June 9, 2008

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
April 9-10, 2008 Public Meeting
Docket Number: EPA-HQ-ORD-2008-0033
HSRB Web Site: http://www.epa.gov/osa/hsrb/

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

Dates and Times:	Wednesday, April 9, 2008, 8:30 AM – 5:45 PM Thursday, April 10, 2008, 8:30 AM – 3:30 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.
	Board Members:	Alicia Carriquiry, Ph.D. Gary L. Chadwick, PharmD, MPH, CIP Janice Chambers, Ph.D., D.A.B.T. Richard Fenske, Ph.D., MPH Susan S. Fish, PharmD, MPH Suzanne C. Fitzpatrick, Ph.D., D.A.B.T. Dallas E. Johnson, Ph.D. Kannan Krishnan, Ph.D. Michael D. Lebowitz, Ph.D., FCCP Lois D. Lehman-Mckeeman, Ph.D. Jerry A. Menikoff, M.D. Rebecca Parkin, Ph.D., MPH Sean Philpott, Ph.D. Richard R. Sharp, Ph.D. Linda J. Young, Ph.D.
	Consultant:	KyungMann Kim, 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 April 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) and Office of Research and Development (ORD) in planning and preparing for the meeting. She welcomed a new Board member, Dr. Linda Young, a professor in the Department of Statistics, Institute of Food and Agricultural Sciences at the University of Florida.

Welcoming Remarks

Dr. George Gray (Science Advisor, EPA) welcomed Board members and conveyed EPA's appreciation for their work in preparing for and participating in the HSRB meetings. He also thanked EPA staff for their efforts in preparing for the meeting. He noted that the Board's efforts over the past 2 years in reviewing studies involving human subjects have led to the strengthening of both the scientific design and ethical conduct of these studies.

Dr. Gray noted that Dr. KyungMann Kim's appointment to the Board has ended. He acknowledged Dr. Kim's valuable advice on statistical and study design matters and presented him with a plaque in recognition of his outstanding service as a founding member of the HSRB. He acknowledged the Board's new member, Dr. Young, and thanked Drs. Jan Chambers, Suzanne Fitzpatrick, Michael Lebowitz, Lois Lehman-Mckeeman, Jerry Menikoff, and Sean Philpott, who have agreed to be reappointed to the Board.

Dr. Gray described the topics for this meeting. In October 2007, the Board reviewed the draft document titled Scientific and Ethical Approaches for Observational Exposure Studies (SEAOES), presented by EPA's Office of Research and Development's (ORD's) National Exposure Research Laboratory (NERL). Dr. Gray stated that during the meeting the Board would be presented with an update on this project including the Agency's response to Board comments. He stated that the Board also would review wipe and mop protocols from the Antimicrobial Exposure Assessment Task Force (AEATF) and review one proposed and two completed insect repellency studies.

Opening Remarks

Dr. Debbie Edwards (Director, OPP, EPA) welcomed participants and Board members to the ninth HSRB meeting. She thanked Dr. Kim for his advice and appreciated his interest to serve as a consultant for review of the proposed pesticide handler research at this week's meeting. She thanked the Board for their work in preparing for these meetings and particularly for the advice on scientific and ethical matters that they have provided for the pesticide handler research. She thanked Drs. Gray and Lewis, and other EPA colleagues for their efforts in preparing for and managing these meetings.

The proposed pesticide handler research is designed to characterize human exposure to pesticides during the mixing, loading, and application of pesticides. EPA is seeking new, improved handler data to improve its assessments of exposure and inform risk assessment activities related to pesticide handling. The HSRB has played a major role in the design of the handler studies. The Board's comments at the October 2007 HSRB meeting have improved the clarity, scope, documentation of need, and standard operating procedures (SOPs) described in the governing documents for this research. The Board also identified areas for improvement in research methodology, resulting in more rigorous measurement of exposure and an increased number of monitoring events. Based on Board advice, the documents have provided increasing emphasis on subject safety and recruitment issues. The Board also provided valuable advice concerning the design of sampling strategies. Dr. Edwards stated that at this meeting Mr. William Jordan (OPP, EPA) would describe EPA decisions related to Board recommendations for the proposed pesticide handler research governing documents.

At this meeting, the Board will assess two protocols designed to measure exposure incurred when applying antimicrobial compounds by mopping or by two different wiping techniques. These protocols should produce scientifically sound and useful data, with appropriate attention to ethics. The Board also will review two completed mosquito repellent protocols and one new protocol designed to test repellency against stable flies. EPA believes that both the completed and proposed studies meet applicable standards.

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 also works with the appropriate officials to ensure that all applicable ethics regulations are satisfied. Each Board member has filed a standard government financial disclosure form that has been reviewed by Dr. Lewis and the OSA Deputy Ethics Officer in consultation with EPA's Office of General Counsel to ensure that all ethics disclosure requirements have been met. Dr. Lewis reminded participants that meeting times would be approximate and that public comments would be limited to 5 minutes.

Dr. Lewis welcomed Dr. Young as a new member to the Board. He also thanked Dr. Kim for his work in strengthening proposed protocols in the areas of statistical design and analysis and human research protection. As a consultant, Dr. Kim will provide specialized information to the Board but will not be involved in the deliberative process.

Update on Revisions to the EPA Document "Scientific and Ethical Approaches for Observational Exposure Studies"

Dr. Roy Fortmann (ORD, EPA) complimented the Board on their comprehensive review of this document. Their review prompted improvements and clarifications in the document, which has been revised in response to both the Board comments and comments received from the public.

Based on HSRB review, EPA revised several specific parts of the document. The document now includes expanded explanations of observational studies and how they are used; clarification of the distinction between observational exposure studies and intentional exposure research; and examples to help distinguish between these types of studies. The appendix also contains additional examples of these studies and definitions of applicable terms. The Board noted that the document originally had a strong focus on the ethics of observational studies, and suggested an increased emphasis on the science and inter-relationship between science and ethics, because a study that is not scientifically sound cannot be ethical. EPA revised the document to place a stronger emphasis on the integration of scientific and ethical approaches in study design of human subjects research protocols and on the need to integrate scientific and ethical review.

EPA revised and expanded Section 2 (Elements to be Considered in Study Conceptualization and Planning) to better justify observational studies involving human subjects, from both scientific and ethical perspectives. The word "scoping" has been eliminated from the document and replaced with references to conceptualization of planning. The document includes increased discussion of sample size, which should provide sufficient power yet still remain ethical; examples of sampling designs also have been included. Issues related to determining sample size and ensuring the representativeness of a sample have been clarified. The section on subject vulnerability also has been enhanced, and issues surrounding fair subject selection have been addressed.

Regarding interactions with community and stakeholders, the definitions of these two groups have been clarified and discussion of such interactions expanded. The document contains additional information on approaches to community involvement and community engagement principles, and greater emphasis on the importance of developing and maintaining two-way community interactions.

Issues pertaining to communication were addressed in several sections of the document. The importance of acknowledging language and cultural differences, and the unique characteristics of individual communities (other than socioeconomic status) has been emphasized. The document also includes expanded discussion of the importance of communicating at different levels and using "plain language" in oral and written communications whenever possible. Further explanation of the purpose and use of Certificates of Confidentiality has been added. Discussion of the importance of monitoring scientific and ethical issues during a study, including collateral observations, has been expanded. The document also includes further information on mandated reporting and training of study staff to avoid potential hazards when in the field. Additional discussion of payments to participants was incorporated.

Appendix A was revised to include additional discussion of terminology (such as observational versus intentional exposure), descriptions of 28 NERL studies (type of study design, sample size, study questions, etc.), and descriptions of types of samples collected and types of data analyses performed. The 28 NERL studies range from small pilot studies to large

research projects conducted by a team. These studies also provide examples of a number of different types of study designs.

EPA plans to publish this document as an EPA report; final editing and formatting is underway and the anticipated release date is May 2008. The document will be available on EPA/ORD's Web site. A draft version is currently in use by NERL researchers for planning upcoming studies and the final document will be used in NERL's researcher training programs. NERL expects this document to be useful both for NERL and extramural researchers.

EPA Follow-up on Pesticide-Specific HSRB Recommendations

Mr. Jordan reviewed EPA follow-up on HSRB recommendations from the October 2007 HSRB meeting. At that meeting, the Board provided recommendations on the SEAOES document, which has been revised accordingly.

The Board also addressed EPA's request to use data from a previously conducted study (Black et al.) as a point of departure to estimate a safe level of acute and chronic exposure to sodium azide. The Board concluded that the study did not contain sufficient information for this activity. The Board did not find evidence that the conduct of the study was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted, but because of deficiencies in the science identified by the Board, Mr. Jordan stated that EPA will not rely on this study for human health risk assessment activities for sodium azide.

The Board also reviewed two completed insect repellent field studies from Carroll-Loye Biological Research. The HSRB concluded that the study SCI-001 was not sufficiently scientifically sound to be used to assess the repellent efficacy of the tested formulation against mosquitoes. In addition, the Board found that the research failed to meet the applicable requirements of 40 Code of Federal Regulations (CFR) 26, subparts K and L, due to failure of the study investigator to obtain Institutional Review Board (IRB) approval for substitution of an unregistered compound for the study compound. Based on the Board's review, EPA has not relied on this data. Dr. Scott Carroll (Carroll-Loye Biological Research) has repeated the study and submitted reports for review at this meeting. The Board reviewed an additional protocol from Dr. Carroll (WPC-001) and found this study does meet the applicable scientific and ethical standards; EPA will rely on this data for registration decisions.

The Board also reviewed two proposed protocols from Dr. Carroll, SPC-001 and SPC-002. The HSRB concluded that if problems noted by the Board were addressed, the studies would be sufficiently sound to generate data adequate for the intended purposes and would meet the applicable requirements of 40 CFR 26, subparts K and L. Dr. Carroll revised and executed SPC-002; execution of SPC-001 is scheduled. Reports from both studies likely will be reviewed by the HSRB at its October 2008 meeting.

The Board reviewed the insect repellent protocol ICR A117. This protocol was designed to test the efficacy of insect repellents against *Culex* species mosquitoes. The Board concluded that if the study was revised consistent with EPA's recommendations and the Board's suggestions, the study should yield valid data to determine the efficacy of these products against

Culex and should meet the applicable requirements of 40 CFR 26, subparts K and L. The protocol has been revised and executed; the HSRB is expected to review the report at its June 2008 meeting.

Sampling Strategies in Proposed Pesticide Handler Research

Mr. Jordan provided an overview of issues related to the proposed handler exposure research. EPA has discussed the proposed handler research with groups including the California Department of Pesticide Regulation (DPR) and Canada's Pest Management Regulatory Agency, as well as other Agency offices, to ensure that the data gathered in the course of this research provides usable information for EPA risk assessment activities. The HSRB also has reviewed this project at three previous HSRB meetings. Significant issues requiring additional attention include clearer, more thorough justification of this project, better science to produce stronger data, and better ethical conduct to ensure compliance with applicable regulations. Specific areas of discussion included determining the adequacy of hand rinses and face and neck wipes to collect residues, the need for biomonitoring, and the value of repeated measures of intra-individual variability. Statistical justification of the numbers of clusters and monitoring events (MEs) also was discussed, as well as design of the sampling strategy (random versus purposive diversity sampling [PDS]). The HSRB also suggested that EPA revise its heat stress management and recruitment and enrollment procedures. Clearer documentation that includes a better description of the research's scope and the need for new data also was generated. The task force SOPs, which outline the overall administration, report generation, and quality assurance (QA) oversight, have been revised. A rationale for not collecting data on intra-individual variability also has been developed.

The existing regulatory framework for data generation includes the Registrants' Burden of Proof, 40 CFR part 158 Data Requirements, Test Guidelines (A/M/L Exposure), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) §3(c)(2)(B) and Data Call-Ins, and the Paperwork Reduction Act and Office of Management and Budget (OMB) review. Pesticide manufacturing companies must provide EPA with information to demonstrate that their products are in compliance with standards established by Congress, which require that pesticides have no unreasonable effects on the environment and leave no harmful residues in foods, among other characteristics. These companies spend large sums of money on research to generate the data to satisfy these regulations. As part of 40 CFR part 158, EPA requires information to estimate exposure to workers when mixing, loading, or handling these chemicals. The regulatory framework also includes test guidelines concerning how to conduct this research to generate scientifically sound information that supports the applicable regulations. If EPA determines that the data is insufficient to meet its requirements, it can request further information under FIFRA.

Data call-ins involve informing a company that new research is needed to meet the regulatory requirements for a given pesticide. If this research is not performed, EPA can suspend the company's right to sell that pesticide. Although this can be an effective means for obtaining the necessary data, it is not a simple process. Before requiring a company to collect additional data, the data call-in must satisfy the OMB review process and requirements of the

Paperwork Reduction Act. This requires documenting the cost of the process and ensuring that EPA does not request more information than the regulations require.

Under the policy framework for decisions to require additional data, EPA must determine if it can meet its regulatory obligations to judge the safety of a pesticide by using existing data. If EPA determines it requires additional or better data, the Agency must determine how this data can be obtained, how the study should be designed and conducted, whether chemical-specific data is needed or generic data will suffice, and whether the work should be performed by a contracting company, EPA's ORD, or another federal agency, such as the Department of Agriculture.

Questions that EPA must answer to meet its regulatory responsibilities related to handler exposure include the amount of pesticide exposure people could receive by different routes when handling a pesticide (in this case, "handle" includes mixing, loading, or applying the pesticide), the factors that most affect exposure levels, how exposure varies from scenario to scenario, and whether, within a scenario, exposure is essentially proportional to the amount of active ingredient handled (AaiH).

Mr. Jordan described key terms related to this research. A handler is a person (worker or consumer) who mixes, loads, or applies a pesticide. A scenario is a set of related activities, pesticide formulations, equipment, and engineering controls. Clusters or sites are particular locations and times at which exposure data are collected. The Monitoring Unit or ME refers to the set of data describing the exposure of a single subject carrying out a specified handler activity at a particular place on a particular day. The governing document includes a general description of the overall research plan for gathering handler exposure data for multiple scenarios. Scenario design refers to a discussion of the sample design and other scientific and ethical aspects of research specific to a particular scenario. The study or protocol is a detailed proposal of the testing methodology to be employed at one or more specific monitoring sites. The handler database is an array of data on multiple handler exposure scenarios.

Each monitoring program is comprised of many specific scenarios. The AEATF defines the scenarios it plans to monitor in Appendix A of their governing document. At present, there are 14 scenarios for application of anti-microbial products. The behavior of handlers, formulation of products used, and equipment used for application will be described for each scenario. Topics, such as statistical design and recruitment procedures that are generally described in the governing document, are refined and made specific to each scenario. Each scenario thus represents a distinct research project for which the AEATF will: a) develop a comprehensive sampling plan designed to address the primary and secondary objectives, b) conduct one or more studies to collect MEs from different locations, and c) analyze the exposure data from the collected MEs to evaluate whether the objectives were met.

Data for each scenario will be collected in clusters. A cluster is a set of related handler-days from the same scenario and is considered to be a higher-level sampling unit for the purposes of statistical design and analysis. A cluster can be viewed as all possible MEs available at a particular location and time. In the AEATF program, scenarios will typically include three clusters each. Within each cluster, subject-specific sets of monitoring data (MEs) will be

collected. ME refers to a complete set of monitoring data for one subject on one monitoring day. In each cluster eight subjects will be recruited to ensure that all six MEs can be collected, even if one or two of them withdraw or fail to qualify. A typical AEATF scenario design consists of three clusters, each with six MEs.

The proposed "mop" field study calls for collecting data sets for MEs 1 through 6 in Cluster 1, MEs 7-12 in Cluster 2, and MEs 13-18 in Cluster 3. Because this scenario involves indoor use, the clusters can be in different buildings in the same geographic area, and all three clusters and all 18 MEs called for by the scenario design can be monitored in the same field study. Once all ME data is collected in a study, the data is assembled, analyzed, and placed in the Pesticide Handler Exposure Database (PHED); the data then will be analyzed and reported for use by EPA in exposure assessment. It may be necessary to combine data from different scenarios to characterize exposure associated with use patterns. For example, exposure to anti-microbial compounds through mopping can occur while diluting the compound, mopping the floor, and disposing of the mop water. Mopping and disposing will be analyzed in the same scenario, but a separate scenario will assess exposure from diluting the compound. Both these scenarios will be combined to analyze total exposure.

There are several key assumptions implicit in estimating handler exposure. The first is that exposure is largely independent of the chemical composition of a formulation for products that have a low vapor pressure. Other assumptions are that the key variables defined by the scenario are handler activity, formulation type, equipment, and engineering controls. In addition, EPA has assumed that exposure data can be used generically across each scenario, and that, within a scenario, exposure is proportional to the AaiH and that factors other than AaiH may also affect exposure.

Two commonly used databases for exposure assessment activities include PHED and the Chemical Manufacturers Association (CMA) database. The PHED contains information primarily on agricultural exposure, while CMA has information on exposure to anti-microbial products. Although EPA has used data from both these databases for a number of years, both have limitations. New pesticide application methods are not covered by the data in the databases. The data quality in these databases is inconsistent, often below current standards. The CMA database also has issues with coverage; the database has limited useful data due in part to the large number of "non-detects," or exposure below the level of detection, given available detection techniques. It also is difficult to combine data provided by different studies because the studies were designed to evaluate individual products. Each protocol also varies in its use of dosimeters, hand wash, and rinsing collection strategies. Limited QA and quality control (QC) was performed for these protocols, and there are also problems with calibration. The data in these databases does, however, tend to support the assumption that exposure is generally proportional to AaiH. Because of these issues, the Scientific Advisory Panel (SAP) and the HSRB have agreed with EPA that new studies could improve the basis for estimating handler exposures.

The new handler exposure studies are expected to cover all major handler exposure scenarios; use consistent, reliable measurement methods; measure typical activities of population(s) of concern; and meet contemporary ethical standards. Considerations affecting the

design of sampling strategies for these studies include the value of the data developed, the generalizability of the data, the degree of knowledge concerning variability, feasibility, and practicability, and both the dollar and time costs of data development. EPA's goal is to generate generalizable data for a representative population and use this data to understand variability across the population with respect to amounts of exposure.

The choice of sampling design for these experiments led to many discussions between EPA and the AEATF and Agricultural Handlers Exposure Assessment Task Force (AHETF). The types of sampling considered by EPA included pure probability-based random sampling and pure purposive sampling. Random sampling minimizes the potential for bias and supports statistically-based inferences about a target population, including quantification of variance and uncertainty. However, this design may not be practicable for pesticide handler research and is expensive in terms of both cost and time. Pure purposive diversity sampling can ensure inclusion of certain independent variables, supporting hypothesis development and assessment; limits inferences about the target population; and is least expensive in both dollars and time; however, variance and uncertainty cannot be quantified for the target population and each purposive choice introduces potential for bias. Based on evaluation of both these strategies, a hybrid sampling design was developed. This design consists of a purposive design that incorporates random elements wherever feasible. It marginally reduces the potential for bias, as compared to pure purposive sampling and provides a somewhat better basis for inferences than pure PDS, but not as good as random sampling. It is intermediate in cost in dollars and time between PDS and random sampling. Based on discussions at the June 2007 HSRB meeting, EPA understood that the Board supported a hybrid sampling design.

In 2006-2007, the AEATF and AHETF put forth proposals for voluntary exposure monitoring programs that use rigorous, standardized methods. These programs would cover a negotiated range of rigorously defined scenarios, with sampling using a PDS design. EPA considered accepting these proposals and the PDS design strategy based on a number of issues. EPA desires better handler exposure data, which will improve its ability to assess potential exposure. Without the new data, EPA would have to rely on data contained within PHED and the CMA databases, which have many limitations. The task forces indicated that their willingness to perform this research voluntarily depended on whether EPA would insist on a pure random sampling design; the task forces did not believe that a random sampling approach would be either practical or affordable for this research. If EPA insists on the use of random sampling and the task forces do not volunteer to perform this research, EPA must initiate the data call-in procedure, which requires meeting OMB and Paperwork Reduction Act stipulations, resulting in a process that would last several years with no guarantee that EPA's call for research using a random sampling design would be supported.

