candidates and subjects from coercion or undue influence to participate, again with the potential exception of employees of the LSC. The AHETF agreed to eliminate the exemption of LSC employees from the exclusion group in its June 13, 2008 response to EPA's review of the protocols. As per protocols of this type, growers must agree not to coerce employees to participate, or to influence their decisions in any way. Employers of potential subjects also are excluded from all recruiting meetings of the investigators and subjects. EPA's overarching concerns in recruiting, screening, and obtaining consent can be divided into four categories: equitable subject selection, fully informed choice, fully voluntary choice, and respect for subjects.

Matters related to equitable subject selection include appropriate inclusion/exclusion factors, appropriate recruiting strategy, and representativeness of the sample. The proposed inclusion criteria are appropriate and acceptable, and include the following:

- willingness to participate and sign the Informed Consent Form (ICF)
- handles pesticides as part of their job
- trained in safe pesticide handling per Worker Protection Standards (WPS)
- experience within the past year applying pesticides to the target crop using the airblast sprayer and tractor to be used in the study
- at least 18 years old with government-issued identification
- in good general health
- willing to follow all label and WPS requirements.

Exclusion criteria include being a pregnant or nursing mother, normally wearing more PPE than is required by the label of the surrogate pesticide, lack of understanding of English or Spanish, and employment by a pesticide manufacturer or a contractor to the AHETF. Procedural exclusions include workers employed by growers who were unlisted or who declined to participate; these exclusions arise because of the sampling strategy developed for these protocols. Exclusion of workers who normally wear more PPE is necessary to avoid confounding the data; the surrogate pesticides were chosen in part because they do not require more protective clothing than long-sleeved shirts and long pants. Literacy is not required and appropriate provisions have been made for informing and obtaining consent from workers who do not know how to read.

Representativeness of the sample is achieved by thoughtful selection and justification of purposive elements in the sampling design, and the elements of random selection that were incorporated appropriately into the sampling design. The resulting sample is likely to include diverse characteristics expected to affect exposure, with minimal selection bias and be useful for modeling future exposures.

To ensure fully informed choice, the consent forms contain all elements required by 40 CFR §26.1116 in accessible form and language. The consenting process is adequately described in the protocol. Equivalent processes for Spanish and English speakers, relying on

bilingual investigators, have been described; however, EPA raised concerns regarding the use of interpreters, which has not yet been addressed by the AHETF. The SOPs indicate that if best efforts to obtain a bilingual investigator fail, the AHETF reserves the right to use translators, but how these translators will be identified and qualified has not been documented.

To adequately communicate risks and benefits, the organization and content of risk discussion in consent forms have been found to be acceptable; however, the label and Material Safety Data Sheet (MSDS) summaries cited in the SOP have not been approved by IRB, and may not be available in Spanish. EPA recommended that this SOP be revised to delete this reference and include all necessary information in the consent forms. Benefits include knowledge about individual exposure results that are presented in context. EPA has advised that information about an individual's exposure related to the exposure of others be included for comparison. The AHETF has agreed to provide this context as well as individual results, if requested. The study director currently is responsible for confirming subjects' understanding; however, this will be difficult if the worker speaks Spanish. Appendix 3 to SOP 11-B provides example questions for confirming understanding.

Study candidates must speak English or Spanish, but are not required to read; "impartial witnesses" will ensure that non-readers are fully informed. The SOP calls for a bilingual impartial witness, but how to ensure that the witness is fully bilingual and impartial is not explained. If English is the candidate's preferred language, recruitment will be conducted in English by the principal investigator. If Spanish is the candidate's preferred language, recruitment will be conducted in Spanish by a bilingual member of research team. The AHETF has decided to include bilingual investigators in all research protocols, which would obviate the need for translators.

To manage dependent relationships, cooperating growers must promise neutrality; employers are excluded from recruiting meetings, and employees of interested entities (except the LSC) are excluded as subjects. To minimize peer pressure, the recruitment interview is private. Pregnancy testing is managed to maintain privacy. Because of the need to provide real alternatives to participation since the research takes place at potential subjects' work sites, if a worker declines to participate, the research will be conducted elsewhere, with another worker. Candidates who attend an individual interview will be paid $20. Enrolled subjects who wear the dosimeter will be paid $80, regardless of whether spraying occurs and the research can be conducted. Subjects are free to withdraw at any time, for any reason, individual results will be made available by request, and medical care for research-related injuries will be provided at no cost to the subjects. To ensure privacy and confidentiality, no records will be kept of candidates who do not qualify or consent to participate; positive results of pregnancy testing will discussed only with the individual candidate, and records will be shredded; collected data will be identified only by subject code; observations will not be shared with subjects' employers; linkage of subject names/addresses to subject codes will be maintained securely; and subjects will not be identified in reports or in databases.

EPA has concluded that the processes for recruiting, informing, and obtaining consent from the worker-subjects of the proposed research, with minor changes the AHETF has agreed to make, satisfactorily address all of the Agency's overarching concerns.

Risks and risk minimization activities fall into six categories: 1) heat-related illness; 2) exposure to surrogate chemicals; 3) scripting of field activities; 4) psychological risks; 5) exposure to detergents; and 6) background risks of agricultural work. To minimize risks of heat-related illness, unhealthy subjects are excluded, tractor cabs are air-conditioned, subjects are closely observed by research staff trained to recognize signs and symptoms of heat-related illness, and medical staff will be available onsite. SOPs to address contingencies were developed, and stopping rules based on subject activity and heat index with thresholds lowered as recommended by the HSRB will be in place. Exposure to surrogate chemicals will be mitigated by using AIs that are fully tested and well understood and by ensuring MOEs are substantially greater than the target. Because there will be little scripting of field activities, scripting is unlikely to substantially affect worker risk; however, subjects must be trained (or exempt) per WPS, and experienced with the specific equipment to be used. The degree of scripting may vary with tank size, etc., to achieve the target AaiH. Psychological risks attributable to pregnancy testing and assisted dressing or changing into the whole body dosimeters are minimized by ensuring privacy of testing and results and by providing same-sex assistance for dressing. Risk from exposure to detergents present in hand wipes or face/neck wipes is minimized by using highly diluted, freshly mixed detergents. The detergent concentrate is an eye irritant and eye wash stations will be available in case of need. Background risks of agricultural work include those associated with operating the tractor and airblast sprayer, and those associated with potential tank-mix products which may be combined in the tank with the surrogate pesticide. Investigators will ensure that workers are familiar with the equipment and that all label requirements for tank-mix products are observed. Additional products in the tank will not confound analysis of the surrogate residues.

This research has no direct benefits to subjects. Indirect benefits to subjects include knowing their own exposure and how it compares to that of others. The societal benefit from improved data for risk assessment is likely to be realized. Growers benefit from free product but also absorb the costs of inconvenience and lost time. Sponsors benefit from the lower cost of shared surrogate data development. EPA considers the risks associated with this research to have been fully identified and effectively minimized. Any residual risks to subjects will be low and are reasonable in light of the potential societal benefits of obtaining reliable data on dermal and inhalation exposure while applying liquid pesticides to crops with airblast sprayers drawn by vehicles with enclosed cabs.

Independent Investigational Review Board, Inc., of Plantation, Florida (IIRB) reviewed and unanimously approved the protocol and English and Spanish consent forms and product-specific supplements. IIRB is independent of the sponsors and investigators, is registered with the Office for Human Research Protections (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. IIRB provided the Spanish translations and reviewed the product-specific supplements to the consent forms. 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.

Deficiencies noted by EPA that require adjustment include identification of the LSC in the protocol; justification or elimination of the exemption of LSC employees from the general exclusion of employees of AHETF contractors; ensuring that all materials provided to candidates in the recruiting and interviewing processes, including label and MSDS summaries and other materials described in SOPs, are IRB-approved before use; and clarification of the use of the questions in Attachment 11-B-3 to SOP 11.B.1 to confirm candidate understanding. The AHETF has agreed to eliminate the exemption of LSC employees from the general exclusion of employees of AHETF contractors.

EPA also requests that the AHETF define the standard of documentation required to support a decision to rely on an interpreter rather than a bilingual investigator, and procedures for how interpreters and "impartial bilingual witnesses," if required, will be recruited and compensated, and how their competency and impartiality will be assessed. The AHETF claims they will rely on bilingual investigators, but the SOPs and protocols provide for use of interpreters, and these issues are of concern to EPA. EPA also asks that the AHETF count and report the number of potentially eligible workers linked to each grower, and the numbers attending initial group meetings, attending individual consent interviews, signing consent forms, subsequently withdrawing or being withdrawn, and completing participation; the AHETF has agreed to provide these numbers.

EPA has concluded that all requirements of 40 CFR §26.1111, §26.1116, §26.1117, §26.1125, and §26.1203 are met. If all noted deficiencies are addressed, the AHETF Closed-Cab Airblast Scenario and Field Studies AHE55 and AHE56 will likely meet the applicable requirements of 40 CFR part 26, subparts K and L.

Charge Questions to the Board:

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

a) does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply liquid pesticides using airblast equipment drawn by vehicles with closed cabs?
b) does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Clarifying Questions

Dr. Fish noted that the supporting documents did not indicate how literacy would be assessed. Mr. Carley agreed that this information may not have been included in the documents. Dr. Jerry Menikoff questioned whether the reimbursement for purchasing pesticides to be used in the research could be considered an incentive for the growers. He stated that previous studies have shown that growers usually are not interested in participating; however, if a grower with only one qualified employee is interested in participating, that employee could be vulnerable to coercion. He asked how the AHETF would ensure that growers will not learn that their

employees did not consent to participate and if it was possible, given the sampling strategy that growers could somehow determine which employees declined to participate. Mr. Carley answered that such a situation would be more likely to occur if the AHETF under-recruits growers. If the working pool contains more than the minimum required number of growers and at least three qualified workers, the AHETF can choose workers randomly and inform growers that their employee(s) was not selected. EPA is satisfied that growers will not learn the reason that they were not chosen for participation.

Dr. Rebecca Parkin inquired if workers must agree to be filmed while applying the pesticide as a condition of participation. Mr. Carley responded that the AHETF would need to answer this question. EPA acknowledges that observations are needed, but has advised the AHETF to minimize complications associated with observation. EPA has recommended that many observations could be done from a distance, which would help mask the identity of the subject. He agreed that the Task Force should clarify the number of people observing the workers and also which activities would be observed. Dr. Parkin remarked that the ICF should more adequately address this issue. She also noted that no option was given for having one's face obscured if films or photographs will be used for records or reports. She expressed concern that this would result in exclusion of subjects who wished to participate, but did not wish to be recognized. The AHETF also needs to consider storage of these materials with respect to protection of identify. Mr. Carley replied that EPA intends to encourage the AHETF to include information on this matter only in the SOP and not in the protocol, because including the information in both places results in confusion.

Dr. Prentice asked if the participating workers would be seasonal employees. Mr. Carley explained that this would probably not be the case. Typically, very few workers apply pesticides, and these workers are almost always permanent workers, or, in some cases, the growers themselves. This is a specialized task and only a few workers at each site ever perform it. Dr. Prentice asked if, given average salaries, the $20 payment for the initial interview was high enough to be considered coercion. He also asked if, after completing the first interview, there was any likelihood of coercion to continue further in the process. Mr. Carley responded that the consent form clearly states that subjects are free to withdraw at any point. Dr. Fisher commented that the protocol should clarify that workers who attend the initial interview receive $20 whether they choose to participate further or not. Mr. Carley added that there are no scripts for the initial meeting or individual interviews, which is not unusual. Dr. Menikoff noted that the ICF does explain that workers attending the initial interview receive $20 regardless of further participation.