EPA did not accept the task forces' original proposals. Instead, EPA informed the task forces in October 2007 that it would accept data reflecting a hybrid sampling strategy that incorporates random elements into a purposive overall design whenever feasible, provided that the task forces describe in detail their sampling design for each scenario, incorporate random elements when possible, and document their rationale for using a particular approach, including all decisions regarding the feasibility of randomization of specific elements in the design. The task forces agreed to this strategy. AEATF's response to these decisions regarding sampling

designs is evident in the revisions to their governing document, and in the specific designs and protocols for the mop and wipe scenarios discussed at this meeting.

EPA will perform QA/QC review on all task force data to ensure that the observations and measurements are valid. EPA will derive Unit Exposure values by compiling all of the data relevant to a particular scenario, typically from multiple field studies, and calculating the mean Unit Exposure value (AaiH) based on dermal and inhalation exposure rates and associated confidence limits for the scenario data set; EPA may also estimate an upper-end percentile for the data set. EPA will then select high-end and mid-range values of AaiH for use in estimating handler exposure for various pesticide activities and exposure durations. To assess assumptions of proportionality, EPA will analyze the data set for each scenario, using the techniques presented to the SAP in January 2007 to quantify the relationship between exposure and AaiH, to assess the assumption that exposure is proportional to AaiH, and to explore possible hypotheses for other variables that might significantly affect exposure.

EPA has carefully considered the issues associated with designing sampling strategies for collecting handler exposure data, taking into account a variety of scientific, regulatory, and economic factors. From this analysis, EPA has concluded that a hybrid sampling strategy incorporating random elements whenever feasible is likely to generate data adequate to meet EPA's regulatory needs. EPA will review the sampling strategy proposed for each handler exposure scenario to ensure it meets EPA's criteria.

HSRB Workgroup Report on Sampling Strategies in Proposed Pesticide Handler Research

Dr. Fisher described discussions between EPA and the HSRB workgroup on issues surrounding sampling strategies for the proposed pesticide handler research. The goal of these efforts were to clarify the details and rationale for these studies, the details of the sampling design, how EPA will use the data, how the HSRB will evaluate the protocols, and determine if clear criteria can be established that will permit expedited review of these protocols.

Members of the workgroup were Drs. Fisher, Chambers, Fenske, Johnson, Kim, Lebowitz, and Lehman-McKeeman. The workgroup held a teleconference on January 17, 2008. The goals of this teleconference were to clarify the details and rationale for the AEATF and AHETF for their respective pesticide handler exposure monitoring programs, discuss the protocol sampling designs for both task forces, develop a better understanding of how EPA plans to use data from these studies, and develop and recommend to the full HSRB criteria for fair and consistent assessment of the protocols presented to the Board. The Board reviewed materials provide by EPA in preparation for the April 2008 meeting, discussed EPA/OPP planning procedures and summaries with Mr. Jordan, and held discussion of criteria for protocol review.

At the teleconference, EPA explained that it has determined that generation of handler exposure data using a PDS design is acceptable, in light of the importance of EPA's need for new handler exposure data, because the task forces and EPA have already spent time and resources on this project, a random sampling design is associated with unacceptable delays and costs, and the data generated using this strategy will meet EPA's informational needs. EPA intends to use the AHETF and AEATF data to generate conservative exposure estimates,

determine whether exposure is proportional to the AaiH, and if proportionality is not supported, to find other variables that may influence exposure to develop hypotheses for future studies.

The workgroup agreed with EPA's assessment of the costs for randomized sampling. Although EPA did not have an estimate of the costs of a randomized sampling design, costs for such a design are expected to be higher because of higher costs to identify and recruit participants. EPA acknowledged that difficulty in identifying potential participants might be the same for a PDS study as for a randomized sampling design. EPA's decision to accept the PDS design also was influenced by the timing of data generation. Random sampling could delay submission by a year or longer and would increase the testing costs such that testing would be unaffordable and the program could be ended or monitoring reduced.

EPA acknowledged that an estimate of uncertainty for high-end values cannot be determined with the PDS design; however, EPA clarified that its decision to accept PDS means that sponsors are nonetheless expected to incorporate random elements into their designs whenever feasible. Sampling requirements for the PDS protocols call for each scenario-specific design to specify the sampling frame. EPA will evaluate the frame for representativeness and bias. Scenario-specific justification of sampling strategies should include full documentation of methods and rationale for selection of locale, study site, crop, and equipment; relevant agricultural statistics and production figures; identification of contributing professional contacts; incorporation of random elements in sampling design; and cost estimates for alternatives.

EPA and the members of the workgroup agreed that the current PHED data set has limitations and that better data should be used for future assessments. Both groups also agreed that a randomized sampling strategy would allow statistical analyses that could not be performed using PDS. The workgroup and EPA agreed that an expedited review process is desirable, but that the process can be developed only after the HSRB has experience with evaluating exemplary protocols.

The workgroup made several recommendations. Regarding submission criteria for sampling designs, the workgroup first acknowledged that random sampling designs were preferred. They recommended that each protocol be individually assessed for the feasibility of random assignment. When random sampling is not possible, a PDS protocol must have a well-developed sampling frame based on knowledge of the range of ingredient concentrations and distribution methods used in the field. When random sampling is not possible, each protocol should be individually assessed for the adequacy of the PDS sampling frame. Regarding criteria for additional design and analysis plans, the protocols should include a description of the rationale and methods for data collection; description of efforts made to incorporate random elements in each scenario-specific design; description, rationale, and justification for the selection of clusters, and what will be done with each cluster and why, for both random and PDS designs; explanation of how data will be analyzed and interpreted by the task forces; and an explanation of the data anticipated to be analyzed by EPA and how it will be useful for EPA risk assessment activities.

To streamline the meeting process, the workgroup proposed that EPA oral presentations at Board meetings should provide a brief abstract on the nature and purpose of the study;

discussion of EPA's evaluation of the study's scientific validity; description of how the data collected might be used by EPA; critique of whether information derived from the specific design and data analysis plan will be useful for EPA decision-making; identification of aspects of the design that might raise human subjects concerns; and avoidance of the details of either scientific or human subjects protections that were previously provided in materials submitted to the Board.

The workgroup clarified that the HSRB makes recommendations to EPA and not directly to the sponsors or investigators; therefore, EPA—not the sponsor—should present the protocol and EPA's critique and conclusions to the HSRB. Sponsors may provide their perspectives and may be asked for clarification during the public comment periods. During Board discussions, the Board may ask available sponsors to answer any clarifying questions that were not fully addressed in the materials provided by EPA. Sponsors also should have the opportunity to inform EPA when they believe the Board has insufficient information for its decision-making responsibilities. In such cases, the Chair, together with EPA and the DFO, may ask the sponsors to present this information to the Board.

Board Discussion

Dr. Susan Fish commended EPA and the workgroup on their efforts. She suggested that, under the topic of how the data will be analyzed and used for risk assessment by EPA, a discussion of the limitations of the utility of the data be included. This will be affected by the degree of randomness, particularly in terms of generalizability and variability, which will be different for each protocol. Mr. Jordan agreed that limitations will be obvious at the level of the protocol (sampling strategies will be the same at the scenario level), and that discussions of these limitations should be part of EPA's review. Once the protocol is executed, other limitations may become evident. Dr. Fisher stated that sponsors should discuss limitations of the data when they submit their protocols, and should also acknowledge these and any other limitations after the protocol has been performed.

Dr. Gary Chadwick commented that it is unfortunate that OMB procedures may place limitations on EPA's ability to gather data that will inform its mission to protect the public. He acknowledged that there were benefits to OMB procedures, but that these procedures also sometimes present serious roadblocks. He suggested that EPA work with OMB to try to streamline some of these procedures. Dr. Chadwick added that the hybrid design discussed here is not exactly a combination of PDS and random sampling. The hybrid design is not significantly better than PDS because such a design is still biased. The hybrid sampling design is essentially PDS with techniques to help control for bias.

Dr. Chambers commented on the workgroup's suggestion to abbreviate discussions of the specifics of the protocols. FACA rules for public meetings will determine what must be presented. She requested clarification of material that must be presented at the meeting and also what must be described in the written reports. Mr. Jordan answered that EPA's goals when it develops presentations for these meetings is to bring to the Board's attention matters requiring focus. The presentations could be shortened, but EPA also must maintain transparency and demonstrate that it has thoroughly and appropriately assessed the protocols submitted for review.

Because these are public meetings, sufficient material must be presented to ensure that the audience is informed enough to appreciate Board discussions and concerns. He said that EPA is working to streamline the meeting process. Dr. Fisher suggested that more time be spent on discussions, critiques, and rationales for Board decisions, both at the public meeting and in the Board reports, rather than re-iterating what is made available to the Board and on the HSRB Web site. She suggested that EPA could prepare a one-page abstract that could contain a description of the study, including the science and ethics, which would permit the Board to spend more time on its critiques. Dr. Lewis explained that FACA does not specifically mandate what must be presented. EPA provides background to help the Board understand the material so that it can respond to the charge questions, and also to allow the public to understand the material and discussions. The Board reports are presented to provide the HSRB's responses to the EPA charge questions and also provide the opportunity for the public to review Board discussions and rationales.

Dr. Johnson asked whether EPA had made any decisions regarding the number of clusters and number of MEs per cluster. Mr. Jordan explained that the clustering of data points is best addressed at the scenario level; Mr. John Carley (OPP, EPA) and Mr. David Miller (OPP, EPA) will provide a discussion of this for the mop and wipe scenarios. EPA has established guidelines that call for 15 MEs per scenario level. Organization for Economic Co-operation and Development (OECD) guidelines for agricultural handler exposure studies call for less than 15 MEs per scenario level. Dr. Fisher said that the Board's concerns about this matter relate to how the sample size in each site allows for analysis of variability in the population and how this will inform Board review.

AEATF Governing Document

<u>EPA Science and Ethics Assessment of Revisions to AEATF's Governing Document</u>

The objective of the AEATF is to generate handler exposure monitoring studies to estimate and characterize exposure distributions for a number of occupational/industrial and consumer exposure scenarios involving antimicrobial products. The data will be used to populate a database and also will be used for risk assessment activities by EPA and others. The AEATF Governing Document describes the technical and ethical aspects of the program and also frames scenario designs and field study protocols for proposed monitoring studies. Specific changes were made to Section 16 (volume 5, pp. 58-66) of the document. This section, formerly entitled "AEATF-II Program Design," is now entitled "Monitoring Event Selection" and has been substantially revised. This section provides the generalized discussion of the statistical design for the AEATF-II monitoring program. Appendix E, "Designing Monitoring Events to Predict Future Exposure," also has been substantially revised. Other changes of less significance have been made but were not described in detail during the meeting.

Mr. Miller described antimicrobial testing scenarios. The basic element of a scenario is a handler day, which corresponds to a particular worker and scenario that is performed. The target population is the universe of future handler days. EPA has regulatory interest in predicting exposure under an identified specific set of future handler-day conditions. Specifically, EPA

wishes to be able to characterize exposures resulting from future use of an antimicrobial product in a defined-use scenario, with a quantified estimate of AaiH.

Mr. Miller explained the general approach to sampling for AEATF protocols. The basic element is the ME, each of which is a data set fully describing one handler-day of scenario-specific activity chosen, simulated, or constructed to represent expected future conditions. Each ME will include dermal and inhalation exposure potential for a single subject over a time span representing a typical workday. Thus, the set of MEs for each scenario should characterize both typical and high-end exposures expected in a single workday. The measured exposures from each scenario-specific set of MEs will be used to represent the future handler-day exposures to antimicrobial compounds. The goal of this strategy is to gather MEs for each scenario that will reflect current and projected antimicrobial handling practices in North America, emphasizing different subjects (such as handling techniques and anthropometric parameters, such as body size) and diversity in conditions (such as area and types of buildings) either known or assumed to be related to exposure. A national sampling frame is not possible and a national survey is not feasible. Based on EPA and HSRB discussions and recommendations, the AEATF will employ a hybrid sampling approach, which comprises an overall purposive design that incorporates random elements whenever feasible.

Diversity selection employed by these protocols attempts to maximize the regulatory utility of the set of MEs collected. This selection technique should improve the chance that different MEs differ with respect to factors known or assumed to affect exposure. It should also help to achieve, given small sample sizes, diversity in the conditions that are expected to influence exposure. This approach should increase the likelihood that the range of conditions in the future handler-day population expected to impact exposure is reflected in the 'pseudo-sample' of MEs monitored.

Given this sampling strategy, the predicted exposures obtained from the set of MEs should adequately characterize the "middle" and "larger" values of the future handler-day distribution, where "middle" refers to average or typical exposures, and "larger" refers to high-end or extreme one-time events. It is acknowledged that a set of constructed MEs cannot be a random (probability-based) sample from a distribution of future handler-day conditions, and it is thus impossible to estimate complete population-based distribution or associated means or percentiles. However, regulatory interest is most often focused on the "middle" and "larger" values/aspects of this distribution.

EPA expects the data gathered from these protocols to be useful for risk assessment activities; however, EPA acknowledges that the resulting distribution is not representative of exposures to a target population. The distribution is believed to adequately characterize for regulatory purposes the "middle" and "larger" values in a target population, because PDS incorporates random elements, marginally reducing potential for bias, and a diversity selection sample will tend to over-represent extreme exposures and under-represent exposures "in the middle." The estimate of central tendency is better than estimates of the tails, and, to the extent that the diversifying conditions are associated with exposure, diversity selection will tend to under-predict lower percentiles and over-predict upper percentiles.

EPA Review of AEATF-II Mop and Wipe Scenarios

Background, Context, and Sampling Design

Mr. Carley presented background information on the AEATF-II Mop and Wipe Scenarios. AEATF-II submitted IRB-approved scenario designs and study protocols for mop and wipe exposure studies on February 25, 2008. EPA's science and ethics reviews of March 10, 2008, were based on the February 25, 2008 proposals, and informed by the associated AEATF-II Governing Document and SOPs. AEATF responded to EPA's review on April 2, 2008, and its responses were noted where appropriate. Because these proposals for research involve intentional exposure of human subjects, with the intent to submit the resulting data to EPA under FIFRA, 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) are applicable. The February 25, 2008 submissions contained all the documentation elements required by 40 CFR §26.1125, and although some refinement is needed to address EPA's comments on both science and ethics, EPA believes these proposals are ready for HSRB review. These are the first scenario-specific sampling designs for handler exposure studies to be reviewed by the HSRB, the first task force responses to EPA's November 2007 decision to accept purposive sampling with random elements, and are also the first fully realized, IRB-approved protocols from AEATF-II to be reviewed by the HSRB.

Many elements in the two mop and wipe proposals are the same. For example, monitoring for the mop scenario and the two wipe scenarios will be conducted in the same buildings, at roughly the same time. A single process, executed only once, will be used to select the buildings, to identify cooperating employers to post recruiting flyers, and to recruit and enroll subjects. In addition, the analytical phases of the studies are essentially identical.

Mr. Carley described sample size and selection for the AEATF mop scenario and the trigger spray-and-wipe and ready-to-use (RTU) wipe scenarios. The AEATF rationale for 3x6 sampling (3 clusters per scenario, 6 MEs per cluster) is essentially unchanged since June 2007, but now includes acknowledgements that the assumed "reference model" of random clustered sampling is a tool useful in estimating an appropriate sample size, but the use of this tool is not an assertion that the sample is randomly selected, or that statistical inferences can be drawn from the results. This rationale assumes that exposure normalized for AaiH is log normally distributed, with Geometric Standard Deviation (GSD), and that the within-cluster correlation of log normalized exposure is the interclass correlation coefficient (ICC). The benchmark accuracy target states that estimates of arithmetic mean and 95th percentile of normalized exposure are accurate within 3-fold 95 percent of the time.

To determine the expected variation, specifically relevant CMA studies (mop or wipe) were identified to provide a crude estimate, but the sample size of each study is very small. This estimate can be improved by considering additional data from CMA and PHED for similarly repetitive indoor tasks where individual behavior is likely to be the main source of variation. The differences in variability among the four appropriate studies were not statistically significant. Using dermal data only from these four studies, the common GSD of exposure was 2.86. There are no data to support an independent estimate of ICC for these AEATF studies. The

AHETF has estimated the ICC for agricultural handler exposure research to be 0.3. Because less site-to-site variation is expected in the AEATF indoor studies than in agricultural settings, it is likely that the ICC for these AEATF studies will not exceed 0.3 and could be much lower.

Performing a number of Monte Carlo simulations with different assumed values for GSD and ICC and different numbers of clusters and MEs found that the most efficient way to achieve a benchmark accuracy target with a GSD of 2.86 and ICC of 0.3 is with 3 clusters of 6 MEs. The benchmark accuracy target can be exceeded with 3 clusters of 6 MEs if the ICC is less than 0.3, which is likely. Because the unit cost per ME is high, this also was considered in the analysis. The simulations provided models calling for a larger sample size, but the 3x6 model was deemed the most efficient.

Mr. Carley described caveats to use of this model. The 3-fold-accuracy objective is specified in terms of the reference random sampling distribution. This reference model has the same 2-stage nesting structure as the actual sampling approach, but the reference model assumes simple random sampling at each stage. The reference model does not—and cannot—incorporate the hybrid combination of purposive and random diversity sampling actually used.

EPA has determined that this method is reasonable and knows of no other way to estimate sample size for research using PDS. The model incorporating 3 clusters of 6 MEs each exceeds the minimum sample sizes called for in EPA and OECD guidelines. Adding clusters could impede data collection for additional scenarios; however, EPA acknowledged that more clusters might be needed if location is likely to have a significant effect on the variability of exposure; for mopping floors and wiping surfaces, a cluster effect by location is not likely. If the benchmark accuracy target is not met, the protocols note that additional data collection and/or higher estimates of exposure will be considered.

If EPA determines that additional research on “cluster effects” is needed, EPA would be willing to support efforts or grants for this type of research for the long term; however, a shift toward more clusters and fewer scenarios would unacceptably compromise EPA progress on registration review of antimicrobial products, and would prevent registrants from responding in a timely manner to the reregistration data requirements already imposed. In addition, specific chemicals requiring a more thorough review can be reviewed on a case-by-case basis.

In response to a question from Dr. Philpott regarding determination of the benchmark accuracy target, Mr. Carley explained that the calculated value of the 95th percentile of the mean has to be within 3-fold of the true value. Dr. Kim added that the metric EPA has chosen as a measure of accuracy is legitimate. The ratio of the 95th percentile of the distribution to the true 95th percentile provides confidence that the upper level of 3 is maintained. Dr. Young asked if use of the assumption of a log normal distribution in the simulations was correct. Mr. Carley responded that this assumption was correct and added that Dr. Larry Holden (Silken and Associates), who performed this analysis, would be available to answer questions during the Board discussion period. Dr. Kim said that designation of 3 clusters and 6 MEs per clusters was determined using certain assumptions. The current protocols uses a different sampling frame because the sites are picked as a stratified sample rather than a random sample. This affects justification of the 3x6 model.

Mr. Carley described the sampling design for the mop and wipe scenarios. Each of the three clusters represents a different type of building. There are 6 MEs for each cluster. Data from each cluster feeds into the scenario in the database. The mop protocol consists of 2 independent scenarios. In one, workers will use a trigger spray and wipe procedure to apply the antimicrobial product; in the other they will use RTU wipes impregnated with the antimicrobial product. This study will involve 2 sets of 18 MEs. The clusters, which are the sites at which the research will be conducted, will be the same, both for the two wipe scenarios, and for the mop study/scenario. The processes for recruiting and enrolling the subjects also will be the same.

The mop scenario involves mop-based application of a label-specified, end-use formulation containing an antimicrobial chemical. The scenario includes mopping floors with a string mop, using a bucket with a wringer, and disposing of the dirty mop-bucket solution. The scenario does not include handling the concentrated antimicrobial product or mixing the concentrate with water to make the mop-bucket solution. The wipe scenarios involve wipe-based application of a label-specified end-use formulation containing an antimicrobial chemical. The two distinct wipe scenarios are the trigger pump spray-and-wipe scenario and the RTU wipe scenario. The scenarios do not include use of an aerosol spray and wipe technique or a dip and wipe technique. The scenarios also do not include handling the concentrate or mixing the concentrate with water to make the spray solution, or disposal of used solution.

Sample selection began with initial purposive choices. Fresno County, California, was chosen as the site of this research; indoor mopping and wiping tasks likely do not vary geographically and a single location for the research is convenient, efficient, and economical. Vacant commercial buildings were chosen because they provide large surface areas for mopping and wiping, have fewer distractions, and offer greater control over the test conditions. The chosen buildings were of different types, resulting in stratified selection of buildings rather than equivalent clusters tested on different dates. Professional janitors were selected for the research to ensure exposures are of sufficient length to obtain usable data. Also, data to show the time spent performing these tasks by professionals are available. Similar data for consumers shows that exposure periods are so brief that they would likely produce undetectable exposures. There will be no repeated measures of within-subject variability.

Site selection was performed by categorizing all vacant properties in Fresno County as office, retail, or meeting space. The lists of properties were randomized and properties were screened in random order against criteria including availability for a 1-month rental; functional heating, ventilating, and air conditioning (HVAC) and electric systems; at least 10,000-square feet in area with appropriate surface materials; and did not require cleaning or maintenance before use. The first qualifying property in each category was selected as a research site. This process will be performed only once for both the mop and wipe scenarios, and will result in identification of three buildings, one in each category. At EPA's request, AEATF plans to add a further criterion requiring an appropriate disposal point for dirty mop water, such as a mop sink or floor drain convenient to the area where mopping will occur.

Purposive variation of task duration was employed to ensure tasks of differing duration would occur, because exposure varies based on task duration and subject-specific behavior. All

task durations are greater than or equal to 30 minutes to ensure detectable residues. Maximum task durations were consistent with the International Sanitary Supply Association (ISSA) survey data. Six pre-defined task durations were established for each site. For mopping, the task durations will range from 30 to 90 minutes, with 10-minute intervals. For wiping, tasks durations will range from 30 to 120 minutes, with15-minute intervals. The duration ranges for consumer use exposure, as determined by the Antimicrobial Exposure Joint Venture, will be covered by this range of task durations.

Subjects will be selected by identifying cooperating janitorial service providers, and compiling a list of service providers in Fresno County using telephone directories, information from the Chamber of Commerce, and word of mouth. The list of service providers will then be randomized and contacted in random order to determine their willingness to post recruiting flyers using standard telephone scripts. The task forces worked to minimize the influence of employers on participation. This procedure for selecting subjects will exclude all non-professional janitor wipers and moppers. The AEATF believes this is acceptable because professional janitors are likely to have higher levels of exposure. Professional janitors whose employers chose not to participate in this research also will be excluded. These exclusions are unlikely to compromise the utility of the data.

AEATF staff will meet with service providers who are willing to post flyers and provide them with the flyers and sample consent documents. They will provide an explanation and demonstration of the monitoring equipment and methods. AEATF staff will emphasize the importance of maintaining neutrality concerning participation by their employees, to minimize the potential for undue influence.

Interested workers will call task force investigators directly in response to flyers posted at their workplaces. The names of interested workers will be added to a list, which then will be randomized. Interested workers will be called in for interviews based on the order of the randomized list. Qualified, consenting workers will be enrolled and then assigned randomly to a site and task duration. No subject will be used more than once, thus, no within-subject repeated measures will be taken.

The elements of purposive choice are the choice of region (Fresno County), use of vacant buildings, use of professional janitors with task-specific experience employed by janitorial services firms, predefined task durations to ensure variation in exposure, and the decision to use no subject more than once, which eliminates the possibility of within-subject repeated variations. The random elements of these protocols include the sequence of screening and selecting vacant buildings, which will be random within each of three categories of vacant buildings. The sequence of approaching janitorial service providers also will be random, as well as the call-back sequence of interested candidates and assignment of enrolled subjects to a site and task duration.

EPA has determined that AEATF has met its provisos by providing a detailed description of sampling designs for each scenario, incorporating random elements whenever feasible, and documenting a rationale for using a particular approach, including all decisions regarding the feasibility of randomization of specific elements in the design.

EPA Science Assessment of AEATF Mop and Wipe Protocols

Mr. Tim Leighton (OPP, EPA) presented EPA's science assessment of the AEATF mop and wipe protocols. Data from all three clusters will feed one scenario in the PHED. Once a scenario is complete, the data can be used by EPA for risk assessment activities. The objectives of these studies are to develop more accurate information on worker exposures to antimicrobials to support exposure assessments for mopping and wiping applications; to satisfy a condition of continued registration imposed by EPA's Reregistration Eligibility Decision (RED) documents; and to support pending and new registrations for various antimicrobial products.

For the mopping study, 18 subjects will be monitored. There are 3 clusters (or sites) and 6 subjects (plus 2 alternates) will be present at each site. If the data gathered under the 3x6 model does not achieve predefined accuracy goals, more data can be collected. Currently, there is no existing data that is adequate to substitute for any of the proposed new MEs.

The test material is SANI-CARE Lemon Quat (EPA Reg. No. 47371-131-559). Active ingredients are 2.54 percent didecyl dimethyl ammonium chloride (DDAC) and 1.69 percent n-Alkyl dimethyl benzyl ammonium chloride (ADBAC). The product will be diluted 1:64 for use by participants, to give active ingredient concentrations of 0.0397 percent DDAC and 0.0264 percent ADBAC. The participants will handle only the dilute material.

The dermal No Observed Adverse Effect Level (NOAEL) for DDAC reported in the EPA RED documents is 1,000 milligram (mg) or kilogram (kg) per day at 0.13 percent active ingredient (AI) (highest dose tested). Neither systemic effects nor dermal irritation have been observed. The proposed use of DDAC in a dilute solution (yielding an AI concentration of 0.04 percent) is below the NOAEL. The DDAC inhalation NOAEL reported in the EPA RED is 10 mg/kg/day, based on an oral study. Because of low vapor pressure, inhalation exposure from mopping is expected to be low. The dermal NOAEL for ADBAC reported in EPA RED is 20 mg/kg/day (333 microgram per square centimeter ($\mu g/cm^2$) for dermal irritation; there is no dermal toxicity data available for low concentrations. No systematic effects have been observed. The margin of exposure (MOE) for dermal irritation is approximately 2,400. The ADBAC inhalation NOAEL reported in EPA RED is 3 mg/kg/day based on an oral study. Again, inhalation exposure from mopping is expected to be low because of low vapor pressure.

The mop study has both a field phase and an analytical phase. The field phase includes both scripted and unscripted elements. The scripted elements of the field phase include location (3 vacant buildings in Fresno County), equipment (string mop and bucket), test material (1:64 Lemon Quat in water), task duration (30 to 90 minutes), a 10-minute rest period every 30 minutes, and use of a fresh mop bucket every 15 minutes. The 8 enrolled subjects at each site are ordered randomly and the last 2 on the list serve as alternates. The 6 pre-defined mopping task durations are 30 to 40 minutes, 40 to 50 minutes, 50 to 60 minutes, 60 to 70 minutes, 70 to 80 minutes, and 80 to 90 minutes. The first subject is assigned the longest task duration and subsequent subjects are assigned to the longest remaining unfilled mopping task duration; if the first subject is unable to complete the task for the assigned duration, subsequent subjects will be asked to mop for that duration until that task duration has been completed.

Unscripted elements in the field phase include the manner in which the participants mop; they will be told to use their usual practice. The subjects will mop 2,000- to 6,000-square feet of floor as they normally would. The participants' application methods, wringing methods, and thoroughness of wringing will vary. They may ask for a fresh bucket of mop solution more often than every 15 minutes and also may request a rest more often than every 30 minutes. After mopping is complete, participants will dispose of all buckets of dirty mop water as they normally would.

The collected samples (dosimeters, hand/face washes, air samplers) will be shipped to and analyzed at the laboratory. Method validation will be performed and QA/QC evaluations conducted. Losses can be corrected by using field recovery samples. Analysis of travel recovery and storage stability also will be performed, as will analysis of possible breakthrough.

Measurements taken during the field phase include air temperature and relative humidity, location in the buildings, building design and materials, characteristics of the HVAC system, the amount of material applied, the area mopped, and observations (video and photographic) of the participants' activities. These observations will include a description of how the participants disposed of the used mop solution.

Dermal residues will be collected using whole body dosimeters. Inner dosimeters ("long-johns") will provide an estimate of dermal exposure. Outer dosimeters (consisting of normal work clothing, complying with requirements for personal protective equipment) will provide an estimate of the protection provided by a single layer of clothing. Socks will be analyzed for residue to determine foot exposure, which will be measured because there is potential exposure of the feet while mopping. Hand-washing to collect residues will take place every 30 minutes and face and/or neck wipes will be taken at the end of the task.

Inhalation exposure will be analyzed by collecting respirable residues using a sampling cartridge in the breathing zone. The sampling cartridges consist of OSV tubes with glass filters backed by XAD sorbent. Particle size will not be measured; instead, all residues will be assumed to be respirable. Storage stability of DDAC-fortified matrices will be tested and the analytical method will be validated.

EPA has noted some deficiencies to this protocol. More specific information is needed on how and where the used mop-bucket solution is disposed of, to ensure that the activity is representative of typical disposal events. AEATF provided additional information on this matter in an April 2, 2008 letter. The efficiency of residue removal of the hand-wash method also needed to be addressed, using the same methods proposed for use in the study itself. In its April 2, 2008 letter, AEATF reported plans to rely on an appropriate existing study. EPA found this study to be in compliance with applicable exposure monitoring guidelines, namely, EPA Series 875 Group A - Applicator Monitoring Test Guidelines, OECD Applicator Guidelines, and Good Laboratory Practices (GLPs) (40 CFR part 160). If EPA's comments are addressed, this protocol is likely to yield scientifically reliable information, satisfying the applicable criteria from the framework recommended by the Board. The study would produce important information that cannot be obtained except by research with human subjects, has a clear scientific objective, and the study design should produce adequate data to achieve the objective.

EPA Science Assessment of AEATF Wipe Scenarios and Protocol

Dr. Cassi Walls (OPP, EPA) presented EPA's science assessment of the AEATF wipe scenarios and protocol. This study involves 3 sets of clusters, each of which have 6 MEs. The clusters will feed 2 scenarios, 1 for the trigger pump-spray and wipe method of application and the other for the RTU wipe application. The objectives and sample size justifications for these protocols are the same as for the mop protocol.

The same test materials are used for the wipe protocols as for the mop protocol, so assessment of toxicity is largely the same; however, because of the use of a trigger pump spray, inhalation toxicity is of greater importance to this protocol. The inhalation NOAEL for DDAC reported in EPA RED is 10 mg/kg/day based on an oral study. Aerosol inhalation exposure from the trigger pump spray portion of the wipe study is estimated to be 0.00013 mg/kg/day; the inhalation MOE is approximately 77,000. This is significantly higher than the target MOE of 100 and thus is not expected to be problematic. The inhalation NOAEL for ADBAC reported in EPA RED is 3 mg/kg/day based on an oral toxicity study. Aerosol inhalation exposure from the trigger pump spray portion of the wipe study is estimated to be $9x10^{-5}$ mg/kg/day; the inhalation MOE is approximately 30,000 (target MOE = 100). The MOE for dermal irritation of ADBAC in the wipe protocols is 110 (target MOE = 10). The lower MOE for dermal exposure than was found for the mop study reflects the greater hand exposure potential in the wipe protocols.

The scripted elements of these protocols are similar to those for the mop protocol, with a few exceptions. The equipment used will be 32 ounce trigger-pump spray bottles with a cloth wipe, and RTU impregnated wipes. Task duration will be 30 to 120 minutes, and fresh wipe solution or RTU wipes will be provided every 10 minutes or as needed. The 6 pre-defined wiping task durations are 30 to 45 minutes, 45 to 60 minutes, 60 to 75 minutes, 75 to 90 minutes, 90 to 105 minutes, and 105 to 120 minutes.

Unscripted elements include participant wiping methods. Subjects will wipe between 1,000- and 4,000-square feet of vertical and horizontal surfaces as they normally would; thus, application methods will vary by subject. Subjects also may request fresh spray solution or RTU wipes more often than every 10 minutes.

Dr. Fisher inquired whether the use of multiple wipes will be added into analyses of variability. Higher exposure occurs with a fresh wipe; thus participants will receive more exposure the more wipes they use. Mr. Leighton agreed that participant exposure will vary based on the number of wipes they use. AEATF plans to count the number of wipes each person uses. Mr. Carley added that different participants are likely to use wipes at a different pace, which is an unscripted element of participant behavior. This is similar to the vigor of mopping that will affect foot exposure in the mop protocol. Unscripted individual variations are important to EPA. Mr. Leighton stated that information on how many wipes typically are used in a given time period also will be provided. Dr. Fisher asked whether greater exposure of the compound occurs when a new wipe is handled. Mr. Leighton indicated that this had not been confirmed, but will be examined.

The analytic phase of these protocols is essentially the same as that for the mop protocols. Similar measurements also will be taken in the field phase of the wipe studies as for the mop study, with a few exceptions. Prior to commencement of the study, the concentration of DDAC on the RTU wipes will be determined. The number of RTU wipes used or amount of material applied also will be assessed, as will the area wiped and the amount of solution dispensed in a single pull of the trigger of the trigger-pump spray bottle. Data collected in the analytical phase of the study are the same as for the mop protocol, except sock residues will not be measured.

EPA asked that more specific information be provided on the type of towel wipe to be used in the spray-and-wipe scenario, to ensure it is representative of typical practice. AEATF reported in its April 2, 2008 letter that the wipes will be cotton cloths. EPA has determined that, if its comments are addressed, this protocol is likely to yield scientifically reliable information that will satisfy the necessary criteria from the framework recommended by the HSRB. This research will produce important information that cannot be obtained except by research with human subjects, it has a clear scientific objective, and the study design should produce adequate data to achieve the objective.

Clarifying Questions – Governing Documents

Dr. Fenske requested clarification of the reference to diversity of participants' body sizes and other related measurements. Mr. Leighton responded that the protocols do not appear to record weight or height and agreed that this needed further clarification. Dr. Fenske requested clarification of the term "strata" from the description of the AEATF governing documents. Dr. Fish added that the documents referred to "stratified diversity sampling." Mr. Carley answered that the 3 clusters, or test sites, were selected from 3 lists that were generated based on the function of the building space (such as office space or large meeting space), and that this may be what is meant by "stratified diversity sampling." He agreed that the phrase was unclear. The term "stratified" also is used with reference to the pre-defined task durations.

Dr. Fenske inquired if the design of the sampling strategy would overestimate high levels of exposure and underestimate middle values of exposure. Mr. Carley explained that this is what the AEATF reported, but the Board should ask Dr. Holden for clarification of this issue. Dr. Johnson said that, in a sample with normal distribution, more samples will fall in the middle of the curve than at the extreme. Mr. Carley added that if the curve is flattened, this will underestimate middle values and result in relatively more samples at the ends of the curve.

Dr. Kim noted that the dose used in the protocols was calculated as mg/cm^2 (skin surface area) or as mg/kg/day, but if the critical effect is irritation, the amount of systemic exposure is unimportant. Because irritation is dependent on concentration of the product, he asked whether it was relevant to calculate dose based on the amount of product retained on clothing for the products for which irritation is crucial. Mr. Leighton agreed that the dose causing irritation could best be quantified as $\mu g/cm^2$ or as a percentage. Additional studies are needed to determine when (at what percentage) irritation begins.

Dr. Lehman-Mckeeman questioned how samples below the level of quantitation would be handled in the analysis of the data. Mr. Leighton replied that a technique similar to that used

to account for "non-detects" in dietary studies would be used. Mr. Miller added that a sensitivity analysis would be performed, along with a maximum likelihood estimation procedure, with the assumption of a maximal distribution.

Dr. Rebecca Parkin inquired whether "normal activity" was the same as "actual use conditions." Mr. Carley explained that these terms are both interpreted to mean mopping or wiping as the participant usually performs these activities. This parameter is one of the variants in the unscripted activity of each protocol. Actual use conditions should be conditions of use consistent with the terms of registration and with product labeling. Mr. Jordan said that for protection of humans, a combination of scripted and unscripted activities encountered in a protocol are used to determine actual use.

Dr. Fisher commented on AEATF's statement that if benchmark accuracy targets are not adequately met, cluster effects will be sacrificed for scenarios. She asked how, if EPA prefers filling more scenarios, the Board should evaluate a protocol that has a degree of variability that would render the data unusable. Mr. Carley answered that the research program described in the governing documents includes analyses to justify the 3x6 model for these scenarios; however, this model is not universally applicable. The data from these three scenarios will have more data points than studies used to pre-estimate the degree of variability that may occur, and thus variability occurring in the proposed mop and wipe studies will be better understood. Variability will be estimated for each scenario as the research proceeds. Dr. Fisher asked if the companies sponsoring this research would be reluctant to perform activities or analyses not described in the governing documents. Mr. Carley answered that if EPA takes that position that a 5x5 model, for example, would be more appropriate, EPA must understand that this would be significantly more expensive and more logistically complicated. If instead EPA determines that there are likely to be site-to-site differences, EPA could call for more data for a particular situation. The goal is to start with a less costly model and then ask for more data if needed. Mr. Leighton added that once the Antimicrobial Division of EPA receives data from these protocols, they will determine if the design was adequate, compared to existing research. The new data are expected to be better and immediately useable.

Dr. Fisher asked if subsequent protocols could be adjusted if the Board identifies the need for changes when reviewing the earlier protocols. Mr. Leighton said that this is possible; the governing documents do not specifically call for the 3x6 model. Dr. Fisher noted that the governing documents indicate that each study will determine its own best sampling design. She asked about the level of background analyses the Board would receive from other protocols concerning their sampling design. Mr. Carley answered that the Board will see scenario design descriptions similar in scope to what has been presented at this meeting and in supporting documents provided to Board members. He cautioned that the Board should expect the designs to be slightly different; it is not possible to predict *a priori* the number of clusters and MEs a study will require, but similar analyses will be performed to determine these values. Dr. Fisher suggested that for an expedited review, the protocols should include a rationale for why a previous design is applicable or why it might be different. Mr. Carley explained that the Board always will receive a rationale for study design. Dr. Fenske inquired how many scenarios are predicted to be needed to populate the antimicrobial product exposure database. Mr. Leighton answered that the Board is likely to review between 15 and 20 scenarios.

Clarifying Questions – Protocols

Dr. Young inquired if all participants are present on the same day at the same site. Mr. Carley replied that not all participants would be present on the same day and that arrival times and performance times might be different. Dr. Young questioned if the participants could watch each other perform the mopping or wiping tasks, because this might result in carryover, particularly for inhalation exposure. Mr. Carley responded that members of the AEATF would need to answer these questions. Mr. Leighton added that detection of DDAC is highly sensitive, so it is likely that participants will be separated from one another during use of this product.