Dr. Prentice inquired about the educational level of the subjects. Mr. Carley stated that members of the Task Force would need to answer that question. Dr. Carriquiry asked whether workers who apply pesticides are required to be trained or certified. Mr. Carley explained that certification is required for those who supervise application of toxic pesticides, which is regulated though a certification program. The two surrogates used in this research do not require certification, but the eligibility criteria require that workers have received minimal training as defined by the WPS. All involved workers will be experienced applicators, which implies that most participants will be able to read, probably in English. The full labels for the products could cover over 100 pages, and it is unlikely that all of this will be available in Spanish. Dr. Fenske

countered that in Washington State approximately 80 percent of applicators cannot read the English labels. Dr. Suzanne Fitzpatrick asked if a grower could serve as a MU. Mr. Carley replied that this is possible and is provided for in the Task Force documentation. The exclusion criteria refer to those working in the pesticide business or those who are employed by Task Force contractors.

Public Comments

Dr. Victor M. Canez of BASF Corporation, Mr. Curt Lunchick of Bayer Crop Science, Dr. Richard H. Collier of Landis International, and Dr. Larry Holden of Sielken and Associates Consulting, Inc., all on behalf of the AHETF

Dr. Richard Collier (Landis International), on behalf of the AHETF, thanked EPA and the Board for the opportunity to provide comments. He proceeded to answer questions that arose during the review of the AHETF protocols.

Dr. Collier explained that AHETF's position is that the LSC is best viewed as a member of the research team and the SOPs and documentation will be changed to reflect this. Thus, the LSC and his or her employees will not be eligible to serve as growers or MUs. This change in designation and accompanying clarification will address a number of scientific and ethical issues raised by EPA.

Regarding the numbers of workers per grower, two workers per grower or commercial applicator will be placed in the working pool but only one worker per grower will be selected for participation. With this limitation, most application equipment would be used only once. More than one worker per grower will be used only if the grower has more than one applicator and sufficient acreage to avoid application of the pesticide twice to the same part of the orchard.

Based on studies of the surrogates to be used in this research and the sensitivity of the methods used to analyze their residues, the AHETF is convinced that measurable residues will be detected in most or all of the samples even for the lowest stratum (5 to 9 pounds) of AaiH; however, if non-detects do occur, the sensitivity of the analysis means that the data will still be useful for risk assessment. The non-detect level for previous research was significantly higher than for this research; the analytical method used in this research has a stable matrix and high sensitivity.

The AHETF agrees that county extension agents will be useful sources of information about growers. The list of resources provided by the AHETF was not a priority ranking. Extension agents will be used as a source of information.

Workers who volunteer to apply the pesticide will not be involved in mixing and loading duties, but the AHETF will not control the degree to which they are in contact with these activities. The Task Force wants a minimal amount of scripting; the goal is to observe normal applicator behavior and document it in detail.

The AHETF will reimburse growers for their purchase of the pesticide, but the grower will obtain the product from a local distributor. This decision was made based on logistical

matters; it is more straightforward for each grower to purchase the products than for the Task Force to distribute them.

Concerning historically low response rates for participation in agricultural research, this is based on the experiences of Task Force members who have performed such research for a number of years. This matter is not documented now, but will be in the future. The degree to which a responder indicates a reason for non-participation will be tracked.

The AHETF plans to use one observer per applicator; members of the research team present at the site will also include the study director, a medical professional, and members of the team who will take the field fortification samples at the site. The Task Force expects that the observer will be located at the edge of the field while observing the application process and recording observations. The AHETF recognizes that the presence of an observer influences behavior.

SOPs are available that describe the storage, transport, and analysis of the samples in great detail. Samples from the dosimeters and the hand and face/neck washes are frozen onsite with a corresponding field fortification sample. Analysis of the samples may take place some time later. The surrogates chosen for this research are known to be stable under these collection and transport conditions.

The AHETF, as part of a regulated industry, recognizes the importance of the issue concerning the proportional relationship between AaiH and exposure. Even in a low-exposure scenario, pesticides are regulated based on this proportionality assumption; therefore, it was important to include in this scenario design stratification by AaiH to generate data to test this proportionality assumption. Even if the degree of proportionality is uncertain, measures of absolute exposure may be low enough that the question of proportionality becomes irrelevant for this particular scenario.

Regarding the use of bilingual investigators and interpreters, the AHETF agrees with EPA's concerns and has decided to always include bilingual investigators when Spanish-speaking workers volunteer to participate. Interpreters will not be used; therefore, bilingual witnesses will not be needed. The QA officer will ensure that all aspects of the protocol are followed and will document any deviations.

Dr. Victor Canez (BASF Corporation), on behalf of the AHETF, explained that there is a high probability that more small growers will populate the lower strata of AaiH, but over-recruiting should provide some variation in grower size for these strata. Regarding schedules for application, the Task Force will ask growers when they intend to apply pesticides. Most growers have scheduled applications based on the presence of certain pests. The rate of application can be adjusted slightly, but applications at non-efficacious rates, according to label instructions, will not occur.

Dr. Young questioned whether small growers would be excluded if the applicator also usually performs mixing and loading duties. Dr. Canez responded that in cases where one worker performs all these duties, a member of the research team, such as the LSC, will

perform the mixing and loading. Dr. Chambers inquired whether having the Task Force provide the pesticides would result in better control of the quality and age of the pesticides. Mr. Curt Lunchick (Bayer Crop Science), on behalf of the AHETF, replied that the Task Force will record lot numbers and perform GLP characterization of the pesticides to determine the amount of AI in the product. Dr. Canez added that this approach also provides growers with the opportunity to use their preferred pesticide. Dr. Lebowitz requested clarification concerning accidental or other exposures of the MU during mixing or loading that may complicate exposure measurements. He also asked if the Task Force SOPs stated a specific time period in which samples must be analyzed. Dr. Canez explained that no time period had been specified, but the Task Force believes that the stability of the samples and the QC measures in place are sufficient to ensure that deterioration will not be a significant issue. He added that the samples will probably be analyzed less than 90 days after they are collected, but this has not been specified.

Dr. Johnson requested clarification of the identities of the LSCs. Dr. Canez explained that having a LSC usually is a GLP or the LSC usually is an agricultural researcher located in a particular area. The LSC will be familiar with the local farmers and their growing practices, crops, and the chemicals they use. LSCs may operate in several states; for example, one LSC works in Florida, Georgia, and South Carolina. The Task Force intends to employ one LSC per area. LSCs have been identified for AHE56 and the Task Force is in contact with several LSCs in California. Once the LSCs are identified, they will be specified in amendments to the protocol.

Dr. Krishnan inquired about the similarity of the application rates of the surrogates. Dr. Canez responded that the amounts of AI applied for each surrogate are probably similar.

Dr. Gary Chadwick asked about the number of different types of closed cab tractors and airblasters among the 25 MUs. Dr. Canez explained that there are likely to be 25 different kinds of equipment. The equipment is similar in construction; most airblast sprayers spray the pesticide upward or outward. The closed cab tractors also will differ in type, age, and upkeep, but the AHETF has specified that the cabs must have functional air conditioning and closed windows. In addition, growers often modify nozzle positions, fan outputs, and other aspects of the sprayers.

Dr. Carriquiry stated that the 5 percent response rate expected by the AHETF is quite low. In her research, use of trained interviewers usually results in a high response rate. She encouraged the Task Force to work with people trained to make initial contacts; such people can be found at land grant colleges in any state and will probably have more experience in these matters and thus be more successful than the LSCs in recruiting growers.

Regarding sample size and the five MUs, Dr. Carriquiry explained that if the need for five MUs was calculated under the assumption that all five will work for different growers, five MUs will not be sufficient if two workers can be selected from a single grower. Dr. Larry Holden (Sielken and Associates Consulting, Inc.), on behalf of the AHETF, explained that the assumption was not that there would be five workers and five growers. The assumption was that a random sample would be drawn from within a cluster; two MUs could be selected from the same grower by chance. He acknowledged that Dr. Carriquiry was correct that if

"sub-clustering" or grouping within the cluster occurred, there is a potential for a variance component to exist. Analysis at 25 different sites would be logistically difficult; grouping into five "clusters" was done to contain costs and because the Task Force believed it would be difficult to recruit 25 growers. The Task Force is aware that there would be one variance component and that there would be structure beneath that and so tried to make each MU as diverse as possible. When the data are analyzed, any structuring will be considered. In addition, there may be two MUs from a single grower, but there will probably be differences in the way each MU handles the sprayer equipment. Dr. Johnson inquired if it would increase costs to have one MU per grower rather than include the possibility of having two MUs for some growers. Dr. Canez explained that this would increase monitoring time and thus increase costs by approximately 50 percent; this would include salaries for staff and other logistical issues. The optimal approach was to be at a site for one day to set up and take 3 days to perform the research. Increasing the time needed could add approximately $5,000 per day.

Dr. Young questioned if two MUs at the same grower would be spraying at the same time. Dr. Canez confirmed that this was possible if the grower had sufficient equipment and acreage. Dr. Young asked if this meant that more observers would be needed at the site. She also questioned the increased costs for monitoring at additional sites, given that the growers are not located far from one another in Florida. Dr. Canez explained that the research days are long because they include setting up, dressing the participants, 8 hours of spraying, undressing the participants, and processing the samples. The researchers may not be able to leave for the next site until 11:00 p.m. Mr. Lunchick added that two MUs at one farm could be monitored on two consecutive days, but if the design is changed to one MU per farm, this might space out data collection over a week. In addition, if the next spraying is not scheduled for some time, this also could increase costs.

Dr. Fenske inquired how the AHETF would address variations in worker behavior. For example, although the study materials state that the windows of the cab must remain closed, a worker might open the window. The instructions to the observer state that the observer will report unauthorized activities to the study director. He asked if anyone would intervene if unauthorized behavior is observed. Dr. Canez explained that this would be treated in the same ways as refusing to wear PPE, i.e., data would not be collected from that MU.

Board Discussion

Scientific Considerations – Protocols AHE55 and AHE56

Dr. Fenske recommended that the reference to "liquid" pesticides in the Charge Questions be changed to "pesticides applied as water aerosols." He stated that the research is likely to generate scientifically sound data that will be useful for EPA risk assessment activities. He commended the Agency's evaluation and presentation of the materials and the Task Force for addressing most of EPA's concerns in its June 13, 2008 letter.

Specific issues of concern have been largely allayed. On the topic of AaiH, Dr. Fenske expressed some concern that the 5 to 9 pound stratum would be too low to generate detectable residues, but experience of the investigators involved in this research seems to indicate that this

amount will be adequate. Dr. Fenske also was concerned that the highest stratum of AaiH would not be high enough, but a recent study of 35 applicators working over multiple days and performing 150 applications found that the upper limit of AaiH was approximately 100 pounds. He agreed with AHETF's decision not to examine higher levels of AaiH.

Dr. Fenske stated that he had been concerned about the vagueness of contacting local resources, but the documents related to the research have clarified this issue. He also was concerned that small growers would be excluded, given some of the language in the governing documents, but the random listing of growers according to size might alleviate this issue. Applicators working on small farms might have more opportunities for exposure and therefore should not be under-sampled.