Dr. Kannan Krishnan noted that the protocols provide an estimate of what is potentially absorbed, but not what is actually absorbed. He asked if it was safe to assume there was no absorption from clothing to skin. Mr. Leighton answered that the participants would be wearing two layers of clothing and would be using a diluted product; thus contact of the products with skin is unlikely. Dr. Krishnan inquired if assumptions were made to calculate the relative accuracy (K factors). Dr. Holden responded that all simulations assumed a log normal distribution, with an extra component for clusters, certain ICCs, and GSDs as described. The table detailing the results of the simulations presents a K factor that is bound on the relative error between the calculated value from the simulations and the true value.

Dr. Fish questioned if the maximal duration of exposure (90 minutes) for the mop scenario was based on a survey of how professionals mop, and asked why elsewhere in the document, an average use time of 80 minutes was noted. If 80 minutes is average, 90 minutes might not be long enough to capture longer duration use. Mr. Leighton explained that the data was obtained from ISSA, which while it is not specifically a survey it does provide recommendations for duration of mopping activities. The 10-minute value comes from a survey performed as a joint venture with EPA's Antimicrobial Division to determine how long consumers generally mop. Dr. Lehman-McKeeman noted that the low end of task duration was 30 minutes, but the rationale for the study design claimed that historical data indicated that 30 minutes did not provide sufficient exposure for analysis. Mr. Leighton responded that this was true, but the old data had poor recovery of residues. The new dosimeters will detect lower levels of exposure. Dr. Lehman-McKeeman asked how often dumping of buckets occurs, if a fresh mop bucket is provided every 15 minutes or more often. Mr. Carley replied that the task force has indicated that the contents in the used buckets will not be disposed of until the duration of mopping is complete. At that point, all the bucket contents used will be disposed of at one time. Monitoring time will include both mopping and disposal of used bucket contents.

Dr. Fisher asked if, given the 3x6 design and sample size, whether variation in the number of buckets or number of wipes used could be calculated. The data will not be usable if there are no constraints on the numbers of buckets or wipes used. Mr. Leighton answered that the protocols are not designed to compare the number of buckets or wipes used; this data will be collected to develop an idea of how people perform these tasks and use these products in a normal workday. Allowing workers to work as they normally do introduces diversity to the data.

Dr. Young inquired if consistent task durations will be generated for the mop and wipe tasks. Mr. Carley responded that the precise times for which workers perform the designated

tasks will be recorded. If, for example, the first worker assigned to wipe for 2 hours does not achieve that time, his data will be used to fill the data cell for a shorter duration. Subsequent workers will be asked to wipe for longer time periods, if possible, to fill the longer duration data cells. The amount of product each worker handled also will be known, which will likely be more significant than the time for which they performed the task.

Dr. Fisher asked if some participants will be allowed to participate in more than one protocol, and if the three scenarios are ever analyzed as a group. If participants can participate in more than one protocol, this could lead to overlap and limitations on understanding variability. Mr. Leighton answered that the data would be presented separately for risk assessment, but eventually would be aggregated. Mr. Carley added that each scenario collects data separately. The data placed in the database are specific for specific scenarios. Exposure is determined per unit of AaiH. Thus, a person who works quickly (and perhaps sloppily) for 1 hour may have more exposure than someone who works more slowly for a longer period. The database will provide the information needed to determine this. If EPA determines in the future that workers are likely to mop and wipe on the same day, EPA can use the unit exposure values from all three scenarios to determine the average exposure per day. Dr. Fisher said that this could be problematic if there are only three subjects per task duration. Mr. Carley clarified that there are more than three subjects for determining exposure per unit of AaiH and that this value is not dependent on the time worked. The task forces have indicated that all 18 MEs are different people, and 2 alternates also will be present at each site. There may, however, be some participant overlap at different scenarios. Mr. Jordan stated that EPA performs risk assessment by using calculations of exposure designed to avoid underestimating potential exposure. Potential exposure for mopping and wiping includes endpoints such as AaiH, and unit exposure, which will be determined from this study. The AaiH will be driven by the time spent working. EPA will choose the high end values and will try to estimate the amount of AI the "busiest" of workers could handle during a specified timeframe and use manner as the upper exposure limit and will multiply that by the amount of exposure observed for the "sloppiest" workers. These values will be combined to obtain the highest end of exposure and the labeling of the product will reflect this.

Dr. Philpott noted that the AaiH for the wipe scenarios will be determined by the number of wipes handled and calculated based on a prior measurement; a concern for this is that the amount of products on the wipes may not be consistent. Mr. Leighton explained that each person will have a set of wipes that will be weighed before and after use. Dr. Chambers asked if the 10-minute breaks would count against the time spent mopping or wiping. Mr. Carley stated that he could not answer this.

Dr. Fenske requested more details on indoor environmental parameters, how these are measured, and whether parameters such as room volume, ventilation, temperature, or building layout (one large room or many smaller rooms) affect exposure. He noted that many statements made in the governing documents do not have supporting data. He also questioned the idea that professional applicators would have the highest exposure, as highly trained professionals often have less exposure. He noted that the label for Lemon-Quat indicates that the product can be applied using a cloth, mop, sponge, or spray, and then rubbed in using a brush or cloth; use of a brush is not accounted for by any of the scenarios. He also asked about the label indication that

calls for leaving the product in contact with the surface being cleaned for 10 minutes. The label also indicates that it is unnecessary to rinse after mopping, but many people will rinse, which could affect exposure.

Dr. Fisher summarized Board questions for these protocols. Board members asked about the size of the space and whether more than one participant would be present during performance of a task and for how long, because this could result in cross-contamination. Questions were raised concerning the nature of the room (i.e., ventilation, temperature). Board members asked about the photographer and how the task duration times were chosen. Information is needed about the times at which dumping of the used buckets occurs and how this may affect controls. The Board also asked about participation of individuals in multiple protocols and how this would limit analysis and use of data. Dr. Fenske raised questions concerning the extent to which the protocols are consistent with the instructions on the label of the product.

EPA Ethics Assessment of AEATF Mop and Wipe Scenarios and Protocols

Similar to the science component of the protocols, because the ethics of both the mop and wipe scenarios are identical, Mr. Carley reviewed EPA's assessment of the ethics of both protocols in a single presentation.

The value of this research to society lies in its ability to provide exposure data on mopping and wiping that are needed to support EPA exposure assessments; the existing data are inadequate. This research is likely to generate knowledge useful for exposure assessments for both professional users and consumers, all types of mopping equipment, and the tested wipe application methods.

The proposed recruiting processes are the same for the mop and wipe protocols. The process begins when a worker responds to a flyer describing the protocol by calling the Field Coordinator. The workers' names are added to a list; once filled, the list is randomized. The workers are called in for an interview with the primary investigator (PI) based on the order of the randomized list, and this process continues until all slots are filled.

The PI meets with interested candidates; a translator is provided if the candidate prefers to communicate in Spanish. The PI describes the research, obtains demographic information from the candidate and applies eligibility criteria, checks the candidate's California driver's license or other non-driver identification, reviews the Informed Consent Form (ICF) and "Experimental Subject's Bill of Rights" (English or Spanish), provides the product label and material safety data sheets (MSDS) (English only), answers questions, and solicits consent to participate.

Overarching concerns in recruitment and consent process are equitable subject selection, fully informed choice, fully voluntary choice, and respect for subjects. Equitable subject selection requires appropriate inclusion/exclusion factors, an appropriate recruiting strategy, and seeks to maximize the representativeness of the sample. The inclusion criteria for these protocols specify males or females ages 18 to 65 years, good health, willing to sign the ICF and Subject Self Reporting Demographic Form, ability to speak and read English or Spanish,

residence within Fresno County, and has task-specific experience working in janitorial services. Exclusion criteria include having skin conditions on the surface of the hands or face/neck (e.g., psoriasis, eczema, cuts, or abrasions); pregnancy, as shown by a urine pregnancy test (for females less than 50 years old), or lactation; allergies to household chemical-based products, soaps, or isopropyl alcohol; severe respiratory disorders (e.g., asthma, emphysema); cardiovascular disease (e.g., history of heart attack or uncontrolled high blood pressure); or is an employee of Golden Pacific Laboratories or Grayson Research, or is related by blood or marriage to personnel in either company. The recruiting strategy excludes janitors who are employed by entities other than janitorial service providers, employed by service providers randomized to the end of the list and not called, employed by service providers who decline to post flyers, uninterested in participation, interested but insufficiently literate in English or Spanish to complete the demographics form, and illegal immigrants. Although the governing documents claim neutrality regarding legal status, requiring picture identification may result in excluding illegal immigrants. The representativeness of sample is achieved by the thoughtful selection and justification of purposive elements in the sampling designs, and incorporation of elements of random selection into the sampling design. The result is likely to be a usefully characteristic sample, although not statistically representative.

Fully informed choice also is an overarching concern in the recruitment process. In response to concerns about the complexity of consent materials, the mop and wipe protocol consent forms have been simplified and clarified since the last HSRB review. The consent forms now contain all elements required by 40 CFR §26.1116 in accessible form and language. Regarding circumstances and process, the recruitment process is adequately described in the protocol, but there are different processes for Spanish and English speakers.

Fully informed choice also depends on adequate and accurate communication of risks and benefits. The organization and content of the risk discussions in the consent forms are acceptable. Providing the label and MSDS for the concentrated product is irrelevant because the participants will not handle concentrated product. This may be confusing to the participants. In addition, this information is available only in English. EPA suggested that this information not be provided to potential participants. A potential benefit for the participants is learning how their exposure compares to others performing similar tasks with the same product. However, if this information is provided to participants, investigators must confirm participants' understanding of the results and provide translators who can accurately convey the results to the participant if the participant speaks Spanish.

The protocol states that candidates must read English or Spanish, as shown by their answers to the demographic form; however, the protocols are silent concerning how literacy will be assessed. If English is the candidate's preferred language, the recruitment interview will be conducted by the PI in English and all documentation will be provided in English. If the candidate prefers to communicate in Spanish, the recruitment interview will be conducted by the PI in English and translated by an interpreter; however, the source of the interpreter has not been identified. The ICF and California Bill of Rights will be provided in Spanish, explained in English, and translated. Other documentation will be provided in English. The recruiting flyer has been provided only in English; translation has been promised, but was not requested of the Independent Investigational Review Board, Inc., of Plantation, Florida (IIRB, Inc.). IIRB, Inc.

also has not approved the flyer, although the application indicates that they must approve all advertisements.

As the current protocol stands, language differences may compromise fully informed choice. The processes and documents for English-speaking and Spanish-speaking workers are not equivalent. The process also relies on an interpreter, which may affect workers' willingness to ask questions. The interpreter also may not understand the research well enough to translate it accurately, and the PI may be unaware of this. The PI may be unable to confirm worker understanding if there are language differences. EPA prefers that, when the worker's language of preference is Spanish, the recruiting and consent processes, as well as the field research, should be conducted in Spanish with minimal reliance on interpreters whenever possible. To resolve these issues, the AEATF letter of April 2, 2008, promises to add Spanish-speaking individuals to the research team.

The AEATF has undertaken strong measures to ensure fully voluntary choice. To manage dependent relationships, the cooperating service providers have promised neutrality and play no direct role in recruiting; providers agree only to post recruiting flyers. The employees of interested entities also are excluded as subjects. To minimize peer pressure, recruitment is initiated by worker expression of interest and the recruitment interview is private. Employers will not know if employees have applied to participate. Pregnancy testing is conducted in a manner that maintains privacy. The need to provide real alternatives to participation is minimal because research participation occurs independently of employment and employer.

Respect to subjects includes the issue of payment. The protocol indicates that candidates who attend the recruiting interview but do not consent to participate will not be compensated. Enrolled subjects who are not actually monitored (the alternate subjects) will be paid $50 per day. Enrolled subjects who are monitored will be paid $100 per day. Based on suggestions from EPA, AEATF revised their proposed payment schedule to provide a $20 payment to each candidate who attends a recruiting interview and a payment of $100 to all enrolled subjects who spend a day at the research site, regardless of whether or not they are monitored. The payments proposed are considered by EPA to be appropriate. In addition, subjects are free to withdraw at any time, for any reason. Participants can receive their individual results upon request. The protocols also provide for medical care for research-related injuries at no cost to the subjects.

To maintain privacy and confidentiality, information from candidates who do not qualify or consent to participate will not be kept, results of pregnancy testing will not be recorded and will be discussed only with the candidate, collected data will be identified only by subject code, linkage of subject names or addresses to subject codes will be securely maintained, and subjects will not be identified in reports or in databases. With some modification to protocols for addressing language differences, EPA believes the protocols address the relevant concerns for recruitment and consent.

The AEATF has identified seven categories of risk to participants. The first risk category is allergic response to Lemon-Quat; this risk has been minimized by excluding subjects sensitive to similar compounds. To avoid risk of over-exertion, possibly leading to heart attack, unhealthy subjects are excluded, subjects are closely observed while working, and rest periods are provided

at least every 30 minutes or more by request. Discomfort due to the use of an air pump and extra clothing has been deemed to pose negligible risk. The possibility of stinging from use of alcohol rinses or wipes is minimized by excluding subjects with broken skin. To minimize the risk of heat-related illness, the research will be conducted indoors, in buildings with functioning HVAC. The SOP also calls for monitoring of both subjects and heat index, with stopping rules beginning when the heat index rises to between 80 and 90 degrees Fahrenheit. Possible embarrassment while changing into the required dosimeter garments is minimized by using experienced, same-sex technicians and providing private facilities for changing. Subjects risk being surprised by the results of a pregnancy test, but these results are not recorded and are discussed only with the subject.

No direct benefit to subjects has been identified. A potential indirect benefit to subjects is learning their individual exposure results and how these compare to others. The sponsors will benefit by maintaining regulatory compliance. The likely societal benefit from this research is development of higher quality exposure and risk assessments for antimicrobial products applied by mopping or wiping. Comparison of risks and benefits has found the risks to have been effectively minimized, with low residual risks to subjects. EPA finds these risks reasonable, given the potential societal benefits of obtaining reliable data on dermal and inhalation exposure while mopping or wiping with an antimicrobial product.

IIRB, Inc. reviewed and unanimously approved the protocol and English and Spanish consent forms on January 22, 2008. IIRB, Inc. is independent of the sponsors and investigators, is registered with Office for Human Research Protections (OHRP), but is not accredited. IIRB, Inc. procedures have been submitted directly to EPA under a Confidential Business Information (CBI) claim; EPA has determined they meet regulatory standards. IIRB, Inc. was not asked to translate the recruiting flyer or demographics form; however, they state that all recruiting material must be approved by them. Because this is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws, the primary ethical standards applicable to this research are 40 CFR 26, subparts K and L.

Deficiencies noted by EPA are primarily related to language issues. AEATF must ensure that Spanish-speaking candidates are fully informed and fully comprehend what they have been told. EPA would prefer that the candidate interviews be conducted by a member of the research team fluent in Spanish rather than relying on a translator. AEATF has been asked to replace references in the consent forms to “normal business hours” by references expressed in California time and to ensure that a Spanish-speaking responder can be reached at any telephone number cited as a source for further information. In the letter dated April 2, 2008, AEATF has promised to make the appropriate revisions to the protocol to address these concerns.

EPA has determined that all requirements of §26.1111, §26.1116, and §26.1117 are met, as are all requirements of §26.1125 and of §26.1203. If the noted deficiencies are corrected, the AEATF Mop Scenario and Protocol and Wipe Scenario and Protocol will likely meet the applicable requirements of 40 CFR part 26, subparts K and L.

The Board was asked to address the following charge questions:

- If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by mopping and does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?
- If the proposed research described in AEATF's proposed wipe scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by wiping and does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Clarifying Questions

Dr. Menikoff inquired whether data gathered through these studies could result in expanded use of the products. Mr. Carley responded that the data EPA currently uses to determine unit exposure is not optimal. These data are expected to be better; exposure limits could be defined as higher or lower, but the data on which risk assessments are based will be stronger. Dr. Fisher added that the benefit of these data will be to increase the accuracy with which EPA can determine exposure values for the product label.

Dr. Menikoff asked if the task forces have considered that candidates may use fake identification, resulting in enrollment of illegal immigrants in the research. Mr. Carley replied that the provision for use of photo identification is based on requirements from the California DPR. He acknowledged that this approach may be ineffective for verifying legal status.

Dr. Menikoff questioned whether a benign compound could be substituted for the test compound to determine the amount of skin exposure. Mr. Leighton answered that DDAC at the low concentration used in these protocols is essentially benign. Dr. Menikoff asked why the stopping rules began at 80 degrees Fahrenheit, which seems high for a building with air conditioning. Mr. Carley explained that the reference to 80 degrees was the level at which extraordinary measures to protect individuals from heat-related problems are invoked.

Dr. Menikoff noted that changes were made to the approved consent form, but these changes did not appear to have been approved by IIRB, Inc. Dr. Philpott asked if IIRB, Inc. would translate the applicable materials and asked how accurate translation would be confirmed. Mr. Carley answered that the submitted materials indicate that the investigators sent the English ICF and California Bill of Rights to IIRB, Inc. IIRB, Inc. claimed that these documents would be translated, but did not indicate that the recruiting flyer, demographic form, label, or MSDS would be translated. Included in the protocol documentation was an approved translation of the California Bill of Rights and ICF, and a certificate from the translator describing his/her credentials. Mr. Carley added that the accuracy of the translation will be addressed in a meeting

with the recruitment staff before recruiting participants to ensure that the documents are understandable by Spanish-speakers.

Dr. Parkin inquired whether those who were interviewed and consented to participate, but did not come to the site for testing, would be compensated. Mr. Carley answered that the AEATF has explained that these participants will be compensated. Dr. Parkin asked if subjects would be excluded if they had broken skin at the time of the recruitment interview or at the time of testing. Mr. Carley responded that this was unclear, but that the protocol provides for alternates at the test site in case a subject does not qualify or must withdraw from testing.

Public Comments

Dr. Jeffrey Driver of Infoscientific.com, on behalf of the AEATF

Dr. Driver responded to Board clarifying questions. Regarding people present during testing, the research team members will be present, but because testing takes 4 to 6 hours per person, no more than 2 people will participate in the protocols each day. The participants will be physically separated to avoid cross-contamination; AEATF is cognizant of air and surface cross-contamination issues. To ensure that no surfaces are re-mopped, the buildings selected as sites must be able to provide at least 6,000-square feet of floor space. Subjects also will not watch one another perform the assigned tasks.

Regarding characteristics of the rooms, ancillary information will be collected, including floor plans indicating placement of floor drains and sinks relative to mopping areas. Humidity and air exchange rates will be measured, as well as other parameters described in the protocol. In response to questions asked about the identity of photographers or videographers involved in the study, Dr. Driver answered that members of the research team would perform these duties.

Dr. Driver explained that the manner in which task duration times were determined is listed in the appendix of the Statistical Scenario Design document. An ISSA survey of time and motion involving fairly scripted tasks supported development of average of typical times it takes to accomplish very specific tasks, such as wiping a sink. The tally for mopping time was determined to be approximately 3.3 minutes per room. The AEATF focused on medical settings, because in these settings, mopping and other tasks are likely to occur more frequently. The average time spent per room was applied to the medical setting with an upper bound of 25 rooms per day, leading to the calculation of 90 minutes as the upper bound of the time per day spent mopping. A similar calculation was performed for wiping, because wiping also occurs more frequently in a medical setting; a maximum of 120 minutes was determined for wiping.

Regarding overlapping participation in more than one protocol, exclusion criteria have been proposed to ensure that workers do not participate in concurrent studies. This will improve randomization.

Two bilingual research staff members have been identified. These staff members will perform the consent interviews and AEATF will share their resumes with the Board, if desired.

These staff members will be present at each day of the study and will respond if Spanish-speaking workers call the number on the recruitment flyer.

Regarding the use of RTU wipes and the AaiH, wipes are prepared specifically for the study and are placed on a shaker for 30 minutes to ensure a homogenous distribution of product through the wipes. Ten wipes will be analyzed before each study begins to ensure homogenous distribution. The AaiH can be determined by multiplying the mass of product in each wipe by the number of wipes used. The dry container also could be measured and the wipes measured before and after use.

The ISSA time and motion data were collected for professional workers; data from the Antimicrobial Exposure Joint Venture Survey for consumers also was used. This survey found a range of 5 to 60 minutes for mopping, and a similar range for wiping. Consumers average approximately 10 minutes per day mopping and approximately 13 minutes per day wiping. These durations overlap with the time professionals spend performing these activities.

After mopping tasks are completed, members of the research team will rinse the floor between test days to remove any residue. Product applied by wiping can be allowed to air dry. In practice, workers may spray, then come back and wipe a surface, but for these protocols they will wipe as they spray. Dr. Fenske asked if the protocol provided details on whether workers would wait for 10 minutes after spraying before wiping. Dr. Driver remarked that some details on this matter were provided; Dr. Fenske stated that these details should be described in the protocol.

Dr. Fisher asked if the recruitment flyer had been submitted for translation. Dr. Driver answered that the ICF had been sent for translation and its accuracy was verified by IIRB, Inc. AEATF intends to send the flyer and telephone script for similar translation and will include the documents in the final protocol. Dr. Fisher noted that the Board should not review protocols until an IRB has reviewed all relevant documents.

Dr. Driver stated that compensation rules had been revised, which impacts sections of the ICF and protocol. Anyone who comes in for an interview will receive $20. Both alternates and participating MEs (whether they complete the study or not) will receive $100.

Dr. Fisher inquired how participants would dispose of the mop water. Dr. Driver explained that the protocol calls for having workers complete all mopping, and then empty all the buckets. Each worker will have a different number of buckets depending on the time spent mopping. Normal practice varies; how often buckets are emptied depends on the location of the sink or drain. The protocol could be changed to specify intermittent disposal; however, AEATF wishes to keep mopping and disposal activities as separate tasks. Dr. Fenske countered that, when mopping as part of normal activities, most janitors use only one bucket. Dr. Driver stated that the protocol initially called for use of separate dosimeters, but the task force decided to combine dosimeters so intermittent disposal could take place.

Dr. Johnson asked if new workers would mop or wipe a previously cleaned surface. Dr. Driver answered that the research team will perform a potable rinse of the surfaces each day. He added that it is not uncommon to re-mop or re-wipe surfaces in usual practice.

Dr. Chambers inquired how data will be gathered if the person assigned to the longest duration interval cannot complete the task for that duration. Dr. Driver explained that more MEs could be assigned to certain intervals. In addition, there will be alternate participants and others could be recruited to ensure that the longer durations are accomplished. It is possible that researchers may observe a trend that appears to indicate a certain duration period is too long and perhaps too physically exerting, but this is not expected. Dr. Chambers questioned if all data would be recorded if multiple MEs wipe or mop for the same duration. Dr. Driver responded that this data would be collected, but data also will be collected for the longer durations.

Dr. Fenske noted that the ISSA survey stated that the average worker mops for 83 minutes during the average working day and asked about variability around that value. Dr. Driver answered that the appendix to the protocol lists various tasks and the time for which they are performed. Those times were scaled up based on a maximum number of rooms cleaned per day, based on cleaning activity taking place in a medical setting, to determine the upper duration limit of 90 minutes; 90 minutes is not an average value. The survey does not indicate that workers mop for an average of 90 minutes per day. Dr. Fisher noted that the protocol gives equal weight to each of the 10-minute segments. There are statistical reasons not to do this because inappropriate attention is placed on time intervals that do not occur as frequently. She asked if the intervals described in the protocols are sufficient to understand exposure. Dr. Lebowitz suggested that since the average time spent mopping a room is 3 minutes, with a range of between 1 and 10 minutes, and the maximum number of rooms mopped is 25, 25 minutes may be a more appropriate interval. Dr. Driver explained that logistics—taking breaks and distributing supplies to rooms—must be considered, as well as physical exertion; mopping for 90 minutes per day is considered a long duration.

Dr. Fisher inquired if proportionality could be assessed using the indicated task duration periods. Mr. Leighton replied that ISSA information is the best available information on task duration. Information from this survey states that 90 minutes is the upper end of task duration; if 120 minutes is found to be the upper bound, the data can be extrapolated. Dr. Lehman-Mckeeman commented that 10 minutes appears to be a narrow timeframe, given possible uncertainty in the measurements. She also questioned if the data would cluster given the narrow time intervals. Dr. Driver responded that the range normally observed for task durations is fairly narrow. People likely perform these tasks intermittently. The task force chose the number of intervals indicated in the proposals because, given the protocol design, 6 intervals were most convenient. Dr. Fisher commented that if the data appear to cluster inappropriately, changes can be made to the protocols.

Dr. Chadwick questioned why the medical setting was used to determine task durations. In public facilities, mopping is often performed on only one day per week, for an entire 8-hour shift; this would lead to more exposure than that predicted in the protocols. He acknowledged that it may be possible to extrapolate from 90 minutes to 2 hours, but extrapolation to 8 hours may be problematic. Mr. Leighton explained that in the past EPA has extrapolated to that

degree, which is 1 reason why more data on exposure is needed. Mr. Miller suggested that the 30- and 90-minute intervals could be checked for proportionality once the data are analyzed. Dr. Fenske stated that proportionality is being tested by these protocols. EPA does not know if exposure is proportional to AaiH for antimicrobial product users; therefore, it is not valid to say that extrapolation is possible. He continued by asking if the protocols truly assess the full range of mopping activities performed by professional janitors. In addition, trained personnel usually have lower levels of exposure than casual users. Use of professional janitors may therefore not include the group likely to have the highest levels of exposure. Dr. Fisher noted that additions and changes to the protocol could be proposed and cautioned Board members to keep in mind how EPA intends to use this data when evaluating the protocols.

Board Discussion

Scientific Considerations – AEATF Mop and Wipe Protocols

Dr. Fenske opened the scientific discussion of the mop and wipe protocols. He stated that diversification of the types of buildings chosen as research sites was good, but it was unclear why the specific types of buildings were chosen. This approach also may limit statistical power. He noted that it also was unclear whether the task forces expected different exposures to occur in different building types and whether any of the characteristics of the buildings were considered to be important when designing the study. Information on site characteristics, such as building layout and the sizes of the rooms could affect behavior and exposure, but this was not discussed in the protocol. Details regarding how ventilation and temperature measurements would be made also were not described. The compound has low vapor pressure and the protocol contends that inhalation exposure is not a significant concern; this could result in a lack of measureable quantities in air samples. Because the database will contain information on a large number of products, “low” vapor pressure should be defined. Other products in the database may have a higher vapor pressure and it would be inappropriate to use data from a lower vapor pressure product to assess exposure of all products. Evidence indicates that outdoor inhalation exposure is small, but exposure may be different in an enclosed environment.

Dr. Fenske concluded that the public recruitment process was reasonable and the documentation was generally excellent. He disagreed that professional janitors would represent the group with the highest levels of exposure per AaiH. Consumers might have higher exposure data, because untrained handlers in general usually have higher exposure levels. Dr. Fenske commended the aspects of the design that allowed variability in work behaviors. He noted that the participants are told that the chemicals being used are hazardous but are not given protective clothing. The products also are diluted, which may result in the participants being less careful in their handling of the products; it will be interesting to see how this affects exposure. He asked about the use of certain equipment to detect bucket drips and stream-off and asked if there was any data to support the contention that this leads to a high level of exposure.

Dr. Fenske stated that the choice of chemical was practical and useful. Sensitivity analysis will be important because 30 minutes is not a long time during which material can get on the dosimeter. The label indicates that the product can be applied using a brush, and also

cautions against inhaling the product when it is sprayed; the protocols do not indicate how these matters will be handled.

Disposal of mop solution is a significant issue. Dr. Fenske recommended that workers use the solution until they decide it needs to be changed, and then dispose of it. The method described in the protocol, namely storing used buckets until the end of the task and then disposing of all solution at once, does not reflect most cases of real life work. The separation of subjects at the test site, as described by Dr. Driver, should be written in the protocol.

Dr. Fenske asked that the Board be provided with the ISSA survey. He said that the calculations of timeframes were unclear and lacked information on standard deviation or distribution. The exposure duration periods of the study should encompass average daily mopping times. One approach is to broaden the time intervals and/or increase the duration of the study, rather than including more MEs.

The air sampling equipment was described, but flow rate was not. Information is needed on particle size, including the range of particle size expected and what sizes will be captured using this sampling method. QA calls for field spikes of whole body (uncovered) dosimeters. The inner garment dosimeter is covered by clothing during testing; it therefore seems inappropriate to perform QA using uncovered dosimeters. Exposure to the feet is likely, and Dr. Fenske agreed that measuring residue on socks was appropriate; however, this is likely to be a site of heaviest exposures, and the PIs should perhaps consider using double socks to determine if breakthrough occurs. This information would be relevant to assess skin exposure. In case of a spill, participants should be provided with a back-up pair of socks.

Dr. Parkin noted that issues for the mopping and wiping scenarios are similar. She stated that observed people change their behaviors; therefore, it is important to know who will be in the room as the participants perform their tasks. The identities of these people need to be clarified. The participants also should be informed that they will be observed. The protocols also are unclear concerning which activities will be photographed and whether every person, or a subset of participants, will be photographed. This raises issues with the informed consent form. The protocol does not describe whether a specific number of "observers" are required for the research to proceed.

Dr. Lehman-Mckeeman stated that the protocol was sound and that she had only minor changes to suggest for the existing protocol. It is clear that EPA requires new data for exposure assessment. The quality of this data should be superior, based on the strengths of the study design and execution of the mopping and wiping protocols, along with advances in analytical methods. Clarification of disposal of mop buckets is needed; she agreed with Dr. Fenske that disposal of buckets as they are used would be more appropriate. She said she was less concerned that using data on exposure of professional janitors would lead to underestimation of exposure because the nature of the activity does not necessarily require an experienced user.

One critical element is the duration of the time intervals. Dr. Lehman-Mckeeman questioned whether 90 minutes would be a sufficient duration, especially if EPA expects to extrapolate to longer times from this data. The 10-minute interval also may be insufficient to

observe the correlation of AaiH to exposure. More justification of the total duration of time spent performing the tasks and the time intervals are needed, particularly in terms of the effect of time on the relationship between AaiH and exposure.

Dr. Kim opened his discussion stating that he was uncomfortable with the sample size justification provided in the governing documents. The simulation presented in the governing documents used an assumption of the sampling frame. For the protocol, stratified cluster sampling was used. This raises questions regarding the ability to adequately analyze the data and derive error estimates. Because sampling is performed by designating three building types and then choosing one of each type, there are zero degrees of freedom for estimating variance. Placing one subject in each of 6-time interval bins also results in zero degrees of freedom and the inability to develop an error estimate. This approach violates assumptions made in the governing documents. There appears to be a disconnect between the governing documents and the actual protocol.

The simulations in the governing document rely on an estimated ICC. Based on 4 previous studies from CMA and PHED, a common GSD was used as the basis for developing the 3x6 model. The mop data from CMA has a GSD of 3.53, but available data for mop exposure indicates more variability; therefore, the sample size justification is inadequate for the mop scenarios. The wipe data from CMA indicates a GSD of 5.0, versus the 3.6 used to justify the 3x6 model. The wipe protocol thus has an inadequate sample size.

Dr. Fisher noted that there are three examples of each time period with one subject at each site. She asked how having 1 subject at each of 3 sites, each performing the same task for 30 minutes, added to the degree of freedom calculation. Dr. Kim responded that error estimates can be made across time durations, but not across sites. The justification for an upper bound of 90 minutes was based on the ISSA database; the wipe duration for an average worker day is given as 212 minutes per day for wiping and 82 minutes for mopping. The governing documents indicated a desire to choose a wide range of task durations, but 30 to 90 minutes does not appear to be a wider range. One scenario was justified based on ISSA data but the other was not. It is unclear how 120 minutes for the upper bound of wiping activities was justified. Dr. Kim noted that the description in the governing documents of intent to oversample high exposures and underestimate middle level exposures was unclear.

Dr. Lebowitz stated that the SOP for mopping needs refinement of its definitions of usual practices. His major concern was with aerosol inhalation. Many studies have shown that low volatile and non-volatile products can become trapped within water aerosols and can be inhaled. Thus, the assumptions in the current protocol about aerosol size relative to the monitoring equipment may be inadequate.

Dr. Lebowitz remarked that he also had concerns about the adequacy of the Spanish translations performed by an IRB located in Florida. The workers for whom these documents are intended may speak a different dialect than that used by the translator. AEATF should carefully consider how translation is performed to ensure that workers understand the documents.

Dr. Johnson commented that the protocols are likely to provide useful information. He commended the task force on the amount of randomization included in the protocols, and on the use of three different buildings as testing sites. Dr. Johnson noted that generalization of activities in one type of building to other types is based on expert opinion rather than statistics, but these generalizations are reasonable. The numbers of clusters and MEs also are reasonable at this point in time. The way the clusters were chosen suggests a fixed-effect factor rather than a random effect. Although three types of buildings were chosen, only one of each type will be used; therefore, there can be no measure of variance associated with the building types.

Concerning the issue of the proportionality of the relationship between length of time worked and AaiH, the longer the intervals and duration of the tasks, the better the data will be for determining proportionality. Dr. Johnson agreed that emptying the used mop buckets as they are finished would be better than emptying all buckets used at the end of the testing period. He suggested that the task force consider performing a pilot study with a small number of workers to assess normal work activity before commencing the study.

Dr. Young agreed with Drs. Kim and Johnson concerning treatment of the buildings as fixed effects and the problems this could cause. EPA's proposed analyses also raised concerns for Dr. Young. In the first analysis plan, the assumption is that exposure per unit of active ingredient is assumed to be part of the same distribution, no matter how long the subject mops. This could be true for professionals, but consumers may become more careless the longer they mop. This implies that when assessing proportionality, variance will increase as the number of units handled increases. It may not be possible to determine proportionality because there may not be replication of a given number of units handled; the data will not show whether exposure is increasing over time. This could make analysis problematic.

Dr. Alicia Carriquiry expressed her appreciation of attempts to include randomization in the protocols, and noted that the protocol had been improved since it was last discussed by the Board. She agreed with the conclusions of Drs. Kim, Johnson, and Young.

Dr. Fenske stated that his conclusions regarding the science of the wipe protocols were similar to those for the mop protocol. Dr. Lebowitz expressed concern about aerosol size and the impact this would have on inhalation for the spray and wipe protocol. The protocol does not address this issue.

Dr. Fisher summarized the science discussion for the mop and wipe protocols. There is little expectation of diversity across sites, but it is questionable whether sufficient data will be collected to determine if there are differences (such as those related to building layout, air exchange rate, or temperature) in the buildings that could affect exposure. Dr. Fisher noted that some variables, such as air exchange rates and temperature, will be measured. Dr. Young stated that the data is insufficient to test if the buildings are truly different and whether the building differences cause differences in exposure. She asked if there was any purpose in stratifying the buildings rather than randomizing across buildings. Mr. Miller explained that three different building types were chosen to increase diversity, not to use as a variance component model. Dr. Fisher said that the 3x6 model emphasized the site, but there is no evidence that the variability of the sites can be measured. Dr. Fenske added that there may be differences across

buildings, but his concern was that within-building activities could have a larger effect on exposure. The layout of the buildings (such as many small rooms versus one large room) could have a significant effect.

Dr. Fisher reviewed the recommendations made by the Board. The selection of test compound was appropriate. The task force should define "low vapor pressure" to permit generalizability of this data to other compounds. The Board found the recruitment process to be generally sound, although care should be taken when translating materials into Spanish. The Board recommends having participants in the mopping protocol empty used buckets as they work rather than at the end of the testing period. Because the product label indicates that it can be applied using a brush, testing of this method of use should be considered for future protocols. Regarding air sampling equipment, more information is needed on flow rate and particle size range captured. The task force should include measurement of inhalation during the spray and wipe protocol. The statement regarding inclusion of a sufficient number of people to monitor the study needs clarification to ensure that there is some control of how many people are present during testing. The execution and monitoring protocols are of good quality, the proposed analytical methods have been improved, and attempts at randomization are appreciated by the Board. The Board also agreed that subjects should not participate in multiple protocols.

Dr. Krishnan stated that the task force had not presented a strong argument that the MOE for inhalation would be greater than 80,000, despite the low vapor pressure of the product. In addition, room size differences are critical for inhalation exposure. Dr. Lebowitz agreed that inhalation exposure is not minimal even with low vapor pressure products. Although the product is not toxic, it is an irritant. Mr. Carley clarified that the protocol calls for collection of air samples for every worker for the duration of the test period. Any respirable aerosols will be detected. Mr. Leighton stated that previous studies of DDAC indicate a standard pressure of 10^{-4} millimeters of mercury (mmHg). Dr. Lebowitz stated that the existing data is inadequate to assume that inhalation exposure is not important.

Dr. Fenske commented on Dr. Parkin's observation that being watched by a number of people may make the worker uncomfortable and affect how a task is performed. Because photographs will be taken, the task force should consider having as few people as possible watch the participant. The goal should be to minimize interaction between the research staff and the participant. Dr. Fisher agreed that the task force should assess the risks and benefits of controlling behavior versus contaminating an activity.

Dr. Fisher asked when the data from this study would be available and whether the Board would review additional protocols before they review the data from this study. Mr. Carley answered that it would be approximately 1 year before the data from this study is reviewed by the Board and that the Board will review additional protocols before then.

Dr. Fisher noted variables of concern that all interrelate with respect to sample size. First, the Board questions whether the 6 defined time periods are too similar and whether the time periods themselves are long enough to capture middle and upper estimates of exposure. The second concern relates to the 3 clusters; although 3 types of buildings have been chosen, there is little assumption of variability and thus no degree of freedom for the environment.

However, 3 data points are collected with respect to the subject. Overall, the protocol is sound and the Board should provide recommendations that will help produce useful data but also a path forward that is feasible.

Dr. Young inquired why different time intervals will be used, rather than different amounts of exposure, which will be used in subsequent analyses. Mr. Carley explained that units of AaiH are a calculated value. It is difficult to define this value *a priori*, but it is possible to ask participants to mop with a set number of buckets and stratify by the number of buckets used rather than duration of mopping. Dr. Fenske noted that agricultural handler studies are usually stratified by the number of tanks loaded. It could be fairly simple to use such an approach for the wipe protocols; participants could be asked to use a specified number of wipes. Mr. Leighton stated that this approach was considered, but for risk assessment EPA must have information on the length of time people use a product. The protocols will gather information concerning the number of buckets or wipes used for a given time period. Dr. Johnson suggested that the protocol could select three buildings at random, based on availability of the buildings, and then estimate variance components. An alternative would be to select three buildings that are expected to be different; variance could not be measured, but it would be possible to test if the relationship between the amount handled and exposure is the same in the three buildings. If the relationship is not the same, EPA may consider using data from the building with the highest level of exposure for risk assessment. Dr. Carriquiry argued that it could still be difficult to determine if the difference was related to building type and said it would be better to ignore the effects of the building.

Dr. Fisher noted that it appears to be difficult to control for variability across individuals and asked how to differentiate between the variability associated with the environment and the variability associated with the individuals. Dr. Kim stated that if the buildings had been selected randomly, it would be possible to differentiate between building and individual variability. Dr. Carriquiry suggested that the protocol could define 3 time intervals and replicate these across building types. Dr. Fisher agreed that choosing 3 time intervals with 2 replicates per interval at each of 3 sites could be useful. Dr. Chadwick noted that selection of the 3 building types—an office with many smaller rooms, retail space with large corridors, and meeting space with large open rooms—was done purposively to test in different environments. Dr. Krishnan noted that dermal exposure would be more likely than inhalation exposure; the Board should thus consider whether dermal exposure would be affected by building type. Mr. Miller stated that random selection could result in testing 3 similar buildings and thus lead to loss of diversity. The purpose of stratifying by building type was to introduce diversity, not to add another layer of fixed components. Determining whether the site or the person is the source of diversity may not be relevant for EPA labeling regulations.