The largest area of concern is the behavior of the applicators. Dr. Fenske remarked that in his experience in such an application situation, worker behavior will be a significant determining variable of exposure, so he had concerns about how "naturally" workers would behave in the research setting. Moving from task to task provides opportunities for exposure; therefore, a worker responsible for more activities will have increased exposure, but such exposure cannot be studied in this scenario because mixing, loading, and handling will be studied separately. This approach may underestimate the exposure of those who normally perform all three tasks. The Task Force notes that exiting and contacting the surface of the cab may be the most significant route of exposure in this scenario, but exiting the cab is usually a rare event. A worker could remain in the cab for the entire application duration and also would not be exposed to the mixing and loading activities; Dr. Fenske recommended that workers should make 0 or 1 exit from the cab or the data should be discounted because other behavior would not be realistic. He commented that normal behaviors are constrained in the protocols because the research will be stopped if a worker opens the cab window or takes off his gloves, for example. Workers often engage in activities that are normally prohibited and thus are exposed in this manner; however, terms such as "sloppy worker" should be avoided because workers often have reasons for failing to comply with all protective regulations. Because of these constraints, the data will exclude exposures at the high end. This is of concern and EPA may have to consider how to account for behavior in its use of the data.

Dr. Fenske described other minor concerns. The documents cite agricultural experts to support certain decisions, but actual citations are not documented. The Task Force should identify the experts with whom it consults and provide references when possible. Although the documents indicate that only 15 percent of pesticide applications are made to dormant crops, this represents one in six applications and it is unclear why these were excluded. The AHETF also might want to reconsider the exclusion of other orchard types because of low acreage. The Task Force should also consider checking the nozzles on the application equipment to ensure they are relatively consistent across applications. Regarding observation of workers, the instructions in the materials state that there are necessary forms and notebooks for observations, but these are not described in the SOP; the forms and observation notebooks should be described in the SOP. Dr. Fenske commented that in his review of the materials he found only the English version of the recruitment form, which had a statement asking volunteers to contact Dr. Larry Smith in Ohio; it may be unreasonable to expect workers in Florida to contact someone in Ohio if they wish to volunteer for the protocol.

Dr. Fitzpatrick stated that the protocol was well thought out and adequately answered the science charge question. She asked if Mr. Carley's request for a SOP describing randomization of growers would include a description of how MUs are chosen at random. Mr. Carley replied that he will request specification of the entire process, including record keeping and reporting activity.

Dr. Parkin commented that the documentation for this research was strong. She requested clarification of how observations would be made if spraying occurred at night or before sunrise.

Dr. Johnson agreed that the data would be scientifically reliable and will be useful for assessing exposure. He agreed with Dr. Edwards that EPA needs this data for its risk assessment activities because existing data are inadequate. He commented that the influence of certain parameters on activities needs to be understood with respect to the variation in exposure, not only on the mean of exposure. Conventional sampling is inadequate because of the inability to obtain a random sample of future conditions. This research sought to generate conditions to deliberately emulate realistic conditions, and the PDS strategy seems to have achieved this goal.

Dr. Carriquiry stated that she was satisfied with the purposive selection of states, crops, and counties. She expressed some concern about selection of growers; with some effort, sampling at this level can be changed to result in a better, more valid design. If the design is valid, EPA is less likely to receive protests from the public or others regarding regulations based on the data generated from this research.

The current plan for selecting growers incorporates random elements, but has some major drawbacks. If there is a high rate of refusal, the current plan does not permit investigation or characterization of non-responders. This will impact the representativeness of the study, especially because the sample is not nationally representative. It will be important to know if the 5 percent of growers who agree to participate are representative of all growers; therefore, whether the responders are similar to the non-responders with respect to size of operation, types of equipment, number of employees, etc., needs to be known.

The current plan also does not have a reasonable chance of including small growers. Small farmers tend to meet regulations less adequately than do larger growers. The Task Force thus should guarantee adequate representation of growers of all sizes.

Dr. Carriquiry proposed an alternative design. Given two Florida counties with approximately 2,500 growers of known size, these growers could be stratified by size (small, medium, large, or small and medium/large). From each size strata, a certain percentage of growers (perhaps 2 percent) would be selected and an interviewer would contact each grower to gather information about crop types, acreage, equipments types, and number of employees. This would create the sampling subframe. Of the growers in the subframe, five could be chosen randomly within each size strata and then randomly allocated to AaiH strata. The advantage of this approach is that it excludes the possibility that workers who refuse to participate are identified, and it permits understanding of the characteristics of the non-responders. Failure to

gather this information means the data will be useless if 95 percent of growers do not respond. This approach will guarantee the presence of small, medium, and large growers in the dataset.

Mr. Carley inquired how MUs would be selected in this approach. Dr. Carriquiry responded that selection of growers by size will be correlated with the number of workers. Over-sampling will be needed because the number of workers who will refuse to participate will be unknown. If five growers are selected from the different size strata, three times as many workers could be chosen and contacted randomly. The main issue in the sampling design was selection of the growers; by using this approach, the working pool will be larger and will help characterize non-responders. Dr. Chambers asked if workers could be randomized from each size strata. Dr. Carriquiry replied that this was possible, but the main problem is that workers cannot participate unless the grower does.

Dr. Fisher noted that Dr. Carriquiry's alternative model may raise costs. Dr. Young stated that the ability to obtain information on non-responders is important. She also expressed some disagreement with Dr. Carriquiry's model. In Dr. Young's experience, larger producers are more likely to deviate from regulations than are small producers. Also, Dr. Carriquiry's model could result in over-sampling of small producers; however, limiting selection of MUs to one MU per grower would be preferable. Dr. Young added that being able to protect the identity of growers and workers who participate is important.

Dr. Fisher noted that there appeared to be a strong preference for a model that samples one MU per grower. Other issues raised by Dr. Fenske included confounding with respect to variability of the data related to exiting the cab of the vehicle. EPA should be given a recording sheet that the observer will use that describes potentially affecting variables, such as exiting the cab and proximity to the mixing and loading activities. Because exiting the cab is an important source of exposure, the Task Force should consider including this variable as part of the MOE equation.

Dr. Fenske stated that, except in some unusual situations, workers generally exit the cab when the tank is being loaded. This occurs at fixed locations and should be easy to observe. The observers will be able to determine if the vehicle is moving, and workers will not exit the cab while the vehicle is moving. If the vehicle stops, the worker may exit it. It should be possible to gather useful data on worker behaviors.

Dr. Fisher noted that the study was acceptable, as long as EPA is given information on how behaviors will be observed. Dr. Krishnan remarked that as long as the data is not over-interpreted and the investigators do not attempt to measure contributors to variability, the data can be used to estimate dose for workers. Dr. Johnson noted that although the cabs are air-conditioned and the air intake is filtered, it is likely that some exposure will nonetheless occur. Dr. Lebowitz added that pesticide is most likely to enter the cab when workers open the door or track in residue on their shoes. Given the amount of modeling occurring after data are gathered, modeling exposure could be used to optimize the design, particularly given that these data are intended for risk assessment activities. The AHETF's review of the existing data in PHED to inform their research plan should be commended. Dr. Lebowitz recommended that the Task Force continue to examine existing data on pesticide exposure to further inform the design.

The EPA review of this research and the Task Force documents contain information that justify departure from the 5x5 design and raise questions about the suitability of the PDS approach.

Dr. Fisher summarized the Board's science review. Overall, the Board was impressed by the design of the research. The Board questions the usefulness of the data and cautions EPA against use of the data for other than the intended purpose. It is difficult to conclude that the data will be "reliable" because of the lack of replicate measures; however, the protocol will collect sound qualitative data that will be useful to EPA. EPA should consider doing the following:

- ensure that workers from small and large farms are recruited
- propose time limits for analysis of samples
- obtain specific information about LSCs prior to implementation of the research
- ask the AHETF to employ experienced recruiters to increase the response rate
- clarify the wording of the charge question
- obtain a form that describes how observational data, such as exiting the vehicle, the quality of the machinery, and the MUs' actions during mixing and loading will be recorded
- obtain information on how observations will be made if work occurs at night
- avoid terms like "sloppy" worker
- provide citations in AHETF documents
- suggest that the Task Force reconsider or explain exclusion of certain dormant or other crop types.

The Board consensus is that selecting only one MU per grower would be optimal. It seems clear that attempting to allocate the 25 data points in terms of farm size is possible. If there are limitations to this approach, the Task Force should articulate these, including increases in costs, more precisely. Continuing with the current plan, which limits distribution, must be justified. The AHETF appears to have a strong analytic plan for the MOE, but exactly how this value is calculated is not clear. The Task Force should consider developing alternative analytic plans in the event that the results of the research are different than what is expected. The Task Force also should consider performing an initial survey to help predict the number of non-responders. If the Task Force surveys 50 growers, it can use this information to determine the effects of non-response. The AHETF should also consider blinding the identity of growers and workers to EPA.

Mr. Carley clarified that the documents state that MUs will not be identified. The intent is to not identify growers, but regulatory requirements for record retention may not permit complete de-identification. For example, if legal issues arose over matters related to consent, EPA is allowed access to signatures and other potential identifiers.

Ethical Considerations – Protocols AHE55 and AHE56

Dr. Fish opened the ethics review by stating that, with some changes, the proposed research meets the applicable requirements of 40 CFR part 26, subparts K and L. She then described several issues that should be addressed. The protocol does not include a description of how literacy will be assessed; merely asking a participant if they are literate is insufficient. Spanish speakers should be available at all telephone numbers that potential subjects are instructed to call for further information, including those listed on the ICFs and for the IRB. The means by which subject understanding of the research will be assessed is unclear; a quiz with suggested answers is provided in the appendix but it is not clear if this will be used for all subjects. The protocol does not describe how persons conducting the consent interviews are trained to assess subject understanding. The background risk of agricultural work should not be used when assessing the risk-benefit relationship. The Task Force should consider offering risk counseling related to working with pesticides while pregnant to subjects who have a positive pregnancy test; handouts or a referral would suffice. The Task Force also should consider obscuring participants' identities in photographs and video footage. There is no discussion of the expected gender distribution of applicators on the IIRB application. The predicted ethnicity distribution is 90 percent White and 10 percent Hispanic in Florida and Georgia, which seems to be a low amount of Hispanic participants.

The protocol states that the documents of those who withdraw from the study because of a positive pregnancy test will be destroyed; EPA must indicate whether this is acceptable. References to interpreters and witnesses should be removed from the documentation and SOPs for this protocol because the Task Force has decided instead to use bilingual researchers. The ICF states that compensation for research-related injuries will cover the cost of "reasonable and appropriate" medical treatment; this phrase should be removed. Dr. Fish agreed with Mr. Carley's suggestion to list certain procedures in the SOP rather than the protocol because of inconsistencies between descriptions in the SOP and the protocol. SOP 11.F.0 for adverse event reporting states that adverse events will be reported to Western IRB. This languages needs to be changed because adverse events should be reported to IIRB. The ICF refers only to the AHETF and not to the sponsor; at this point, a re-write is not necessary but should be considered in the future. The Spanish translation of the recruitment poster states that subjects are not qualified if they are "cognitively impaired;" this language should be simplified. If these changes are made, the protocol meets the ethics charge question.