Dr. Chambers stated that if the number of time intervals is reduced from 6 to 3, there will be fewer participants. Dr. Kim suggested using the same range of task durations, but using 20-minute intervals rather than 10-minute intervals. Dr. Fenske stated that the AaiH as a predictor of exposure is more accurately measured if exposure occurring during a time period longer than 10 minutes is measured. The type of data gathered will permit the investigators to determine the time associated with the number of buckets or wipes used.

Dr. Fisher asked EPA staff to comment on the proposal that the time intervals defined in the protocol be extended. Mr. Leighton remarked that the time intervals will be influenced by how long participants can continue to mop. Dr. Holden explained that the purpose of the study design was to include diversity in a small sample. The original exposure studies repeated the tasks under the same conditions in the same building. It was clear that these studies differed from one another, but unclear why. EPA asked the task force to increase diversity by using different building types. The study does not seek to perform variance component analysis or determine the differences between building types.

Dr. Fisher acknowledged that most of the Board's suggestions would not significantly improve the protocol. In addition, these are the first protocols for this exposure assessment project and changes can be made to future studies if problems are discovered. She reiterated that the goal of this protocol is to collect data from diverse locations. Dr. Carriquiry agreed with Dr. Holden that there is no guarantee that diversity would be increased by deliberately choosing buildings rather than choosing them at random. Dr. Kim asked whether all protocols presented to the Board for this project would have a 3x6 sampling design. Dr. Holden explained that the scenario design document defined a non-random sample with random components. The task force will analyze the data and assess variability. The sampling method may not lead to more diversity, but there should be variability between clusters or scenarios that can be estimated. This is a non-random diverse sample; randomness was included to try to avoid bias. The sampling design is not determined solely by the ICC and variability; the objective of the research also must be considered. Although EPA and the task force acknowledge the limitations of the data collected by these protocols, the data will nonetheless permit more accurate assessment of exposure and risk than previous data. The task force and EPA have agreed that this protocol describes the best way to capture diversity in a sample, given feasibility concerns.

Dr. Fisher noted that the Board had concerns about whether the time periods defined in the protocol would be sufficient. She suggested performing a small pilot study to determine the maximum time a worker could mop and determining the most practical and useful time intervals. The closer the intervals are to each other, the less likely a detectable progression of exposure will be observed. Dr. Krishnan suggested that the Board recognize the limitations of the data to ensure that EPA does not use this data for purposes besides those originally defined. He added that exposure is more likely to occur over the course of several shorter time periods during the day, rather than from a continuous 8 hours of exposure. If the data can characterize exposure for several of these shorter duration intervals, the data can be used as a starting point for determination of exposure and risk assessment. Dr. Fenske requested confirmation of the rationale for the 30- to 90-minute timeframes for mopping. He added that information on averages and standard deviation was lacking; this information would allow the task force to determine if they had covered 90 percent of an average person's workday. Dr. Holden explained that the average time spent mopping a room was multiplied by the number of rooms that are generally mopped per day in a medical facility, which leads to an upper level estimate of time spent mopping. This is a conservative approach for measuring exposure. The average is less important; in addition, much of the data in the ISSA survey is skewed and standard deviation may be less useful than knowing the range around the average. Dr. Fenske said that knowing the distributional characteristic around the average should be used to set an upper bound.

Mr. Leighton stated that he could re-examine the ISSA survey to find information on the high end of work times to justify if the protocol needs to include durations longer than 90 minutes.

Ethical Considerations – AEATF Mop and Wipe Protocols

Dr. Menikoff opened the ethics discussion of the proposed mop and wipe protocols by stating that, overall, the studies are well designed to address most ethical concerns. He agreed with Mr. Carley's suggestions to include Spanish speakers on the research staff. Although the protocols may exclude illegal immigrants, they are designed to protect vulnerable subjects. The test compounds pose little danger to participants, but use of a benign tracer compound instead should be considered.

Participants should be informed that they may be photographed or otherwise observed; this information should be disclosed to participants in the ICF, and participants should be given the opportunity to decline to be photographed. The description of the purpose of the research in the ICF should be modified to more clearly state that EPA will use the information to modify exposure standards. In the description of procedures to improve subject respect, better language should be found to replace the phrase "same sex." The risk section describes the risk associated with exposure to undiluted product, but has only one sentence regarding risk of exposure to diluted product. Although risk is minimal, language should be added to warn participants to avoid contact with the eyes. In the approved ICF, a phrase was added to the discussion of pregnancy risk saying that exposure to the product may be hazardous to pregnant women; it is unclear why this was included in one version of the ICF and not other versions. EPA should review all documents, current and historical, to determine if such changes are serious for possible consideration by the Board. The recruitment brochure does not mention the test product and no reason was given for this. In the section that describes exposure measurement, the risk posed by inhalation also should be mentioned; this risk also should be included in the telephone script. The protocol claims that the data may be used by EPA to reduce risk, but this may not be the case and this claim should be removed because it may result in undue inducement to participate.

Dr. Philpott agreed with Dr. Menikoff's findings and noted that this was one of the most thorough protocols the Board has reviewed. He agreed with Dr. Lebowitz's previous comments on ensuring that the translation of recruitment and consent documents was completed using an appropriate dialect and that the Spanish translation is at the appropriate level of comprehension for the subjects. Although the protocol states that participants may receive their personal exposure results, relative to low, average, or high exposure, the protocol did not include a plan for dissemination of results. The Spanish ICFs should include contact information for Spanish-speaking members of the research staff. Regarding community involvement, the telephone script used to contact employers should also mention how the investigators intend to recruit union leaders and ensure that unions wish to participate. Dr. Philpott also suggested re-naming the community involvement flyer as a community notification flyer.

Dr. Fish agreed with Drs. Menikoff's and Philpott's assessments of the ethics of these protocols. She noted that pregnancy testing for all women under than 50 years of age may miss some pregnancies, because women over 50 have been known to become pregnant. She suggested changing the testing age guidelines to exclude post-menopausal women. Dr. Fish

found no justification for the upper age limit for participation of 65 years. Some janitors are older than this and exposure information for this age group would be useful. She also requested that a typographical error in the section referring to non-pregnant and non-nursing women be corrected.

Dr. Chadwick agreed with the assessments provided by his Board colleagues and Mr. Carley. He also agreed that the protocol was sound from an ethical perspective.

Dr. Fisher summarized the Board's findings concerning the ethics of the mop and wipe protocols. The issues related to observation and photography should be clarified and participants should be given the opportunity to decline participation in these activities. Clarification also is needed regarding protection of participant privacy and confidentiality given the number of staff who may be present at the test site. Translation issues should be corrected, and contact information for Spanish-speaking research staff members should be included in recruitment flyers. The verbiage with respect to vulnerable populations should be changed to reflect that the study minimizes risk to vulnerable groups. The research purpose section should be modified to indicate that the research was not designed to reduce risk, but to inform EPA and provide better data for labeling purposes. Language regarding "same-sex" persons should be clarified. The risk of eye exposure should be clarified. Investigators should consider changing the pregnancy testing requirements to exclude post-menopausal women rather than those older than 50 years of age. A rationale for excluding subjects older than 65 years of age should be included. Clarification of comments regarding sufficient numbers of participants, normal activity, and representative study-related activity is needed.

Several issues related to documentation were raised. The details of communication with IIRB, Inc., particularly regarding changes to documents, were not clear. The test product is not named in the recruitment flyer, but it is unclear why this is so. The details of risk of contact with the test product, particularly through inhalation, needs to be clarified in the ICF and in the telephone script for contacting employers. Clarification of the telephone script used for community meetings and to contact community organizers is needed. A plan for dissemination of test results to participants needs to be developed.

The Board believes that this protocol represents an excellent example of research involving human subjects. With the revisions described by the Board, this protocol could serve as a model for future studies. Dr. Fisher noted that the Board continues to be specifically concerned about the practices of IIRB, Inc. This IRB appears not to notice mistakes or errors in protocols and documentation; their lack of attention to detail has been noted when the HSRB has reviewed other protocols.

Dr. Parkin was not able to attend this part of the meeting. However, her comments were provided to the Board and will be incorporated in the report by the Lead Discussant. The Board reached the consensus that the protocol meets the requirements of 40 CFR part 26, subparts K and L.

Carroll-Loye Biological Research Completed Studies: SCI 001.4 and SCI 001.5

Background

Mr. Carley provided background for the completed Carroll-Loye Biological Research studies SCI-001.4 (a field test of DermAegis LipoDEET 302 for repellency against mosquitoes) and SCI-001.5 (a field test of Coulston's Duranon for repellency against mosquitoes).

The protocol SCI-001 was discussed by the Board in January 2007 and first executed by Dr. Carroll in July 2007. The results of field testing of three test repellents were discussed by the HSRB in October 2007. After receiving IRB approval of amendments, protocol SCI-001 was re-executed with only two registered test repellents in November 2007. Reports of the re-execution of SCI-001 with two test repellents would be presented at this meeting.

The re-execution schedule proceeded as follows. On October 24, 2007, Carroll-Loye reported protocol deviations and July 2, 2007 amendments 1(a) and 1(b) to IIRB, Inc. On October 30, 2007, IIRB, Inc. approved the deviations and amendments and requested a progress report. Carroll-Loye submitted the progress report, request for extension, draft amendment 1(c), and revised consent form to IIRB, Inc. IIRB, Inc. approved the progress report, request for extension, amendment 1(c), and revised consent form on November 6, 2007. The study initiation date for re-execution was November 7, 2007, and subject limb measurement, dosimetry testing, and field testing took place between November 7 and 11, 2007. Completion of study re-execution occurred on November 27, 2007.

The draft final report of the October 2007 HSRB meeting was submitted on January 10, 2008. Reports of re-execution of the protocols were submitted to EPA on January 15, 2008. Supplemental information was requested by EPA on February 26, 2008, and submitted to EPA on March 5, 2008. The final report of the October 2007 HSRB meeting was submitted on March 6, 2008. EPA science and ethics reviews occurred on March 7, 2008, and the re-executed protocols were reviewed by the HSRB on April 10, 2008.

A calendar outlining document submissions and the re-execution schedule showed that none of these activities occurred out of sequence. Amendments to the protocol submitted to the Board on October 24, 2007, had been put in place on July 2, 2007 without IRB approval. These amendments added analysis of aspirated mosquitoes and included changes to the test compounds. Another amendment submitted on November 2, 2007, deleted testing of the Ultrathon product and unregistered product that had been added in July 2007. Appropriate changes to consent forms and process also were made. This amendment was submitted on November 2, 2007, approved on November 6, 2007, and the study commenced on November 7, 2007.

EPA Science Assessment: SCI-001.4 and SCI-001.5

Mr. Kevin Sweeney (OPP, EPA) presented EPA's science review of the two completed protocols. The study objectives were to test the mosquito repellent efficacy of the test materials

in the field, support proposed label claims for extended duration of efficacy of two slow-release DEET products, and determine a "typical consumer dose" for each test material.

The study design was similar to those presented previously by this investigator. The dosimetry phase was used to establish the "typical consumer dose" of each test material for use in the efficacy phase. Subjects' forearms were measured and skin area was calculated. Each of 10 dosimetry subjects applied each test repellent 3 times to each arm. The grand mean of subject means was calculated for each test material, to be used as the standard dose rate for that material in the field. The standard dose rate was converted to an individual dose for field testing by adjusting it to individual subject forearm area.

Before participating in field testing, subjects were trained in the laboratory to aspirate landing mosquitoes before they bite, using laboratory-reared, pathogen-free mosquitoes and hand-held electric aspirators. Subjects in field testing were equipped with aspirators, and worked in teams of two to monitor each other for landing mosquitoes. Untreated subjects were attended by two technicians to assist in aspirating landing mosquitoes.

For the field efficacy phase, 10 subjects treated with each formulation and 2 untreated control subjects participated in field trials in each of 2 habitats. Because of expected long efficacy duration, subjects were treated with test repellents before traveling to the test site (reported as a deviation from the protocol). Untreated subjects were used to monitor mosquito pressure. Treated and untreated subjects were exposed to mosquitoes for 1 minute at a time every 15 minutes until efficacy failure or end of test period.

The sample size of 10 subjects per treatment at each site, with 2 concurrent untreated controls, was justified in the protocols with arguments considered by the Board in previous reviews of similar Carroll-Loye protocols. EPA acknowledged HSRB's comments after these previous meetings, and will consider them when revising repellent testing guidelines; however, EPA's position is that a sample size of 10 treated subjects (which substantially exceeds the size specified in the current draft guidelines) is acceptable for studies of this type.

Field testing continued for each subject until that subject experienced a "landing with intent to bite" (LIBe) confirmed by another LIBe within the same or either of the next two 1-minute exposure intervals, or until the end of test period, whichever occurred first. Duration of efficacy (Complete Protection Time [CPT]) was calculated as the time from treatment to "first confirmed landing with intent to bite" or "FCLIBe." Landing mosquitoes collected by aspiration were subsequently identified and subjected to serological analysis.

Measured variables included subject limb area, weight of test materials delivered to dosimetry subject's limb, mosquito pressure (at least 1 landing per minute on untreated controls), time of all LIBes, and time to FCLIBe for each subject. Mean time to FCLIBe, with standard deviation and a 95 percent confidence interval, was calculated consistent with EPA guidelines. Median time to FCLIBe could not be calculated using Kaplan-Meier survival analysis, because most data were right-censored.

The two field sites used for testing were located in Glenn and Butte counties, CA. The Glenn County site was characterized as the understory beneath a canopy of tall native forest and the Butte County site was described as grassland with scattered shrubs and small trees, around a small lake. Wild mosquito populations present at these sites included *Aedes melanimon*, *Ae. Vexans*, *Ae. Stichticus*, *Ae. Increpitus*, *Ae. Sierrensis*, *Ae. Nigromaculis*, *Culex tarsalis*, *Cx. Pipiens*, and *Culiseta inornata*. The field sites were the same as those used in July 2007, but the numbers and species distribution of mosquitoes differed.

After amendment to reduce the number of tested repellents to 2, protocol SCI-001 as re-executed in November 2007 tested 2 registered slow-release lotions containing DEET: LipoDEET 302 (EPA Reg. No. 82810-1) contains 30 percent DEET and Coulston's Duranon (EPA Reg. No. 50404-8) contains 20 percent DEET. Dosing regimens resulted in a standard dose of 2.24 mg/cm^2 for LipoDEET 302 and 1.89 mg/cm^2 for Duranon. The mean total dose was 1,185.5 mg for LipoDEET 302 and 987 mg for Duranon. The mean DEET dose was 355.7 mg for LipoDEET 302 and 197.4 mg for Duranon. Based on dosage for a 70 kg adult, the MOE was 842 for LipoDEET 302 and 1,518 for Duranon. There was a slightly higher DEET dose for LipoDEET 302 and a significant difference in the mean total dose in milligrams.

Comparison of July 2007 and November 2007 testing showed that more landings occurred in July 2007. A total of 9 landings for LipoDEET 302 and 14 for Duranon occurred in November 2007, while 55 total landings for LipoDEET 302 and 63 for Duranon occurred in July 2007. Complete protection times at the Glenn County site were 11.25 ± 0.0 hours for LipoDEET 302 and 11.25 ± 0.0 hours for Duranon. For the Butte County site, complete protection times were 11.28 ± 0.79 hours for LipoDEET 302 and 10.78 ± 1.30 hours for Duranon.

Some limitations to the study were noted. No positive control repellent was tested. The study was performed late in the calendar year, after the peak season for mosquito activity. Testing was truncated before repellent failure; therefore, most data were right-censored and data analysis was limited. Despite these limitations, EPA has concluded that the study provides scientific results that meet EPA guidelines and demonstrates that both LipoDEET 302 and Duranon repelled mosquitoes for 11 hours.

EPA Ethics Assessment: SCI-001.4 and SCI-001.5

Mr. Carley presented EPA's ethics review of the protocols. Background documents considered in this review included the EPA protocol review of December 20, 2006, the April 16, 2007 HSRB report of its January 2007 meeting, MRID 47322501: SCI-001.4 Test of DermAegis LipoDEET 302 Personal Insect Repellent, MRID 47322401: SCI-001.5 Test of Coulston's Duranon Personal Insect Repellent, and the March 5, 2008 letter from Dr. Carroll to Mr. Carley transmitting supplemental correspondence with the IRB and final approved consent forms.

Three protocol deviations were reported. The subjects did not always cover treated limbs between exposures when it was easy to enter the screen house, dosimetry practice proved unnecessary for most subjects, and the subjects were treated 150 to 180 minutes before the first

exposure. Although these deviations are not largely significant, the same 3 deviations have been reported in earlier similar studies by this investigator. EPA suggests that future protocols be revised to incorporate these variations, none of which are of ethical significance.

Field trials were conducted on successive days with many of the same subjects on both days. Consistent with discussion at the October 2007 HSRB meeting, this did not violate the criterion for excluding subjects using repellents "within 1 day preceding the study" or "within a day prior to the start of the study." These exclusions originally were established to be sure that Dr. Carroll was aware of repellent use by subjects.

Discrepancies in wording among the protocol, the consent form, and the study reports were found related to the timing of pregnancy tests; these were not considered to pose substantive problems. No female subject was tested for pregnancy more than once. Five subjects were tested on the only day they participated, 6 were tested on the first of 2 successive days of participation, and 1 was tested on her first day of participation, and participated further 2 and 3 days later. The consent form calls for pregnancy testing "in the morning prior to the start of each of the two study visits."

EPA comments on the protocol made in EPA's review of December 20, 2006, were adequately addressed in the revised consent form submitted on December 29, 2006, and considered by the HSRB in January 2007. The comments that were addressed specifically included those asking for improved description of the recruiting of "experienced" subjects to serve as untreated controls, correction of consent forms to delete references to alcohol in test repellents, and revision of consent forms to better inform untreated controls. In response to HSRB comments, the protocol was amended to incorporate viral assay of field-collected mosquitoes to confirm absence of known pathogens and clarify recruitment of untreated controls. The ICF was revised to correct a mischaracterization of the test materials as containing alcohol and restructured to clarify treatment of untreated controls. The HSRB also suggested that the ICF should read "up to 48 (10 exposed and 2 controls per arm of the study)" subjects will participate; the ICF was not changed. The original form read "up to about 40"; the actual number of subjects was between 37 and 41 in July 2007 and 29 in November 2007. The HSRB's request for evidence of IIRB, Inc. member training, accreditation, and other related matters has not yet been addressed.

Applicable standards for these protocols are 40 CFR §26.1703, which prohibits intentional exposure of pregnant or nursing women, or of children under 18 years of age; 40 CFR §26.1705, which requires evidence of substantial compliance with 40 CFR part 26, subparts A-L; 40 CFR §26.1303, which requires documentation of ethical conduct; and FIFRA §12(a)(2)(P), which requires fully informed, freely voluntary participation.

EPA found the investigator to be generally responsive to EPA and HSRB comments, with minor exceptions, namely that the description of recruiting of experienced subjects to serve as controls was not revised after the January 2007 HSRB meeting and the HSRB recommendation to change the SCI-001 consent form to estimate up to 48 total subjects was not implemented.

Prior review of the protocol found that the requirements of 40 CFR §26.1125 for prior EPA review of the protocol and 40 CFR §26.1601 for HSRB review of the protocol were met. The protocol was in compliance with 40 CFR §26.1303 to document the ethical conduct of research involving human subjects and 40 CFR §26.1703, which requires all subjects to be at least 18 years of age and neither pregnant nor nursing. As re-executed in November 2007, SCI-001 met the requirement of 40 CFR §26.1703 for substantial compliance with 40 CFR part 26, subparts A-L. As re-executed in November 2007, SCI-001 met the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects. In spite of minor inconsistencies in documentation, reports SCI-001.4 and SCI-001.5 provide EPA with adequate information to determine that the research as executed in November 2007 was conducted in substantial compliance with 40 CFR part 26, subparts A-L.

The HSRB is asked to determine whether these studies are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes and whether the available information supports a determination that this study was conducted in substantial compliance with 40 CFR part 26, subparts K and L.

Public Comments

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

Dr. Carroll offered to respond to Board questions concerning this protocol.

Clarifying Questions

Dr. Philpott asked why EPA stated that dosimetry practice was unnecessary for some of the subjects. Mr. Carley clarified that dosimetry practice, not the dosimetry phase itself, was considered unnecessary. Some of the subjects who participated in the field study did not participate in the dosimetry phase, because more subjects were involved in the field study than in the dosimetry phase. This deviation did not compromise the data collection portion of the dosimetry phase.

Board Discussion

Scientific Considerations – SCI-001.4 and SCI-001.5

Dr. Chambers opened the HSRB's science assessment of the protocol stating that the protocol is likely to generate data that is sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes. The limitations pointed out by Mr. Sweeney, namely that the protocols were executed late in the year and the repellent was applied earlier in the testing day than stated did not compromise the data. The truncation of the study and lack of a positive control did not compromise the data.

Dr. Krishnan expressed minor concern about the time interval between initial application and exposure, which was between 150 and 180 minutes; this could have led to greater absorption into the body and less protection. Because the MOE was adequate in this situation, concern

regarding possible greater absorption was not substantial. Dr. Chambers noted that field testing performed in June or July lasts longer, because the day is longer, providing the same opportunity for absorption.

Dr. Lebowitz pointed out that the mean and median failure times for the second study are similar to those for the first. Reporting this data as mean and standard deviation is not optimal, but is what EPA requests. He agreed with Dr. Chambers that the protocol meets the requirements of the charge questions. Dr. Young commented that in future studies, means and standard deviations may not be appropriate for assessing failure time. Confidence intervals should be used for a sample of this size. This does not affect this particular protocol, but should be considered for future protocols.

Dr. Fisher concluded that the Board's consensus was that protocols SCI-001.4 and SCI-001.5 are scientifically sound to be used to assess the mosquito repellency of the test formulations.

Ethical Considerations – SCI-001.4 and SCI-001.5

Dr. Philpott opened the ethics discussion of SCI-001.4 and SCI-001.5 by concluding that the study was conducted in substantial compliance with 40 CFR part 26, subparts K and L. He agreed with the points raised by Mr. Carley in his review. The risks to subjects—exposure to the test products, biting insects, and vector-borne illnesses—were adequately minimized. Concerning the issue of the timing of pregnancy testing, the intent of the regulation was met, but the ICF should have been clearer about this matter. The protocol deviations were minor and reported, but such deviations have been reported in previous studies submitted by this investigator. Because every change needs to be approved by an IRB before the study commences, it is troubling that the changes were made and not reported to the IRB before the start of the study, rather than reporting the changes as protocol deviations. Dr. Philpott also expressed frustration with IIRB, Inc. for not providing adequate information to the Board concerning its credentials and accreditation status.

Dr. Richard Sharp agreed that the protocol was in substantial compliance with the relevant regulations, but raised some issues of concern. The Board previously reviewed and approved a protocol that included 3 test materials, but only 2 were tested; this represents a substantial change to the protocol. The risk to the subjects was not changed, but the change may have impacted the scientific utility of the study. The Board should be concerned that the results indicate that a different protocol was performed than the one approved by the Board. Dr. Philpott stated that he would defer to the Board members who performed the scientific review of the protocol regarding the impact of the dropped product.

Dr. Fish asked Mr. Carley if Dr. Carroll had consulted with EPA before performing the changed protocol. The Board is advisory to EPA; if Dr. Carroll consulted EPA about the changes, this should be sufficient. Mr. Carley responded that the original protocol called for testing four products. Three of the proposed test materials were registered or conditionally registered. The original design did not call for comparison among the products and also did not designate Ultrathon as the positive control. Ultrathon was included because the sponsor hoped to

sell its product to the military; the military requires evidence that a new product is as effective as Ultrathon. In July 2007, the sponsor decided not to maintain registration of one of the 3 test products; thus, the sponsor did not want to spend the money to test this product. At the October 2007 HSRB meeting, the sponsor indicated that a different product with the same concentration of DEET as the dropped product would be tested. This change was complicated and based on business decisions; because the design did not call for comparison of test products, EPA approved this change. The investigator's substitution of an unregistered product was appropriately denied; EPA does not consider dropping a product to be a substantive problem.

Dr. Sharp noted that the protocol claimed that the study was comparative. Thus, the change affected a primary goal of the study. The study is in compliance, but the intention of these regulations is to provide for prospective review of protocols. Disclosure of changes to EPA does not satisfy Board regulations; the Board must review the protocol in advance of its execution. The Board should be cautious about reviewing a completed study that deviated from the reviewed protocol; if the changes that occurred in the course of execution of SCI-001.4 and SCI-001.5 had been substantial, Dr. Sharp would have concluded that the protocol did not satisfy the ethics charge questions. He emphasized that changing protocols was not just a procedural matter.

Dr. Chambers noted that these are the initial protocols to be reviewed by the HSRB and the reviews are part of a learning process. EPA views all products independently; the claims of comparison are for the sponsor and are not intended for EPA use. The changes made in this case resulted in a less dangerous protocol. Dr. Krishnan stated that if the design had been based on a statistical comparison, concern about dropping a test formulation would be valid. Because the products are tested and approved individually, this change has less impact. In the previous Board report, Dr. Carriquiry had concluded that the protocol was insufficient for developing comparative statements. EPA labels also are not allowed to carry comparative statements. Thus the analysis was not comparative and dropping one of the test compounds is not a significant issue.

Dr. Chadwick stated that the deviation from prohibiting testing on successive days could be significant because of possible carryover. Testing on successive days can affect both the science and ethics review and also can impact the risk-benefit analysis. Dr. Chambers reminded Dr. Chadwick that the subjects washed at the end of the test period and prior to the next testing period; carryover thus is not a significant concern. Dr. Chadwick countered that although carryover may not be a concern, IIRB, Inc. should have noted these changes. This investigator has reported protocol deviations on several occasions. The regulations state that the PI must file the protocol with the IRB, receive IRB approval, and conduct the protocol as approved; deviations are allowed only to protect the subjects. This is a key issue for EPA pesticide studies involving human subjects. This particular study is in ethical compliance with the appropriate regulations, but the Board should emphasize that protocol deviations cannot continue to be tolerated.

Dr. Fisher recommended a procedure for future Board review of protocols of this sort. First, with respect to its ethics review of a protocol the Board will not accept a study executed prior to IRB approval of the ICF and the protocol, or changed in ways that were not approved by

the IRB. Second, with respect to 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 appropriate regulations. Board members discussed different language alternatives for defining what would be considered an unacceptable deviation (e.g. "planned" vs. "unanticipated" deviation). Dr. Fisher agreed with Dr. Philpott's suggestion that Board members work on appropriate language for the Board report.

Mr. Jordan acknowledged the Board's conclusion that acceptance of protocols with deviations could have implications for future reviews. He explained that EPA was aware of the investigators plans to re-execute the protocol using 2 of the original test materials previously reviewed by the Board for protocol SCI-001. In the future, if an investigator proposes to re-execute a protocol already presented to the Board, EPA will decide if the re-execution is covered by the original review or if there are sufficient differences to merit a new review by the Board. It is EPA's responsibility to make these judgments; however, if the Board disagrees or has other comments, it should inform EPA of these issues. EPA ethics reviews also should include discussion of protocol changes.

Dr. Fisher stated that in the future, the Board's ethics review may find that a protocol does not meet the applicable standards if any planned deviations were not approved by an IRB before execution of the protocols. Deviations in reaction to unexpected events will be treated differently. EPA also will inform the Board if it finds that the deviations fall within regulations.

Mr. Carley clarified that participation by the same subjects was not reported by Dr. Carroll; however, treatment of subjects on successive days was explained in the protocol, so this particular matter does not represent a deviation. The ICF is clearer than the protocol about matters related to treatment on successive days.

Dr. Lewis stated that a written public comment had been received from Mr. Stephen A. McFadden. This comment was distributed to the Board members as information and not for specific review.

EPA Review of ICR Protocol G4330108001A382

Background

Mr. Carley presented background information for the protocol ICR A382, submitted by ICR on February 7, 2008. This protocol proposes a laboratory test of stable fly repellency for 2 conditionally registered products containing 20 percent picaridin. EPA's science and ethics reviews of March 7, 2008, were based on reviews of the February 7, 2008 submission.

This is a proposal for research involving intentional exposure of human subjects, with the intent to submit the resulting data to EPA under FIFRA. Regulations 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, thus apply.

The February 7, 2008 submission failed to include an acceptable discussion of the balance of risks and benefits of the proposed research as required by §26.1125(a)(5), but otherwise met the regulatory standard of completeness; this deficiency did not compromise EPA's review. Although additional refinement is needed to address all comments in EPA's science and ethics review, EPA believes this protocol is ready for review by the HSRB.

ICR A382 presents some novel elements. This protocol is the first reviewed by the HSRB that involves testing with stable flies and the first protocol from ICR to include a dose-determination phase. Finally, this is the first protocol reviewed by the Board that has differing eligibility criteria and separate consent documents for dose-determination and repellency phases. Another important difference relates to the ways in which stable flies differ from mosquitoes.

EPA Science Assessment of ICR Protocol A382

Mr. Sweeney presented EPA's science review of ICR A382. This protocol is a cage test of stable fly repellency for 2 formulations of picaridin. The repellents are expected to provide more than 8 hours of protection from stable flies, *Stomoxys calcitrans L.*, in the laboratory. The objectives of this proposal are to determine the mean protection time from bites provided by the test products under laboratory conditions to confirm the hypothesis and to determine the "typical consumer dose" of each product applied by users following label directions.

The test materials are 2 conditionally registered repellents containing 20 percent picaridin, Reg No 39967-53: KBR 3023 All-Family Insect Repellent Spray and Reg No 39967-50: KBR 3023 All-Family Insect Repellent Cream. Both products are conditionally registered by EPA pending new efficacy data, including efficacy in repelling biting flies.

The test laboratory will be maintained at 70 degrees ±15 degrees Fahrenheit and ambient relative humidity, which are the same conditions under which the flies are raised. There will be 6 cages, with dimensions of 2-feet long by 2-feet high by 2-feet wide. The cages have screened tops and sides and mirrors on the bottoms to permit monitoring of the undersides of the arms. There are two sleeved ports on opposite sides of the cage. Two subjects will be tested in each cage (12 subjects total). The protocol calls for one 11-hour day of repellency testing.

The test flies are male and female *S. calcitrans L.*, 3- to 10-days old, and fasted for 24 hours. Twenty-five flies will be initially placed in each cage; flies will be replaced by 25 fresh flies per cage if fewer than 2 landings per minute occur on the untreated control subject. These flies have been laboratory-colonized for many years, are raised on bovine blood, and have no exposure to outside blood sources. Flies are destroyed after a single test. The protocol was unclear concerning whether the test flies would receive a previous blood meal. On page 12 of the protocol, ICR states that the flies have been raised on bovine blood but will not have had a blood meal for 24 hours before use in the test and will not have had a human blood meal at all. On page 28, the protocol indicates that the flies have been fed on sucrose and have not had a blood meal of any type. ICR has promised to clarify this issue and revise the protocol before it is executed.

The repellent phase exposure regimen calls for all subjects to expose their untreated arms to caged stable flies to establish attractiveness. Twelve subjects will be treated to ensure that there are at least 10 subjects even if 1 or 2 subjects fail to qualify or withdraw. The treated subjects, treated with one formulation on each arm, will expose both arms to caged flies for 5 minutes at 30-minute intervals until failure or 10 hours. All data from all subjects will be included in analysis. One untreated subject, selected by lot, will monitor aggressiveness of caged flies for 1 minute at 30-minute intervals.

Twelve subjects will participate in dose determination. Each subject will apply each repellent to a 250 cm^2 area on each forearm, following label directions. The amount applied will be measured by determining the change in weight of the cream product container or the change in weight of the surgical dressing, gauze strip, and rubber bands wrapped around the treatment area for the spray product, scaled up to the full 250 cm^2 area. Each subject will apply each repellent three times; the grand mean of subject mean doses will be the standard dose for the repellency phase. The measurement of the amount of repellent applied by the spray needs to be clarified in the protocol; there is insufficient information about the area covered by the dressing, gauze strips, and rubber bands.

The actual dose to be used in the repellent phase will be determined in the dose-determination phase. Based on an estimated dose of 1 gram per 600 cm^2, each subject in the repellency phase will receive a total dose (both arms) of 835 mg product (167 mg picaridin; when adjusted for ethanol content, about 5.4 mg/kg for 70 kg adult). Based on the World Health Organization-reported picaridin dermal NOAEL of 5,000 mg/kg, the MOE is greater than approximately 926. A standard volumetric dose will be applied by investigators, and only the subjects will be blinded, but the cream and spray products are easily distinguished.

Measurements and endpoints recorded for the protocol include subject limb dimensions, landings observed during attractiveness testing, weight of repellent applied in dose-determination phase, time post-treatment of all bites on treated subjects, and landing rate on untreated control's arm. No forms have been proposed for recording dose-determination or calculating standard dose for the repellency phase.

CPT is defined in this protocol as Time to First Confirmed Bite (FCB). The duration of efficacy will be measured as the time from treatment to "First Confirmed Bite (FCB)" or 10 hours, whichever occurs first. A bite is considered to be an appropriate endpoint for stable fly repellency testing because a single stable fly may land repeatedly without biting, unlike mosquitoes. A "confirmed" bite is a bite occurring in one 5-minute observation period followed by another bite in the same or the subsequent 5-minute observation period.

ICR proposes to analyze the data using the Kaplan-Meier product limit technique. They will report mean and median time to FCB, with 95 percent confidence interval. If all data are right-censored, they will conclude that the CPT is 8 hours ±2 hours. The untreated control will not be used for comparison and the results will not be compared between formulations. If more than 2 subjects withdraw early, conclusions will reflect the power analysis provided in the protocol.

ICR's rationale for sample size is based on EPA guideline recommendations of 6 subjects for this sort of testing. In addition, an analysis by Rutledge and Gupta (1999) shows that a sample of 10 to 11 is needed to achieve with 95 percent confidence a standard deviation not greater than 2 hours after 8 hours of testing with mosquitoes. An ICR meta-analysis of previous stable fly studies performed in the ICR laboratory suggests a minimum sample size of 7. ICR has thus proposed a sample of 10, plus 2 additional treated subjects to ensure a minimum of 10 test subjects and protect the privacy of subjects who withdraw.

EPA agrees that use of a bite instead of a landing as the endpoint is definitive and a more accurate measure of repellent failure because stable flies commonly land without biting, only to land again (when they may or may not bite). Although it is not required by EPA guidelines, a positive control would improve the study design and aid in the interpretation of results; EPA has less data for stable flies than it does for mosquito repellency studies. A potential design for incorporation of a positive control could be to use as a positive control test product a repellent that contains more than 20 percent DEET. One forearm of each repellent-phase subject would be treated with the test product and the other with the positive control repellent. The same subjects would be used to test both repellents on successive days. EPA would help ICR identify an appropriate positive control repellent.

EPA has concluded that if the above comments are addressed, this protocol is likely to yield scientifically reliable information. Per criteria in the framework recommended by the HSRB, the protocol would produce important information that cannot be obtained except by research with human subjects, has a clear scientific objective, and the study design should produce adequate data to achieve the objective.

Clarifying Questions

Dr. Fish asked if the event of a bite would be assessed by the research staff. Mr. Sweeney confirmed that this was so. Dr. Young inquired whether an area of repellency would be created around the arm. Mr. Sweeney answered that previous research has shown that the vapors from picaridin and DEET remain very close to the treated area and thus do not create such an area of repellency. Dr. Lehman-Mckeeman questioned how EPA would use data from a positive control and whether lack of a positive control would affect the ability to interpret the data. Mr. Sweeney replied that if studies from different laboratories are compared, positive controls help calibrate results which may differ because of different laboratory procedures and different mosquito species. A positive control would help understand the difference in CPTs determined by different laboratories and if the difference was due to laboratory conditions or different strains of mosquitoes. Use of a positive control is not essential for determining whether a product functions as a repellent; however, a positive control can assist EPA with comparing data from different products with the same concentration of picaridin (or other active ingredient) or testing performed by different laboratories. This is primarily a regulatory issue, but is of some importance for EPA because of EPA's lack of data for testing products against stable flies. EPA has some data from tests of DEET for repellency of flies. Dr. Chambers inquired whether a lower than expected CPT for the positive control would alter conclusions about the test product. Mr. Sweeney answered that it is difficult to determine if a lower CPT for one type of active

ingredient means that another type is more effective. If the CPT was substantially lower, it might be difficult to know why without a positive control. He stated that he could not make a definitive conclusion about this issue without having data from multiple laboratories.

EPA Ethics Assessment of ICR Protocol A382

Mr. Carley presented EPA's ethics review of ICR A382. The proposed study would test the repellent efficacy of 2 conditionally registered products containing 20 percent picaridin against stable flies under laboratory conditions. The test repellents have previously been field tested against other insects, but have not been tested against stable flies or other biting flies. EPA requires efficacy data to support proposed label claims of repellency against biting flies.

Subjects will be recruited among previous subjects of similar ICR tests and their friends and colleagues. The pool is characterized as being "as representative of potential repellent users as we are able to make it." EPA has noted that, although no race is specifically excluded, the subject pool is all white. Baltimore County, Maryland, which surrounds the ICR location, was 25 percent minority in 2000, and nearby Baltimore City was 68 percent minority. ICR has claimed that a special effort will be used to recruit African-Americans for this study, but this effort is undefined. EPA believes that greater effort is warranted to recruit a subject pool more broadly representative of the target population of potential repellent users in race, age, and other characteristics. No subjects would be drawn from populations vulnerable to coercion or undue influence.

EPA has found the exclusion factors to be appropriate. Anyone under 18 or over 70 years of age is excluded, as are pregnant or nursing women. People sensitive to repellents or to stable fly bites are excluded from the repellency phase; these criteria are not applicable to the dose-determination phase. People in poor health or physical condition will be excluded. Those unable to speak and understand English are excluded. Employees or relatives of employees of ICR, the sponsor, or any other interested party also are excluded.

Subjects participating in the dose-determination phase will receive $99 for approximately 3 hours of "direct involvement." The discussion of this in the consent form is confusing because although the active phase of testing is only 3 hours, the subjects may be at the facility all day. Subjects participating in the repellency phase will receive $134 for approximately 11 hours of testing. These different rates of pay are not acknowledged or explained.

The potential risks from picaridin and from the formulated repellents have been accurately characterized. The expected discomfort from fly bites is accurately characterized, although a confirming bite may not be justified. Because mosquitoes do not bite twice, a confirming bite is caused by a different mosquito. This confirms that the initial bite was not caused by a mosquito unusually resistant to the repellent. Because flies may bite more than once, a confirming bite may not be caused by a different fly. ICR should consider using a single bite to determine loss of protection. The risk of arthropod-borne disease is characterized as zero, which is appropriate because disease-free, laboratory-raised flies are used for testing and stable flies are not known to be vectors for human diseases. The risks of allergic or irritation response from test materials or fly bites are minimized by excluding sensitive candidates, limiting the area treated or exposed, and monitoring subjects closely.