Dr. Chadwick noted that the section discussing use of photographs in the ICF borders on exculpatory. The document states that the AHETF owns the rights to photographs and can use them for any purpose. This asks participants to waive rights that are unrelated to the research. There are ways to document the research using photographs that do not identify the subjects. The ICF should discuss the need for and use of the photographs. Dr. Menikoff agreed that the AHETF should clarify how the photographs can and will be used. Assuming appropriate limitations on use, it is reasonable to not obscure identities at all times. These situations are not as embarrassing as typical medical photographs. The ICF states that subjects will not be photographed while dressing; expanding the explanation of use of the photographs should be sufficient.

Dr. Prentice inquired why the charge questions ask if the research "appears" likely to generate reliable data and if EPA's use of the word "appear" in the charge questions was deliberate. Mr. Jordan explained that the use of "appear" was intended to convey that despite the best plans, in practice the research may not comport with standards. EPA uses the charge question to determine that if a protocol is performed as described, subjects will most likely be treated ethically. Dr. Fisher reminded Board members that the HSRB is not an IRB. The HSRB makes recommendations to EPA to ask for further information or modifications to a protocol. The protocol may return to an IRB after Board review.

Dr. Prentice stated that he largely agreed with other Board reviewers regarding the ethics charge questions. He noted that there was some confusion about when potential subjects receive a copy of the ICF. It appears that consenting may occur several days before or up to the day of the study. Volunteers should receive a copy of the ICF at least 1 day before the study. Mr. Carley explained that subjects probably receive the ICF at the initial group meeting and then can schedule individual interviews; however, EPA will check that this is clarified. Dr. Prentice expressed concern about the payment of $20 to participants who attend an interview, whether or not they participate in the research. Dr. Fish explained that this was usual practice at her institution; the nominal payment is intended to cover the costs of transportation and child or other dependent care.

Dr. Parkin noted that obscuring the identity of participants was important not only for reasons of potential embarrassment but also to protect undocumented participants. She stated that she also was uncomfortable with IIRB both translating and approving the translated materials. Dr. Menikoff asked if undocumented workers were a specific concern, because the study design appears to make it unlikely that undocumented workers will enroll in these studies. Mr. Carley explained that the anti-microbial exposure research taking place in California required proof of age using a government-issued photograph identification form that was not issued to illegal residents. This protocol also requires a government-issued form of identification and thus illegal workers are unlikely to enroll. Dr. Carriquiry noted that the ICF does not specify that the identification must be issued by the United States government.

Concerning translation by the IRB, Dr. Chadwick remarked that the IRB he works with will obtain a translation of a document for an investigator, but the process by which this is done was not known. Dr. Fish explained that commercial IRBs often have Spanish-speaking translators on staff. She added that using IRB staff members to translate documents is preferable because they understand the information that needs to be in the form and the degree of clarity required. Dr. Fisher asked if EPA agreed with the AHETF's decision to destroy the records of women who have a positive pregnancy test. Mr. Carley explained that EPA expects these women to be included in counts of interview participants, but agreed with the decision to destroy their information. Dr. Chadwick noted that testing for literacy was not a requirement for participation in this protocol. Dr. Sean Philpott stated that the ICF as written is too complex for the target population and should be simplified.

Dr. Fisher summarized that the protocol meets the requirements of 40 CFR part 26, subparts K and L with some changes and recommendations. The AHETF should ensure that its test for understandability is objective and should train interviewers in assessing understanding.

All forms need to list Spanish speakers who can be contacted by potential subjects. Destroying the records of pregnant subjects is acceptable. Regarding photographs, any exculpatory language in the ICF should be removed. Use of films should be described in the ICF and restricted in their use (i.e., used only for research or training purposes). Task Force observers should strive to avoid taking pictures of participants' faces or should work to obscure their identity. The Task Force did not provide data on gender distribution and the expected ethnic distribution (90 percent White and 10 percent Hispanic) was surprising; the AHETF should describe the reasons for this distribution. The reference to use of interpreters and witnesses should be modified. The phrase "reasonable and appropriate" should be removed from the provision for medical treatment. Inconsistencies between the protocol and the SOP should be resolved; most of this information can be described in the SOP and referred to in the protocol. Clarification of adverse event reporting to the appropriate IRB is needed. The recruitment poster should list a Spanish-speaking contact and a local contact. Clarification of when consent is obtained is needed.

Dr. Prentice inquired about training of informed consent interviewers. Dr. Fish responded that no information was provided concerning how the consent interview should proceed. The documents mention standard Collaborative IRB Training Initiative or National Institutes of Health (NIH) procedures. Dr. Prentice said that the Task Force should consider including culturally relevant training. Dr. Carriquiry remarked that the Spanish version of the documents is inaccurate; the Spanish version does not state that participation is voluntary until quite late in the document. Clarification that participation is voluntary is needed. In response to suggestions to obtain a back translation of the documents, Dr. Fish explained that many interpreters find this inadequate and prefer use of a certified translator to ensure that the language is appropriate and culturally suitable.

Review of April 9-10, 2008 HSRB Meeting Report

Review Process

Dr. Lewis stated that the Board would review for subsequent approval of its report for the April 9-10, 2008 HSRB meeting.

Public Comments

Dr. Lewis invited oral public comment on the draft April 9-10, 2008 HSRB meeting report. No oral public comments were presented.

Board Discussion and Decision on Report

Dr. Fisher opened discussion on the draft report by asking if Board members had any suggested changes to the Board Recommendations on Review and Format on the AEATF and AHETF Protocols (overall recommendations, format of the protocols for subsequent HSRB review, format of Agency presentations, and Task Force comments at the meeting) (p. 15, lines 25-45 and p. 16, lines 1-38). No comments or changes were made.

Regarding the HSRB Consensus and Rationale related to scientific considerations for the AEATF-II study protocols (p. 21, lines 42-46 and p. 22, lines 1-36), no comments were made. No comments were made for the HSRB Consensus and Rationale related to ethical considerations (p. 26, lines 43-46 and p. 27, lines 1-2).

No comments were made for the HSRB Consensus and Rationale related to scientific considerations for the protocol ICR A382 (p. 28, lines 30-36), studying the efficacy of two formulations of picaridin for repelling stable flies. The Board also had no further comments on the HSRB Consensus and Rationale related to ethical considerations (p. 30, lines 15-19).

The Board had no further comments on the HSRB Consensus and Rationale related to scientific considerations for Carroll-Loye Biological Research Completed Studies SCI-001.4 and SCI-001.5 (p. 32, lines 4-9), testing LipoDEET 302 and Coulston's Duranon for repelling mosquitoes in two field environments. No comments were made regarding the HSRB Consensus and Rationale related to ethical considerations for these protocols (p. 35, lines 10-13).

The Board did not make changes to the section of the draft report describing the Board's decision regarding future review of protocols with planned deviations from prior IRB review (p. 35, lines 15-46 and p. 36, lines 1-2).

Dr. Krishnan inquired if the overview on page 32 should be moved before the science review in the report. Dr. Philpott remarked that there is some redundancy in the report regarding abstracts of the protocols, but this will not occur in the future. An abstract provided by EPA will be included at the beginning of the review of a protocol, followed by the science and ethics reviews. The HSRB will review these abstracts to be sure that issues the Board considers to be of importance are included. Dr. Fisher agreed to eliminate the subheading on page 32, line 20.

Dr. Fisher asked each Board member to approve the changes discussed during this meeting. All Board members in attendance at the conclusion of this discussion approved the report. Dr. Lewis added he will make any necessary grammatical changes to the report.

Follow-up from Previous Day's Discussion

Dr. Fisher summarized Board conclusions for the next AHETF submission. The Board would like to see consideration of the recommendations it made at this meeting. In particular, an observer recording sheet describing how worker behavior will be recorded should be included in information provided to the Board, as should EPA's analytic plan for its intended use of the data. It is difficult to determine if the 5x5 design will provide useful data if the analytic plan is not included. The plan can be based on potential use as well as intended use. EPA is welcome to use consultants to develop its statistical approach.

EPA Review of Completed ICR Mosquito Repellent Efficacy Study A117

Background and Context

Mr. Carley provided an overview of completed ICR mosquito repellent efficacy study A117. This study was a laboratory test of already-registered repellent products for effectiveness against mosquitoes of the genus *Culex*, a principal vector of West Nile Virus (WNV). The products were previously tested in the field against mosquitoes of other genera. Further testing was required by EPA to support the proposed label claim to repel "mosquitoes which can vector West Nile virus."

ICR protocol A117, submitted August 8, 2007, was reviewed favorably by the HSRB in October 2007. In early January 2008, ICR submitted a revised protocol and ICF for informal EPA review, and met with EPA on January 14, 2008, to discuss these documents. On January 10, 2008, the HSRB released the draft final report of its October 2007 meeting. In February 2008, ICR further revised the protocol and consent form, obtaining final IRB approval on February 26, 2008. Laboratory testing was conducted on March 4, 2008, and the final report of testing was submitted to EPA on April 9, 2008.

Because specific events occurring in February and early March 2008 were of specific concern for the ethics review, Mr. Carley described this time period in further detail. On February 8, 2008, ICR further revised the protocol and ICF, reflecting EPA and HSRB comments. On February 14, 2008, ICR submitted the revised protocol and ICF to Essex IRB, Inc. (EIRB). EIRB reviewed and approved the February 8, 2008 protocol and reviewed and conditionally approved the February 8, 2008 ICF, with calls for numerous changes on February 18, 2008; however, none of these changes were of substantive significance. Most were minor editorial changes and a few were requests for insertion of standard language. ICR began recruiting potential subjects on February 18, 2008. On February 19, 2008, EIRB notified ICR by email of the results of its February 8, 2008 review. On February 20, 2008, ICR submitted a further revised ICF to EIRB, which EIRB approved on February 25, 2008. EIRB notified ICR of the approval on February 26, 2008.

On April 9, 2008, ICR submitted its final report and supplement for protocol A117 to EPA. On May 19, 2008, EPA emailed a request for clarification on three points: the rationale for the change in dosing regimen reported as a deviation from the protocol, the number of subjects, and the sequence and timing of recruiting actions. ToXcel responded to EPA's request for clarification on May 21, 2008. EPA's science and ethics reviews were completed on May 22, 2008. On June 6, 2008, toXcel responded to EPA's reviews.

EPA Science Assessment of ICR Study A-117: Laboratory Repellency of Two Registered Picaridin Products to *Culex* Mosquitoes

Mr. Mark Suarez (OPP, EPA) provided EPA's science assessment of ICR study A117. The test materials were two registered repellents containing 10 percent picaridin: Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent (Lotion) (Reg No 806-29) and Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent (Spray) (Reg No 806-31).

The study objectives were to determine the efficacy of the repellents to *Culex* mosquitoes in the laboratory to support proposed label claims for efficacy against "mosquitoes which can vector West Nile virus," based on the hypothesis that the repellent samples will provide 8 hours of protection from *Culex quinquefasciatus* mosquitoes in the laboratory. Because the objectives of the study did not include establishing a typical consumer dose, the dose used was the standard 1 gram per 600 square centimeters, for consistency with the dose used in earlier testing of the same repellents.

Based on the Rutledge and Gupta (1999) meta-analysis, a target sample size of 10 was needed to establish a complete protection time (CPT) of 8 hours ± 2 hours with 95 percent confidence. A total of 12 treated subjects were planned, to ensure an N of 10 even with as many as two drop-outs. One untreated control subject was chosen by lot. All 12 treated subjects completed testing; all results were included in the analysis.

The criticisms of the scientific design of this protocol in EPA's review of September 24, 2007, and in the HSRB's final report of the October 2007 meeting were satisfactorily addressed through the revisions made to the protocol before it was executed. These criticisms include the following:

- use of 200 mosquitoes per cage
- expansion of the statistical analysis plan to include descriptions of how to assess normality of distribution, how to analyze non-normal data, and statistics for all contingencies
- consideration of the Kaplan-Meier test in place of the Q test
- designation of an endpoint as "CPT"
- addition of a form for attractiveness data
- appending the product labels to the protocol
- clarification of the reference to "dose range finding"
- extension of the test duration to 10 hours.

Final revisions to the protocol were made on February 8, 2008. The revised protocol was approved by EIRB on February 18, 2008, and executed on March 4, 2008. The execution was generally consistent with the protocol, with one reported deviation. Instead of treating subjects in six pairs, subjects were treated in two groups of six. This deviation did not affect the experimental outcomes, but should have been done by protocol amendment rather than as a deviation.

The cages used in this study were 2x2x2 foot cubes, sitting on a table. The floor of the cage is mirrored to enable observers to see mosquitoes on the underside of the subjects' arms. The sides and top of the cage are screen wire. On two of the sides there are two fabric sleeves that are secured around the upper forearms of the subjects with large rubber bands. Because there are two sets of sleeves, it was possible to test 2 subjects at once, each testing a different repellent on each forearm.

Two hundred mosquitoes were released into each cage. The mosquitoes were laboratory-reared, disease-free adult (3- to 8–day-old) females that had been fasted for 24 hours

and had never received a blood meal. Before subjects were treated with repellents, each subject established attractiveness to the test mosquitoes by placing an untreated arm into the mosquito-filled cage. Once each subject had shown attractiveness to mosquitoes, they were treated with one test repellent on each forearm and testing began. At 30-minute intervals, the untreated control subject confirmed that the mosquitoes were still aggressive by putting an untreated forearm into each cage. If fewer than 5 mosquitoes landed on the control subject's arm within one minute, (as happened early in the test), 200 fresh mosquitoes were added to each cage. After the aggressiveness of the mosquitoes was confirmed, treated subjects placed their arms through the sleeves into the cage for 5 minutes. This cycle of confirmation of aggressiveness followed by 5-minute test exposures of all treated subjects was repeated for 10 hours, or until a subject experienced failure of efficacy on both arms, defined by a confirmed bite on each treated arm.

A failure of efficacy was defined as a "confirmed bite," which was one bite followed by another on the same arm within the same or the subsequent 5-minute exposure period. For test substance A, there were a total of five bites (three unconfirmed and one confirmed). For test substance B, there were a total of six bites (two unconfirmed and two confirmed). CPT was defined as the time from treatment with the repellent until the first confirmed bite, i.e., until the time of the first bite confirmed by another (confirming) bite within the same or the subsequent 5-minute exposure period. CPTs were 9.417 ± 1.094 hours for test substance A and 9.667 ± 0.421 hours for test substance B. A larger error was generated for substance A (lotion) because of an early failure.

EPA has concluded that the study provides scientific results that meet EPA guideline standards, based on the study protocol as amended in accordance with EPA and HSRB comments before testing began. Both products provided a CPT of approximately 9.5 hours against the WNV vector *Culex quinquefasciatus*.

<u>EPA Ethics Assessment of ICR Study A-117: Laboratory Repellency of Two Registered Picaridin Products to *Culex* Mosquitoes</u>

Mr. Carley provided EPA's ethics assessment of protocol A117. Documents considered in this review were the primary report of ICR Study A117 (MRID 47397701) and supplemental information to address requirements of 40 CFR (MRID 47413601). Additional documents considered were EPA's protocol review of September 24, 2007, toXcel's response to the EPA protocol review (October 17, 2007), toXcel summary of a January 14, 2008 meeting with EPA, the HSRB's final report of its October 2007 meeting (January 17, 2008), toXcel's response to EPA's request for clarification (May 21, 2008), and toXcel's further clarification of recruiting events (received June 6, 2008). The last communication was not received until after this ethics review was completed.

Three deficiencies were noted. The IRB minutes did not explain the basis for requiring changes in the ICF. The IRB roster did not indicate members' experience sufficient to describe their chief anticipated contributions to deliberations and EIRB procedures were not submitted. These gaps did not compromise EPA's review.

All comments from EPA and the HSRB were addressed in the revised protocol and ICF of February 8, 2008. These included the following:

- revision of the discussions of risks and benefits in the protocol and ICF
- correction of the description of risk from repellents
- addition of a discussion of environmental risks
- discussion of risk of disease included in the ICF
- addition of a description of attractiveness testing to the ICF
- removal of the assertion that subjects are representative
- justification or removal of the age cap at 55 years
- adjusting ICF eligibility criteria to track with the protocol
- clarification of descriptions of recruitment and consent processes
- deletion of subject signature from data collection forms
- harmonization of different discussions of control selection
- clarification of how landing mosquitoes will be removed

One protocol deviation was reported. The protocol called for treating subjects in six pairs; instead subjects were treated in two groups of six. The rationale provided was to simplify moving large numbers of subjects in and out of the testing room. EPA believes that this change could have been anticipated and should have been made by amendment, with prior IRB approval. An unreported deviation involving initiation of subject recruitment before final IRB approval of the ICF also occurred.

On February 18, 2008, EIRB approved the February 8, 2008 protocol and conditionally approved the ICF. On February 18, 2008, the principal investigator communicated with EIRB and was told that recruitment could begin. On February 18, 2008, ICR began calling previous subjects to determine their interest and availability for the March 4, 2008 study. On February 19, 2008, EIRB notified ICR by email of its decisions made on February 18, 2008. On February 20, 2008, ICR revised the ICF and submitted it to EIRB. EIRB approved the revised ICF on February 25, 2008 and notified ICR of its approval on February 26, 2008. On February 26, 2008, ICR mailed copies of the approved ICF to candidates who had expressed interest in participating in the study. The communication with EIRB on February 18, 2008, and calling of subjects occurring on the same date were reported in the June 6, 2008 report from toXcel.

Both EPA and the HSRB expressed concern about the recruiting process in their reviews of ICR protocol A117, and called for its clarification. The protocol description of the recruiting process was revised after the October 2007 HSRB meeting to reflect EPA and HSRB comments. The revised protocol was approved by EIRB on February 18, 2008. The recruiting process initiated by ICR on February 18, 2008, and described in the toXcel submissions dated May 22, 2008 and June 6, 2008, differed in numerous respects from the process described in the revised protocol.

Based on the toXcel submission of June 6, 2008, EIRB reportedly told ICR on February 18, 2008 that “recruitment of study subjects could be initiated since the protocol had been approved.” However, no documentation of the reported communication between the

principal investigator and EIRB personnel on February 18, 2008, has been provided. The June 3, 2008 email from EIRB on this matter does not mention any prior communication on this subject. Neither ICR nor toXcel has reported, nor is there evidence of, any imminent hazard to subjects that could have justified a change to approved research without prior IRB approval.

Based on its review, EPA has concluded that subjects were recruited through a process differing from that prescribed in the protocol, although this deviation from the protocol did not put subjects at increased risk. The subjects saw and signed the ICF only after final IRB approval; therefore, the deviations from the protocol in the recruitment process are unlikely to have seriously compromised the informed and voluntary consent of the subjects, all of whom were experienced subjects in ICR repellent tests.

The applicable standards for this research are 40 CFR §26.1703, prohibiting intentional exposure of pregnant or nursing women, or of children under 18; 40 CFR §26.1705, requiring evidence of substantial compliance with 40 CFR part 26, subparts A-L; 40 CFR §26.1303, requiring documentation of ethical conduct; and FIFRA §12(a)(2)(P), requiring fully informed, freely voluntary participation. The requirements of 40 CFR §26.1125 and §26.1601 for prior review of the protocol by EPA and the HSRB were met. The requirements of 40 CFR §26.1303 and 40 CFR §26.1703 were met.

The evidence that investigators initiated recruitment before final EIRB approval of the consent form suggests that the conduct of the study may not have been in substantial compliance with 40 CFR §26.1705 part 26, subparts A-L. The requirement of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects may have been compromised by initiation of recruitment before obtaining final IRB approval of the ICF.

EPA interprets 40 CFR §26.1111(a)(4) and (5) to mean that research is not approved until both §26.1116 and §26.1117 have been satisfied; however, EPA has learned that OHRP is considering guidance that would allow recruiting to begin when the protocol and ICF have received at least conditional IRB approval, as was true in this case. The initiation of this research before full IRB approval did not endanger subjects, but led to procedural deviations from the protocol which may or may not rise to the level of substantial non-compliance with 40 CFR part 26, subparts A-L.

ICR A117 Charge Questions:

a. Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes of the genus *Culex*?
b. Does available information support a determination that this study was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

Clarifying Questions

Dr. Philpott noted that the supporting information on ethical conduct lists a third product to be tested (towelettes) and asked if this was a mistake. Mr. Carley responded that the protocol calls for testing of two products and two products were tested. Dr. Philpott inquired if EPA has requested and received a telephone script for the recruiting process. Mr. Carley replied that there is a passage in the protocol characterized as a "script" but it is vague and lacks detail. EPA does not know the exact context or content of the recruiting script.

Dr. Menikoff questioned how the change from six pairs of two subjects to two groups of six subjects affected the approval of the protocol. Mr. Carley explained that the change was reasonable, given that it simplified the testing and had no impact on results or ethics. The investigators should have submitted a protocol amendment to make this change because it was possible to anticipate and was not made in response to a hazardous testing situation.

Dr. Menikoff requested a description of the IRB communication with the principal investigator on February 18, 2008. Mr. Carley explained that on June 6, 2008, ICR included a copy of the June 3, 2008 email from IRB to the principal investigator as supporting documentation that recruiting could be initiated before receipt of the final approved ICF. The letter does not specifically mention this situation, in which an unconditional approval of the protocol and conditional approval of the ICF had been received. Dr. Menikoff noted that EIRB did not specifically claim that the events violated its terms and said that it appeared that the first telephone call to potential subjects may have been to check availability and the protocol may not have been mentioned. The call might have been supplemental to what was described in the protocol as the first recruitment call. Mr. Carley commented that EPA does not know the exact content of the call. The protocol indicates that an initial contact will be made to ask subjects if they are interested and available for the study, and then subjects will be informed about the study and the ICF will be described. If subjects agree to participate, the ICF will be sent to them and after receipt is confirmed, ICR calls the subject and reviews the ICF within the next few days. There appears to be insufficient time for this process because of when the approved ICF was sent. A compression of the protocol (fewer steps and fewer contacts with potential subjects) may have occurred. Dr. Menikoff noted that the subjects other than the three who did not receive the ICF were offered a chance to discuss the ICF. The fact that three people did not receive the ICF appears to be a violation. Mr. Carley stated that there were procedural violations, but the substantive steps of the process were in place.

Dr. Prentice commented that ICR began recruiting on February 18, 2008, before final approval of the ICF and inquired about the nature of the revisions to the ICF and whether they were substantive. Mr. Carley explained that there were approximately 15 changes to the ICF, and all but two or three were minor editorial changes. The exceptions were the request by EIRB to insert standard language, including a paragraph that informs subjects about resources on participation in studies. These resources include only links to the main portals to OHRP and the NIH, and seem unlikely to be helpful concerning participation in this type of study. EPA believes that addition of this material is unnecessary and will contact EIRB about this matter. Dr. Prentice asked if there was any documentation of the communication between the principal investigator and EIRB that occurred on February 18, 2008. Mr. Carley responded that EPA had

received only the June 6, 2008 clarification that the ICR staff was "told" they could proceed with recruiting. This email from EIRB is dated June 3, 2008, and does not refer to the prior communication. Mr. Carley added that he had not had a chance to speak with ICR about this issue in detail.

Dr. Prentice remarked that the recruiting calls on February 18, 2008 could indicate use of an unapproved script, but the HSRB lacks the information needed to decide if this is the case. Mr. Carley agreed that ICR's characterization of their recruiting process was highly inadequate. Dr. Krishnan inquired if checking availability is considered part of the recruiting process. Mr. Carley replied that this is part of the process. Dr. Krishnan noted that ICR's reply states that potential subjects signed the ICFs, but does not say when they signed them. Mr. Carley explained that all subjects signed the ICF on March 4, 2008, the day of testing. There was insufficient time for the subjects to sign the forms and mail them back to ICR. A statement in the supplemental materials states that all subjects signed the approved ICF on the morning of March 4, 2008. Dr. Krishnan noted that in ICR's response, they indicate that all subjects agreed to travel to ICR to have their questions answered, and agreed to be prepared to sign the ICF on the day of testing. Mr. Carley clarified that all subjects were invited to travel to ICR to discuss the ICF but none did. All subjects arrived on the morning of testing and discussed the ICF at that time. All the subjects participating in the protocol were experienced subjects who had participated in previous ICR protocols.

Dr. Parkin inquired when EIRB procedures had been previously submitted to EPA. Mr. Carley indicated that EIRB had submitted its procedures to EPA approximately 1 year ago. Dr. Parkin stated that because EPA had received no documentation of EIRB procedures, the Board has no knowledge concerning whether EIRB was following its procedures in review of this protocol.

Public Comments

Dr. Robin G. Todd of ICR, Mr. Niketas Spero of ICR, Dr. Ralph Piedmont of Loyola College, and Mr. Andrew Pechko of Avon Products, Inc., on behalf of ICR

Mr. Niketas Spero (ICR) explained that on February 18, 2008, ICR received a telephone call from EIRB, as is typical when they complete a review. EIRB explained that the protocol was approved and the ICF was conditionally approved. During the call, Ms. Karen Radcliffe (EIRB) was asked if recruiting could begin. She responded that recruiting could begin, but the ICF could not be discussed. Later that day, Mr. Spero began the recruitment process but limited the substance of the telephone calls to potential subjects to asking about interest and availability. March 4, 2008 was chosen as the test date to allow sufficient time to raise the mosquitoes and recruit a sufficient number of subjects. Only subject availability was discussed on the call. When the approved ICF was received on February 26, 2008, Mr. Spero called the available subjects back and discussed the ICF and protocol. At this time, subjects also were offered the opportunity to come to ICR and discuss the ICF in further detail, but all declined this opportunity.

Regarding the deviation of the protocol from six groups of two to two groups of six, this was not considered until the planning meeting on the day before testing. ICR decided it would be easier to test 12 people if there were two dedicated times for exposure in the cage. There was insufficient time to amend the protocol. Mr. Spero acknowledged that the investigators should have considered this approach earlier.

Dr. Fisher inquired why the test date of March 4, 2008, had been chosen. Mr. Spero explained that this was based on the sponsor's need to present its report to EPA. Also, raising mosquitoes needs to begin approximately 2 weeks in advance, and ICR believed all paperwork would be approved by this date. Dr. Fisher asked when ICR had notified EIRB of the change in the number of test groups. Mr. Spero stated that this was noted as a deviation and EIRB was contacted 10 days later. Dr. Fisher requested clarification regarding testing of the towelette product. Mr. Spero explained that ICR evaluated only the aerosol and pump spray. Testing will support the towelette product because the three AIs are the same. Although only two product types were tested, the regulatory requirements for the towelette product also will be met. Mr. Andrew Pechko (Avon Products, Inc.), on behalf of ICR, explained that the DASH30 towelette uses the same liquid formulation that is in the pump spray, so this efficacy test supports the towelette product.

Dr. Fisher asked if ICR had provided its written recruitment script. Mr. Spero explained that ICR did not use a script for this study, but has one for future use that has been approved by EIRB. EIRB approved the vague script described in the protocol. During the first call to subjects (on February 18, 2008), subjects were informed that testing would occur on March 4, 2008, and asked if they were interested and available. If they were, subjects were told that the ICF could not be discussed because it had not yet been approved, but that once it was approved, they would be contacted to discuss the form.

Dr. Krishnan inquired if all subjects had seen the ICF only the day before testing, or if they saw it on an earlier date. Mr. Spero explained that the ICF was approved on February 26, 2008. Subjects were called on that day and the ICF was discussed (in particular, the exclusion criteria and parameters of the study), and it was mailed to subjects the same day. Subjects were called again on February 29, 2008, after they had received the ICF. This second call lasted approximately 5 to 10 minutes and indicated that all participants read the ICF and were comfortable with ICR procedures.

Dr. Philpott asked if subjects received compensation for traveling to ICR to discuss the ICF, if they chose to do so. Mr. Spero responded that there was no compensation for this activity. All subjects declined to come in to discuss the ICF because they had participated in many previous studies. Dr. Philpott inquired about the subjects who did not receive the ICF by mail and whether they had an opportunity to review the ICF before testing began. Mr. Spero explained that the ICF was read over the phone (February 26, 2008) to those who did not receive it in the mail. The test day was scheduled to begin at 6:00 a.m., which provided ample time for subjects to read the ICF and ask questions about it before signing.

Dr. Fisher asked if the boilerplate language that EIRB suggested inserting included any language from the EPA Web site or just OHRP. Mr. Spero answered that it did not include EPA

language. Mr. Carley clarified that there were three insertions of standard language, but no major changes to the ICF.

Board Discussion

Scientific Considerations – ICR A117

Dr. Chambers opened the Board's science discussion of ICR protocol A117. Use of a standard consumer dose of the repellent and counting bites as opposed to landings was previously approved by the HSRB and EPA. She agreed with Mr. Carley that the change to two groups of six participants did not affect the science of the protocol. She concluded that the results were scientifically valid.

Dr. Krishnan agreed with EPA and Dr. Chambers that, given the purpose of the study, the results are acceptable and sound. He noted that there was a typographical error in the table on page 4 referring to product numbers.

Dr. Young agreed that the results were scientifically valid, but she commented further on issues related to mosquito studies in general. She expressed concern about conclusions drawn as a consequence of the study. The hypothesis is that the repellents will offer 8 hours of protection; however, at 3 hours the product failed for one of the subjects; this represents 8 percent of the subjects and is thus a significant finding. She expressed concern about how this would affect the labels of the products.

Dr. Young noted the heavy reliance on the Rutledge and Gupta (1999) meta-analysis paper for the sample design. She stated that the designers of this protocol over-relied on the analysis and that the meta-analysis itself is flawed. This analysis is reasonable to use for rough power calculations, but in the documentation of the protocol there is an assumption that if there are the same number of subjects in the experiment, the same conclusions can be drawn as those described in Rutledge and Gupta. This is untrue. In addition, many of the articles used in the meta-analysis are flawed and the meta-analysis is weighted toward large studies with small means; traditional modeling of means and variance were not used.

Dr. Young also noted problems related to right-censoring of the data. Eleven subjects in this study had no bites at 10 hours, but one person was bitten at 3 hours. If these data are analyzed by Kaplan-Meier analysis, the analysis falls apart when attempts are made to compute the mean because more than 90 percent of the data points are censored. This is problematic for statistical analysis of the data. To base the conclusion of 8 hours ± 2 hours of protection on the Rutledge and Gupta article is seriously flawed. Careful consideration of how to analyze these studies in the future is needed. If the results claim to define a mean, the mean is approximately 8 hours of protection; however, again use of the Kaplan-Meier equation would be flawed. Dr. Fisher asked Dr. Young if she had any recommendations or suggestions for future studies. Dr. Young suggested that there are different models that would be more suitable for this work, but nothing is available in the published literature comparable to the Rutledge and Gupta paper for discussion of study power. Re-analysis of the studies included in the Rutledge and Gupta analysis also might be helpful.

Dr. Fisher noted that this issue continues to arise in Board discussions, but the Board has been unable to recommend useful alternatives. Dr. Carriquiry explained that the main problem is the very small sample size. To resolve this issue, either a larger sample size or longer observation period (perhaps 15 hours to observe product failure) is needed. Dr. Young stated that failure should reach at least 50 percent before the study stops. Dr. Fisher inquired if parametric statistics were appropriate for this sort of study. She added that increasing the observation period to 15 hours was probably unreasonable. Dr. Young remarked that, on average, stating that the product offers 8 hours of protection is reasonable, but this will not include those for whom the product fails early.

Dr. Lebowitz agreed that there was no method for analyzing the data in a way that would be statistically significant. The policy issue in question is what sort of information to include on the product label, given the evidence. He agreed with Dr. Young's frustrations, but noted that while these discussions have arisen before, changes in sample size or length of observation period have not occurred. He stated that, regarding the answer to the scientific charge question, he agreed with Drs. Chambers, Krishnan, and EPA, that the data are sound. How EPA uses the data to inform labeling is a regulatory issue for which the Board is not skilled to provide advice.

Dr. Fisher remarked that the charge states that, from a scientific perspective, in conjunction with other available information, the study established what it hypothesized. She asked if the Board wanted to include a statement that the data are sufficient for estimating a range of response times, but not an average. Labeling decisions are beyond the purview of the Board.

Dr. Young stated that it was not possible to obtain an unbiased estimate of the mean or derive the standard deviation using these data. Dr. Brimijoin stated that he agreed with the consensus that the study has adequate scientific validity and answers the charge question. He agreed with Dr. Lebowitz that the science was as good as or better than that in the typical insect repellent study. The Board can offer any suggestions it chooses to EPA to guide them on regulatory decisions, but these are outside the purview of the Board. He expressed sympathy with the frustrated statisticians regarding the study design, power, and interpretation. The raw data from these studies are available and the Board can revisit them to try to determine a more appropriate analytical approach. Dr. Brimijoin stated that these data are consistent with current "best practices" for insect repellent studies. Two changes are needed to improve the studies. Insect repellent investigators must rethink their study designs in light of the proposed statistical analyses. The statistical community also should consider which measurements and endpoints would be appropriate for these studies. He commented on survival analyses for treatments for fatal conditions in which the endpoint is 100 percent death; however, such studies do not need to achieve a 100 percent death rate for detection of the effects of treatment to be possible. Unlike most cancer chemotherapeutics, insect repellents work well, approaching a 100-percent success rate over times that are reasonable for testing. It would not be practical to test repellents in a research setting for much longer than 8 to 10 hours. He disagreed with Dr. Young's assessment that because all data are censored except for one data point that the calculated mean is meaningless. He noted that if 99 out of 100 subjects were protected for more than 10 hours but one was protected for only 2 hours, the protection range would not be 2 to 200 hours; nearly

everyone in this example received complete protection. Dr. Brimijoin stated that he was not prepared to offer EPA advice on regulatory issues or ways to treat the data, but the data presented at this meeting are meaningful for protection; a mix of common sense and mathematics should be applied to assessment of the data.

Dr. Carriquiry countered that, given the data from this study, she would expect there to be 8 to 10 failures in a study of 100 subjects. If investigators wish to observe a rare event, they must increase their sample size. She stated that she would not oppose the Board's conclusion that the study is acceptable, but it was problematic that the data did not allow estimation of an unbiased mean. Dr. Brimijoin commented that instead of increasing sample size, another option would be to increase mosquito pressure to perhaps 10 times that used in these experiments; another alternative would be to decrease the amount of repellent used. Dr. Young remarked that it would be possible to estimate the proportion of users who would receive less than 8 hours of protection if the sample size was larger; current data would estimate a failure rate of 8 percent. Dr. Fisher noted that the typical sample size of 10 was acceptable in part to minimize risk; however, laboratory experiments do not carry the same degree of risk as field studies.

Dr. Lebowitz interjected that the Board was making assumptions about what might or might not happen, given changes to the protocol. The Board can only carefully consider and discuss the information it is given. The Board also does not have any adequate recommendations for changes for future designs. He recommended that EPA consider the issues raised at this meeting and request that the HSRB discuss them further, if the Agency desires. Dr. Chambers stated that EPA needs some consistent guidelines to help the Board focus on scientific issues, rather than study design and regulatory matters. Dr. Fisher stated that in her opinion, the data were useful for assessing efficacy, but not for determining a mean or standard deviation; however, the study was well-executed and questions about limiting the uses of the data have arisen in the past.

Dr. Ralph Piedmont (Loyola College), on behalf of ICR, stated that he agreed that the Rutledge and Gupta study is inadequate and flawed, but it represents the current state of knowledge regarding repellent studies. In designing the study, the goal was to be conservative; the Rutledge and Gupta study was the only report available for guidance on power. With a sample size of 12, it is possible to have a mean estimate of protection of up to 10 hours ± 2 hours. Given the current state of the science, these data indicate that the product works for 8 hours ± 2 hours. He agreed that use of the actual mean is not supported because it is biased and 95 percent confidence intervals cannot be justified; however, the use of 12 subjects was scientifically justified given the existing knowledge. Dr. Lebowitz agreed that the Rutledge and Gupta paper was insufficient, with the Board's assessment of the statistics of the study, and with the conclusion that the Board does not believe the evidence is sufficient to agree with conclusions about means and standard deviations drawn using the results of the study.

Dr. Fisher summarized that the Board consensus was that the study was conducted using best practices following an approved protocol; however, the Board does not believe that the data can be used to develop a mean and standard deviation. EPA will decide if this is possible and how they will use the data. She also agreed that the investigators had used current best practices to design their study.

Ethical Considerations – ICR A117

Before the discussion began, Dr. Fisher reminded the Board of its consensus regarding protocol deviations:

- Any study executed prior to IRB approval of the ICF and the protocol, or changed in ways that were not approved by the IRB will be judged by the Board as failing to meet the applicable requirements of §40 CFR part 26, subpart K.
- If EPA submits to the Board for review a completed protocol with scientific deviations from the original protocol reviewed by the Board, the EPA review of the completed protocol should provide the Board with EPA's opinion regarding why the deviation did not meet the requirement for re-review and why the protocol still meets the applicable regulations.

Dr. Philpott opened the ethics discussion of ICR protocol A117 by stating that the study had been adequately designed to minimize risks. The relevant risks included participating in research conducted under hot and humid conditions, adverse events associated with use of the products, exposure to insect bites, and exposure to vector-born illnesses. The risks associated with the hot and humid research environment are minimized by limiting participants to 5-minute intervals in this environment. The risks associated with use of the product are minimized because the AI (picaridin) is registered and widely used, there are adequate stopping rules, and people with skin reactions to the products are excluded from the research. Bites are expected, but risks from exposure to bites are minimized by excluding participants with a history of severe reactions to insect bites and by close monitoring and providing medical care. The risk of vector-borne disease is minimized because the research uses laboratory-raised mosquitoes that have not had a previous blood meal. The study investigators also contacted participants after the research was complete to ask about any adverse events.

Key issues of concern related to this protocol include the protocol deviation and consent issues. Protocol deviations that appear planned, but are not reviewed by an IRB arise frequently. In this case, the change from testing six pairs of two subjects to testing two groups of six subjects was a planned violation because the investigators discussed this change the day before testing began. It was possible for the investigators to call EIRB and obtain some sort of approval for the change, but they did not do so. The Board has explicitly explained that federal regulations state that the only allowable protocol violations are those that occur to protect the subjects. In addition, ICR did not contact EIRB about this violation until 10 days after the research took place, and did not include EIRB's response in the documentation of the research.

Recruitment took place prior to revisions and final approval of the ICF, although the Board has been told that ICR received verbal approval; however, on page 92 of the report there is a written statement from the Chair of the IRB stating that a study may not commence any further research activity, including scheduling, until a stamped ICF is received. This statement is dated August 2007. ICR has clearly violated IRB rules regarding recruitment. Because of this, Dr. Philpott stated that it was his opinion that the protocol is not in compliance with 40 CFR part 26 and he recommended that EPA cannot use the results of this study.

Dr. Menikoff stated that he disagreed, to some extent, with Dr. Philpott's conclusions. He noted that he had objected to the Board's consensus on protocol violations previously, and believed other Board members did as well, because the statement does not include a consideration of intent. A discussion of intent occurred, but statements related to intent were eliminated from the consensus. The Board is asked to consider if a protocol is in "substantial" compliance; the Board consensus statement appears to demand "perfect" compliance. Given Mr. Carley's thorough review, the Board may not be able to approve any research if it demands perfect compliance. Dr. Fish added that this particular study was conducted before the Board created its statement and thus the consensus statement should not be applied as rigorously. Dr. Menikoff stated that in terms of consent and recruitment, differences in facts exist. The written IRB materials differ from statements that the IRB emailed or said to the investigators. This matter can be investigated. If EIRB informed the investigators by telephone call that recruitment could begin despite the lack of a finalized ICF, then the study is not in substantial noncompliance. Calling people who previously agreed to be contacted about participation in these studies to ask if they are available on a certain date should be acceptable. Dr. Menikoff added that reading the ICF over the telephone to those who did not receive the ICF in the mail also is not necessarily a violation.

Regarding the change in protocol design, this also may not rise to the level of substantial noncompliance, given that it did not increase subject risk; however, because the deviation was planned, Dr. Menikoff stated he was more likely to agree with Dr. Philpott on this matter.

Dr. Fisher agreed that if EIRB gave permission to begin scheduling activities, the sponsor is in compliance. The HSRB has questioned IRB activities in the past; if this IRB did not behave in a legitimate manner, the HSRB should make a strong statement to this effect. Dr. Menikoff agreed, but added that this may be complicated by apparent changes in recruitment policies taking place through OHRP and the IRBs.

Dr. Chadwick stated that the Board is continually disappointed by investigators who do not follow their own protocols; however, it may be unreasonable to expect 100-percent compliance. Many investigators view protocols as guidelines, while regulatory entities and the HSRB appear to view them more as "written in stone." The Board needs to recognize that two types of changes to protocols occur: deviations, which affect neither science nor risk, and violations, which affect subject protection, or science, or both. In this case, a deviation occurred. It is true that the investigators did not follow the written protocol, but this did not result in subject harm or damages to scientific validity, which the Board is charged with reviewing. The Board must carefully consider wording; the HSRB believes that recruitment means enrollment, but a member of an IRB may believe that recruitment includes asking about availability. Dr. Chadwick cautioned sponsors that other agencies have the policy of "if it is not written, it did not happen." Documentation is important for regulatory agencies, and justifying an action on verbal advice is a bad choice. Dr. Chadwick concluded that in his opinion, ICR protocol A117 is ethically acceptable.

Dr. Fish agreed with Dr. Chadwick. Ethicists may consider recruitment to be part of the informed consent process because most recruitment processes provide information about the

study to the potential subjects, and it is important that this information is approved by an IRB. In this case, however, recruitment involved knowledgeable subjects and information on this study was not provided to them, except to tell them that the study would take place on March 4, 2008. If this is the only information provided and no specifics of the study were discussed before approval of the ICF was obtained from EIRB, recruitment is in compliance with the intent of the regulations.

Dr. Prentice agreed with Drs. Chadwick, Fish, and Menikoff. He noted that the risk-benefit balance is highly important to the IRB's approval of a study. In this case, the primary risk is exposure to mosquito bites and the discomfort associated with such bites. There is no direct benefit to the subject, only to society for registration of an alternative efficacious repellent against mosquitoes that harbor WNV. If the Board declines to accept the data, the risk-benefit balance has been negated for every subject, which is a serious matter. Dr. Prentice agreed that any unethical or significant deviations should not be ignored, but in this case, the deviations are minor. The deviations indicate that the system is working; a deviation occurs, is reported, and a mitigation plan is put in place. He disagreed with Dr. Philpott's opinion that the results should not be used by EPA.

Dr. Philpott agreed with the points raised by his fellow Board members, but expressed concern that, based on the written materials reviewed by the Board, the protocol is not in compliance with ethics regulations. He was concerned that the Board might be setting a precedent by making value judgments. In light of the Board consensus on protocol deviations, Dr. Philpott concluded that he could not recommend EPA use of the data.

Dr. Lebowitz noted that for the National Incident Management System, written or oral commands are acceptable, except in unusual cases where the regulations require a written command. He agreed with Dr. Chadwick regarding the difference between deviations and violations. If the Board can conclude that neither the scientific nor ethical standards were violated, deviations should be accepted as "human error." The Board should not be so rigid that it cannot operate within this system.

Dr. Prentice noted that slide 32 of EPA's review stated "led to procedural deviations from the protocol which may be deemed to rise to the level of substantial non-compliance with subparts A through L of 40 CFR part 26," but the charge asks if the "available information supports a determination that this study was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26." "Substantial compliance" indicates that a level of compliance less than 100 percent would be acceptable. This protocol was conducted in sufficient compliance that the Board does not have concerns about the science or blatant violations of the regulations. Dr. Prentice stated that the language in the charge question is limiting and should be revisited by EPA.

Mr. Jordan explained that the charge question language mirrors the standard language in EPA's regulations. EPA may rely on a completed study if there is evidence to indicate it substantially comports with the regulations in subpart L. EPA does not require 100-percent compliance; the drafters of the regulations (Mr. Carley and Mr. Jordan) wanted to include the notion of acceptability. EPA recognizes that demanding 100-percent compliance would mean

that a single deviation would result in rejection of all protocols and would result in large numbers of repeated studies; EPA does not intend for such a situation to arise. The regulations ask the Board to make value judgments. Concerning the Board consensus on protocol deviations, Mr. Jordan agreed with the first point that an investigator who does not follow the approved protocol fails to meet subpart K of the regulations. But subpart Q, which asks if the study is acceptable for EPA, indicates that "substantial compliance" will suffice. The deviations EPA notes are deviations that investigators should not make knowingly, but EPA recognizes that such deviations do happen and when they do, they should be reported and corrected. Mr. Jordan stated the HSRB's statement was acceptable if it does not affect the "substantial compliance" standard of subpart Q.

Dr. Philpott commented that according to the EIRB written statement, recruitment could not be started until the approved ICF was received. Mr. Jordan explained that the August 2, 2007 approval was part of the IRB review cycle preceding Board review in October 2007. Before the information came to the Board, a final protocol with approval of the IRB was received. The protocol was then revised and the telephone calls between the sponsor and EIRB occurred in a different cycle of IRB review. Dr. Philpott noted that the language in the letter was "boilerplate" and that the HSRB has not had access to IRB procedural language because it is Confidential Business Information. The Board cannot assume that EIRB changed its language in the absence of written information that indicates that beginning the recruitment process before receipt of the approved ICF was acceptable. Dr. Philpott stated that he was reluctant to approve this study, and strongly recommended that no study should be commenced in any way without final approval and a stamped ICF.

Dr. Fisher interjected that the Board must consider two issues that relate to recruitment and relate to the change in study design. She agreed that the changes did not result in increased risk to participants; the Board should consider whether this constitutes "substantial" noncompliance. The Board must take at face value the claim from the sponsor (and the email dated June 3, 2008) that ICR was allowed to begin recruitment before receipt of the finalized ICF. The Board may disagree with EIRB's decision, but given that the decision may be based on new directives from OHRP, this decision may not be a violation of EIRB procedures.

Dr. Philpott acknowledged that his was the minority opinion. He would accept the consensus to approve the study, but wanted to include a strong statement that written confirmation of changes is needed and verbal information is unacceptable. Dr. Menikoff agreed that EPA should verify changes in EIRB policies. Dr. Fisher noted that sponsors should not accept IRB procedures that may place them in jeopardy of having a study disapproved.

Dr. Fisher remarked that the change in the study design was a deviation that did not increase risk to subjects, but the fact that ICR waited 10 days to report this deviation to EIRB is troubling. The sponsors should have immediately emailed EIRB about this change. The study was in substantial compliance, but in the future the Board may judge more harshly these non-documented changes. Dr. Philpott added that the Board must explicitly state that it will not accept hearsay as evidence, but instead will require clear written documentation of changes and permissions; the investigators and EPA must ensure that such information is made available to

the Board. Dr. Chadwick countered that a rule saying in effect, "If it is not written, it does not exist," would be too stringent. Dr. Brimijoin agreed.

Dr. Fisher stated that the majority of the Board agreed that the protocol was in substantial compliance with the relevant regulations. The Board also should detail the non-substantial, but important deviations that occurred. Drs. Chadwick, Fish, Menikoff, and Philpott will draft this statement.

Dr. Fisher recommended changing the Board's consensus statement on protocol deviations. The Board always has the option of recommending rejection or acceptance of a protocol. The language of this statement needs to be clarified, especially with respect to the issue of "substantial" compliance. Dr. Chadwick agreed with Mr. Jordan that the deviations in this protocol represented violations of the regulation, but it is more difficult to decide if the protocol is in substantial non-compliance. The Board's statement should incorporate subpart Q; compliance, or lack thereof, with subpart K may be clear, but the Board will need to consider more thoroughly if a protocol is not in compliance with subpart Q. Dr. Menikoff stated that he did not object to such changes, but was not convinced it would greatly influence Board review of protocols. The Board is rarely asked to judge if a protocol is in 100-percent compliance. Dr. Fisher stated that the Board's report for this meeting would include amendment of the Board's statement on protocol deviations, incorporating consideration of compliance with subpart Q.

Concluding Remarks

Mr. Jordan provided a preview of the October 2008 HSRB Meeting agenda. The Board will review at least three completed insect repellent studies conducted in accord with previously reviewed protocols. EPA also is analyzing literature on potassium triiodide, involving intentional dosing in human subjects to evaluate toxicities. EPA may wish to use this information for risk assessment activities, and if so, the Board will review these studies. The Board also will review additional protocols from the AEATF and AHETF. AEATF will present a scenario to measure exposure from aerosol products. AHETF is currently choosing protocols to present for review.

Dr. Fisher asked if there is existing pre-rule data that the Board must review in advance of evaluation of open-cab scenarios planned by AHETF. Mr. Jordan explained that because these studies were initiated before the rule was in place and did not report a toxic endpoint, Board review is not needed. However, EPA will work to provide the Board with data and conclusions of this data in a summary form.

Dr. Lewis thanked Board members for their efforts and his EPA colleagues for their preparation and presentations given at this meeting. He stated that the next HSRB meeting will take place October 21-24, 2008, and will be announced in the *Federal Register*. The Board will release its April 2008 meeting report, prepare its report for this meeting and send drafts to Drs. Fisher and Lewis within the next 2 weeks. Dr. Lewis 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

Celia B. Fisher, Ph.D.
Marie Ward Doty Professor of Psychology
Director, Center for Ethics Education
Fordham University
Bronx, NY

Vice Chair

William S. Brimijoin, Ph.D. **
Chair and Professor
Molecular Pharmacology and Experimental Therapeutics
Mayo Foundation
Rochester, MN

Members

Alicia Carriquiry, Ph.D.
Professor
Department of Statistics
Iowa State University
Ames, IA

Gary L. Chadwick, PharmD, MPH, CIP
Associate Provost
Director, Office for Human Subjects Protection
University of Rochester
Rochester, NY

Janice Chambers, Ph.D., DABT
William L. Giles Distinguished Professor
Director, Center for Environmental Health Sciences
College of Veterinary Medicine
Mississippi State University
Mississippi State, MS

Richard Fenske, Ph.D., MPH **
Professor
Department of Environmental and Occupational Health Sciences
University of Washington
Seattle, WA

Susan S. Fish, PharmD, MPH
Professor, Biostatistics & Epidemiology
Boston University School of Public Health
Co-Director, MA in Clinical Investigation
Boston University School of Medicine
Boston, MA

Suzanne C. Fitzpatrick, Ph.D., DABT
Senior Science Policy Analyst
Office of the Commissioner
Office of Science and Health Coordination
U.S. Food and Drug Administration
Rockville, MD

Dallas E. Johnson, Ph.D.
Professor Emeritus
Department of Statistics
Kansas State University
Manhattan, KS

Kannan Krishnan, Ph.D.
Professor
Département de santé environnementale et santé au travail
Faculté de médicine
Université de Montréal
Montréal, QC, Canada

Michael D. Lebowitz, Ph.D., FCCP
Retired Professor of Public Health (Epidemiology) and Medicine
Research Professor of Medicine
University of Arizona
Tucson, AZ

Lois D. Lehman-Mckeeman, Ph.D. *
Distinguished Research Fellow, Discovery Toxicology
Bristol-Myers Squibb Company
Princeton, NJ

Jerry A. Menikoff, M.D.
Director, Office of Human Subjects Research
Office of the Director
National Institutes of Health
Bethesda, MD

Rebecca Parkin Ph.D., MPH
Associate Dean for Research and Public Health Practice
School of Public Health and Health Services
The George Washington University
Washington, DC

Sean Philpott, Ph.D., M.Bioethics
Science and Ethics Director
Global Campaign for Microbicides
Program for Appropriate Technology in Health
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

Richard R. Sharp, Ph.D. *
Director of Bioethics Research
Department of Bioethics
Cleveland Clinic
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
** Attended via telephone

Attachment B
Federal Register Notice Announcing Meeting

Human Studies Review Board; Notice of Public Meeting

[Federal Register: May 30, 2008 (Volume 73, Number 105)]
[Notices]
[Page 31117-31118]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr30my08-49]

ENVIRONMENTAL PROTECTION AGENCY
[EPA–HQ–ORD–2008–0035; FRL–8573–9]

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 June 24-June 25, 2008 from 8:30 a.m. to approximately 5:30 p.m., Eastern Time (However, the second day may not be needed).

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-2008-0355, 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. Eastern Standard Time (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-2008-0355. 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 address: 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 May 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 your 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-2008-0355 in the subject line on the first page of your request.

a. Oral comments. Requests to present oral comments will be accepted up to June 17, 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, June 17, 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, Eastern Time, June 17, 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

1. 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 Sec. 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.

2. Topics for Discussion

For this meeting of the HSRB, the Board will present for HSRB review scientific and ethical issues surrounding:

- The Governing Document, the compilation of Standard Operating Procedures, the scenario design document, and two associated protocols from the Agricultural Handlers Exposure Task Force (AHETF), which collectively describe research to monitor exposure of subjects who apply an agricultural pesticide using airblast equipment in closed cabs.
- A report from a completed laboratory study to evaluate the efficacy in repelling mosquitoes of the genus Culex of two registered products containing picaridin.

The Board may also be reviewing its draft April 9-10, 2008 meeting report for subsequent Board approval. In addition, the HSRB may also discuss planning for future HSRB meetings.

3. 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 CONTACT**.

Dated: May 23, 2008.
George Gray,
EPA Science Advisor.
[FR Doc. E8-12144 Filed 5-29-08; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
JUNE 24-25, 2008 *
PUBLIC MEETING

Tuesday, June 24, 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-2008-0355

8:30 AM **Convene Meeting and Identification of Board Members** – Celia Fisher, Ph.D. (HSRB Chair)
8:40 AM **Welcome** – Elizabeth Lee Hofmann, Ph.D. (Deputy Director, Office of the Science Advisor [OSA])
8:50 AM **Opening Remarks** – Debbie Edwards, Ph.D. (Director, Office of Pesticide Programs [OPP], EPA)
9:00 AM **Meeting Administrative Procedures** – Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, OSA, EPA)
9:10 AM **EPA Follow-up on Pesticide Specific HSRB Recommendations** – Mr. William Jordan (OPP, EPA)

AHETF Pesticide Handler Protocols: Closed-Cab Airblast Scenario
9:30 AM **Overview** – Mr. William Jordan (OPP, EPA)
9:45 AM **Science and Ethics Assessment of AHETF Protocol** – Mr. Jeffrey Evans (OPP, EPA), Mr. Matthew Crowley (OPP, EPA) and Mr. John Carley (OPP, EPA)
10:30 AM **Break**
10:45 AM **Science and Ethics Assessment of AHETF Protocol (continued)** – Mr. Jeffrey Evans (OPP, EPA), Mr. Matthew Crowley (OPP, EPA) and Mr. John Carley (OPP, EPA)
11:30 AM **Public Comments**
12:00 PM **Lunch**
1:00 PM **Board Discussion**

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

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

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

3:30 PM **Break**

Completed ICR Mosquito Repellent Efficacy Study A117

3:45 AM **EPA Science and Ethics Assessment of Completed ICR Mosquito Repellent Efficacy Study A117** – Mr. Mark Suarez (OPP, EPA) and Mr. John Carley (OPP, EPA)

4:45 PM **Public Comments**

5:15 PM **Adjournment** – Celia Fisher, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
JUNE 24-25, 2008 *
PUBLIC MEETING

Wednesday, June 25, 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 ICR Mosquito Repellent Efficacy Study A117
8:45 AM **Board Discussion**

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

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

Review of April 9-10, 2008 HSRB Meeting Report
9:45 AM **Review Process** – Celia Fisher, Ph.D. (HSRB Chair)
9:55 AM **Public Comments**
10:15 AM **Break**
10:30 AM **Board Discussion and Decision on Report** – Celia Fisher, Ph.D. (HSRB Chair)
12:30 PM **Concluding Remarks** – Mr. William Jordan (OPP, EPA)
12:35 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.