This research provides no direct benefit to subjects. The primary beneficiary of the research will be the sponsor, who hopes to be able to market these products with claims for repellency against biting flies in many countries. There is a likely societal benefit of identification of repellents effective against biting flies under controlled laboratory conditions. The balance of risks and benefits is not discussed in the protocol as required by §26.1125(a)(5), but ICR has promised to provide this discussion. EPA views the risks to subjects as reasonable given the potential societal benefit of identifying products which effectively repel biting flies. The risks have been effectively minimized, and residual risk to subjects will be very low; these risks could be marginally lower if a confirming bite were not required. The test materials are likely to prove effective.

The Essex Institutional Review Board, Inc., of Lebanon, New Jersey (EIRB) reviewed and conditionally approved the protocol and consent forms, subject to revision, on January 28, 2008. EIRB approved Amendment 1 to protocol, revised consent forms, and recruiting script on February 4, 2008. This IRB is independent of the sponsors and investigators and is registered with OHRP, but is not accredited by the Association for the Accreditation of Human Research Protection Programs or Partnership for Human Research Protection. EIRB procedures have been submitted directly to EPA under a CBI claim; EPA has determined they meet regulatory standards.

All subjects will sign consent forms meeting the standards of 40 CFR §26.1116 and §26.1117, and the recruiting and consent processes have been adequately described in the protocol and consent forms. The methods proposed for managing information about prospective and enrolled subjects will generally protect their privacy. Subjects will be free to withdraw at any time and medical care for research-related injuries will be provided at no cost to the subjects.

Because this is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws, the primary ethical standards applicable to this research are 40 CFR part 26, subparts K and L. EPA has noted minor deficiencies. The protocol lacks a discussion of the balance of the risks and likely benefits of the research, as required by 40 CFR §26.1125(a)(5). The consent form discussion of remuneration for dose determination phase needs clarification. Other minor inconsistencies need to be addressed, namely criteria for exclusion of those sensitive to fly bites, how attractiveness to biting flies is demonstrated, and whether the flies used for testing will have received a prior blood meal.

All requirements of §26.1111, §26.1116, and §26.1117 are met. If the promised additional material is provided, all requirements of §26.1125 would be met. The requirements of §26.1203 are met. If revised as requested, protocol ICR A382 and the associated consent forms will likely meet the applicable requirements of 40 CFR part 26, subparts K and L.

If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, the Board is asked to determine whether the research is likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for

repelling stable flies, and whether the research appears to meet the applicable requirements of 40 CFR part 26, subparts K and L.

Public Comments

Dr. Robin Todd and Mr. William Gaynor, on behalf of ICR, and Dr. Ralph Piedmont, on behalf of Loyola College on behalf of ICR

Mr. Gaynor explained that the flies used in this test have never had a blood meal. Normal rearing protocols call for feeding the flies blood meals, but these will be reared on a sucrose solution and then fasted for 24 hours before the test. Regarding remuneration, participants in the dosimetry phase will be paid the same as those in the repellency phase because it is uncertain how long this phase will last. Participants also may have a long commute, so payment must be worthwhile for them to participate.

Dr. Lehman-Mckeeman asked Mr. Gaynor to address the issue of a positive control. Mr. Gaynor answered that inclusion of positive controls would require twice as many subjects and thus increase risk. In addition, if the repellency of the positive control product lasts for the entire duration of testing, all test subjects must be exposed for at least that period of time as well. A positive control also will not be significantly helpful for comparing different products. Dr. Todd added that although inclusion of a positive control may be scientifically desirable, it will significantly increase costs of the study.

Dr. Chadwick inquired why the test population was ethnically homogenous; other Federal agencies would find this unacceptable. Attractiveness to insects may vary across racial and ethnic populations, so an ethnically diverse test population is important. Dr. Todd explained that prior to the requirements for HSRB and IRB review, recruiting was easier. It is difficult to recruit for these tests because the tests tend to be boring and uncomfortable. ICR wishes to include subjects who will be reliable and will not withdraw from the study; thus, ICR tends to draw subjects from a population known to its staff. ICR anticipates inclusion of more African-American subjects in the future. Dr. Todd agreed that the test population should be more diverse and that a higher number of younger subjects should be included.

Dr. Fisher questioned if the assessment of the balance of risks and benefits had been written. Mr. Gaynor responded that this had not yet been written, but would be included in the revision submitted to the IRB.

Dr. Krishnan requested clarification of the typical dose described for the dosimetry phase. Mr. Gaynor replied that those values were determined as the maximum dose that ICR expects people to apply during the dosimetry phase. Such a value needed to be included for IRB review of the protocol, but ICR will not allow the doses applied to be greater than this.

Board Discussion

Scientific Considerations – ICR Protocol A382

Dr. Lehman-Mckeeman opened the science discussion of ICR A382 by acknowledging that this was a high-quality protocol, with only minor revisions needed. The protocol will generate scientifically valid data. She added that she was not convinced that all EPA suggestions needed to be addressed.

The protocol adequately justifies the lack of a positive control. The only benefit to including a positive control would be to add to EPA's data on repellency against flies. If the study is executed as described, the positive control would not add to the strength of the data for establishing efficacy under these particular laboratory conditions using these particular subjects.

Concerning the assessment of CPT using bites, requiring a confirmed bite is adequate. Dr. Lehman-Mckeeman agreed that clarification was needed regarding feeding and fasting of the flies. Clarification of the number of subjects involved in the study also is needed; 13 subjects are included in the protocol, one is untreated and the other 12 are treated. Regarding the handling of the spray products, the dosimetry phase calls for subjects to spray the product on the dosimeter material, and then weigh the material. For the repellency phase, subjects are instructed to spray the product into a container and then a syringe is used to apply it. This is different than usual consumer use and it is unclear why this technique is used.

The protocol does not stipulate subject behavior when not actively participating in testing. There should be some limitations on subject activities so that these activities do not affect the data. This should be included in the protocol to develop a description of a typical experimental day. Regarding statistics, previous research specifies 7 as the minimum number of subjects to include in such studies. This protocol aims to include 12 subjects, but should specify the sponsor's rationale for an adequate sample size.

Dr. Krishnan agreed that the protocol is likely to generate useful data and agreed with other comments by Dr. Lehman-Mckeeman, particularly those concerning the positive control. The dosimetry and MOE calculations were slightly confusing. The protocol references a maximum application rate of up to 4 mg/cm^2, but EPA calculations are based on a typical dose, not a maximum dose. There is a 2.5-fold difference between EPA's typical dose used for calculating the MOE and the maximum dose; however, use of the maximum dose for these calculations does yield an MOE within a safe range. Dr. Krishnan inquired if the maximum application rate would be considered in EPA labeling decisions. Mr. Sweeney responded that it can be factored into risk assessment, but labels do not have to specify dose. Mr. Carley added that some labels for repellents warn consumers not to apply the product more often than a certain number of times per day. He clarified that the purpose of describing the maximum dose was to satisfy a requirement of the IRB, not to predict dose. The dose used by EPA for MOE calculations was the dose that has been determined in several of Dr. Carroll's studies.

Dr. Chambers agreed with Dr. Lehman-Mckeeman regarding the reliability of the data and the inclusion of a positive control. Including a positive control relates to research questions more than regulatory issues and would only lead to involving more subjects.

Dr. Chambers disagreed with Dr. Lehman-Mckeeman's conclusion that a confirming bite was needed, and agreed with Mr. Carley that one bite would be sufficient. Concerning the

technique used to apply the spray product, because spraying is a less accurate application technique, spraying into a container and using a syringe to apply the product is appropriate.

Dr. Fish inquired why, given that the research staff will evaluate outcome, the research subjects are blinded but not the staff and asked if any potential bias could arise from using non-blinded outcome evaluators. The products could be randomized to either the left or right arm; one staff member could apply the products and the others could observe.

Dr. Johnson questioned whether the test population of stable flies were similar to stable flies found elsewhere. He stated that the inference that the flies would be the same was based on expert judgment rather than statistics.

Dr. Fisher requested Board consensus on the need for a confirming bite. Dr. Lebowitz stated that the bites are obvious, so one bite should be sufficient. Dr. Lehman-Mckeeman indicated that if scientifically robust data can be obtained using a single bite, she would agree that a confirming bite is not needed. Mr. Carley clarified that this approach would not affect protection time calculations unless there is an unconfirmed bite, i.e., no other event occurs within 30 minutes. The time of the initial bite would be used to calculate protection time.

Dr. Fisher noted that the number of subjects included in the protocol is not clear. If a subject population of 10 was determined by power analysis, that number should be used. The protocol should clarify sample size and the power analysis on which this sample size was justified.

Dr. Fisher summarized the science discussion. The Board found the protocol to be of generally high quality. They determined that inclusion of a positive control would not add substantially to the usefulness of the data. The Board was open to the opinion that a confirming bite may not be needed. ICR has adequately clarified how the test flies will be fed. ICR should justify and maintain its proposed subject population size. Activities of subjects during the rest periods need to be described. Potential bias arising from using specific arms to test each product should be considered, as should blinding of research staff.

The Board considered the lack of ethnic diversity in the subject pool to be troubling. Lack of non-white participants may affect the scientific validity of the results. Dr. Young commented that because there are no data that can determine whether there are genetic differences or similarities in insect attractiveness between ethnic groups, other groups should be included in this research. Dr. Lebowitz agreed that this is a serious issue and added that ethnic groups other than whites and African-Americans also should be considered. It may not be possible to generalize these results beyond the study populations. Dr. Chadwick suggested that, from a regulatory perspective, the study may not be scientifically sound if it includes only whites. He did not think it would be difficult to recruit subjects from other ethnic groups. Dr. Menikoff agreed that this was an important scientific and ethical issue because these products are marketed globally; however, gathering better information about variations in insect attractiveness or repellency across ethnic groups is beyond the scope of this study.

Dr. Menikoff stated that, from an ethics perspective, the test population should be representative of the community from which the subjects are drawn. Dr. Chadwick noted that

other regulatory agencies sponsor larger trials, which impacts the diversity of the sample. He asked whether a sample size of 12 or 13 was sufficient to globally market pesticides. Dr. Krishnan inquired whether a recommendation for a non-homogenous subject population would be consistent with the Board's reviews of previous protocols. Dr. Fisher answered that the Board asked Dr. Carroll to diversify his subject pool and comments concerning the homogeneity of ICR's pool are appropriate. Mr. Carley clarified that Dr. Carroll supplied information demonstrating that the ethnic and gender balance of his subject pool closely matches the community from which he recruits and is thus more representative of the surrounding area. Dr. Young cautioned that asking a subject pool to be representative of the surrounding area might be inadequate, because some parts of the country may be highly homogenous. Requiring that the subject pool be diverse would be more appropriate.

Dr. Fisher asked Drs. Chadwick and Lehman-Mckeeman to develop language to express the Board's concern over this issue. The Board agreed that, with the noted revisions, the protocol would provide scientifically reliable data for assessing repellency of the products against stable flies.

Ethical Considerations – ICR Protocol A382

Dr. Fish opened the ethics discussion of ICR A382. She noted that the protocol was well written and provided sound justification. She questioned the rationale for excluding participants over the age of 70 years and suggested removing this exclusion factor if there is no scientific justification for it. The inclusion criteria state that the subjects must be able to read, speak, and understand English, but there appears to be no clear rationale for requiring literacy. The investigators should consider whether all women participating in the study require a pregnancy test or whether women could instead be asked if they are post-menopausal or have had a hysterectomy. Regarding the dose-determination phase, the protocol and consent form describe 3 applications, but elsewhere the documents indicate that 4 applications may occur; this needs to be clarified. The number of repeated exposures needed to determine participant attractiveness to flies needs to be clarified. Overall, the protocol does meet the ethical issues raised in the charge question.

Dr. Menikoff agreed with Dr. Fish. He inquired why Dr. Fish suggested asking women about their reproductive status rather than requiring all women to take a pregnancy test. Dr. Fisher added that it may be difficult for some women to determine if they are truly post-menopausal. Regulatory rules state that participants must not be pregnant; EPA must decide how conservative it wishes to be regarding this matter. Dr. Fish suggested that EPA should develop a standard for pregnancy testing.

Dr. Chadwick considered that relying on subjective reports of menopause should be adequate. Regarding how the flies were raised, knowing whether the flies were exposed to bovine blood is of interest because of potential subject exposures to Creutzfeldt-Jakob disease. The IRB may not have noticed this issue if its members lack knowledge of entomological issues. EPA may wish to offer guidance for the expertise an IRB should possess for reviewing EPA protocols. Dr. Chadwick agreed that the protocol satisfied the ethics charge question.

Mr. Carley addressed the issue of pregnancy testing. In addition to assessing due diligence to ensure that an investigator is compliant with this regulation, EPA also seeks input for determining best practices to ensure discretion and respect for female candidates. Dr. Fisher remarked that it is inaccurate to assume that women older than 50 years of age cannot get pregnant. Given that the regulations prohibit participation of pregnant women, she stated that having all women take a pregnancy test would be a conservative approach. Mr. Jordan indicated that EPA would accept as adequate compliance with this regulation either a set of drugstore pregnancy test results or interviews in which questions regarding possible pregnancy were clearly asked of and answered by the subjects. He inquired which approach would be more respectful of the candidate. Dr. Fisher responded that being asked would be more respectful. There is some flexibility to this; if there is little evidence of risk of pregnancy, it would be more appropriate to treat all female subjects equally. Dr. Chadwick suggested that statistics defining the average age of menopause be examined and that age be used as a ceiling for testing. Dr. Lebowitz countered that using the average age of menopause as a cut-off for testing could be problematic because some women experience menopause at an older age than the average. Dr. Fish noted that the IRB on which she serves has struggled with this issue. Although the definition of menopause is a lack of a menstrual period for 1 year, in high risk studies women are asked if they have had a period in the last 2 years (or if they have had a hysterectomy); if this is so, they are not asked to take a pregnancy test. She agreed that basing this decision on the average age at menopause is not useful because some women will not experience menopause until later in life. Asking about the possibility of pregnancy is more respectful; asking all women to take the test is less respectful because it implies that the investigator does not trust the woman to know if she may be pregnant. Dr. Fisher stated that the solution may be to ask if the participant has had a menstrual period within the last 2 years or has had a hysterectomy, and base the need for pregnancy testing on the answers to these questions.

Dr. Fisher summarized the ethics discussion. Justification or removal of the upper age limit and for literacy in English is needed. The number of applications of product should be clarified, as should activity during the attractancy testing phase and payment procedures. Issues related to blood meals also should be addressed. With these changes, the protocol will meet the criteria described in the charge questions.

Concluding Remarks

Mr. Jordan described three topics likely to be discussed at the June 2008 HSRB meeting:

- The AHETF has delivered material (governing documents, protocols, and procedures) for their proposed research, which covers one scenario. Assuming these materials pass EPA review, the Board will review the material in June 2008.
- Additional insect repellent protocols will be reviewed. ICR has executed a mosquito repellency protocol that was reviewed by the Board in October 2007. The Board will review the results of this study, pending EPA review. ICR also has submitted a new protocol testing a space repellent. This type of repellent is not applied to the skin but instead is emitted into an area; the vapors repel mosquitoes from the treated area. Different design issues will need to be addressed for this protocol.

- EPA staff in the Office of Pesticide Programs, Health Effects Division may submit an older toxicology study for review by the Board.

Dr. Fisher inquired whether EPA could provide an abstract or summary of protocols to be used by the Board when the Board develops its report. Mr. Jordan agreed that EPA could provide this. Dr. Fisher stated that it should be made clear that, from an ethics perspective, a protocol does not comply with regulations if every element has not been approved by an IRB prior to execution. It may be inappropriate for the HSRB to review protocols in which EPA discovers that the IRB performed an inadequate review. Dr. Fisher and other Board members have previously expressed difficulty with the inadequacy of some IRB reviews. Mr. Carley noted that for all protocols reviewed, comments regarding science and ethics have gone beyond what could be expected in an IRB review, but he acknowledged that issues overlooked by the IRB have been noticed. Dr. Fisher commented that, given that the Board is not provided with information concerning the processes by which IRBs perform their reviews, the Board must consider whether the IRB has been negligent if the review appears inadequate.

Dr. Fisher acknowledged that because data from the AEATF protocol would not be received for a year, it would not be possible to perform expedited reviews of these protocols in the near future. Mr. Carley stated that the Board will review additional proposals from AEATF at the October 2008 meeting. Regarding expedited reviews, the protocols cannot be executed quicker than they are currently being reviewed; expedited review thus refers to a reduced scope of review. The first time a scenario is presented, a full review will be required. Mr. Carley has discussed this issue with both task forces. It may be possible for the AEATF to include in a single package all field studies associated with a scenario. The AHETF studies are more complicated because they are performed in different areas in the presence of different types of crops. After discussions with the AHETF, it was determined that it may be more efficient to submit all field conditions associated with a scenario simultaneously, to avoid repeated review of that scenario.

Dr. Fenske questioned why it would be a year before the HSRB reviewed the results of the AEATF protocol, given that the task force wished to perform this research as soon as possible. He also asked whether the Board would review the hand wash removal efficiency study that Mr. Leighton mentioned might be purchased to provide information concerning this matter for task force protocols. Mr. Carley replied that the task force estimated the 1-year timeframe. The materials presented at this meeting will be revised and then must undergo another IRB review. In addition, the California DPR must review the protocol and because of staffing issues, this review may be delayed. The AHETF research can be performed only at certain times of the year, depending on when pesticides are applied to the various crops. The AHETF investigators plan to collect data in the summer and generate their reports in the winter; review of these protocols will likely take place in the spring.

Mr. Jordan clarified that human studies regulations call for EPA to bring the results of the studies on which the Agency intends to rely to the Board if the studies involve intentional dosing and/or took place after the new rule took effect. The study mentioned by Mr. Leighton was initiated before the rule was in place and does involve intentional dosing, but will not be used to

assess toxicity. Because of the way EPA plans to use this study in the analysis of data, EPA has not yet decided if this protocol must be reviewed by the Board.

Adjournment

Dr. Lewis thanked Dr. Fisher for serving as chair of this meeting. He also 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 June 24-27, 2008, and will be announced in the *Federal Register*. The Board will prepare its report for this meeting and send drafts to Drs. Fisher and Lewis within the next 2 weeks. This report may be reviewed and approved at the June 2008 HSRB meeting rather than at a separate teleconference, if the agenda permits.

Dr. Fisher thanked EPA again for providing informative and concise presentations and then adjourned the meeting.

Respectfully submitted:

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

Certified to be true by:

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

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Board members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the Board members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final report prepared and transmitted to the EPA Science Advisor following the public meeting.

Attachments

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

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS AND CONSULTANTS

Chair

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

Vice Chair

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

Members

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Richard R. Sharp, Ph.D.
Director of Bioethics Research
Department of Bioethics
Cleveland Clinic

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

Consultants

KyungMann Kim, Ph.D., CCRP
Professor and Associate Chair
Department of Biostatistics & Medical Informatics
School of Medicine and Public Health
University of Wisconsin-Madison

* Not in attendance
** Attended via telephone on April 9, 2008

Attachment B
Federal Register Notice Announcing Meeting

Human Studies Review Board; Notice of Public Meeting

[Federal Register: March 7, 2008 (Volume 73, Number 46)]
[Notices]
[Page 12413-12415]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]

ENVIRONMENTAL PROTECTION AGENCY
[EPA–HQ–ORD–2008–0033; FRL–8539–8]

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 April 9–April 10, 2008 from 8:30 a.m. to approximately 5:30 p.m., Eastern Time.

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–2008–0033, 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 email 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– 0033. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http:/ www.regulations.gov,* including any personal information provided, unless the comment

includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information through *http://www.regulations.gov* or e-mail that you consider to be CBI or otherwise protected from disclosure. The *http:// www.regulations.gov* Web site is an ''anonymous access'' system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through *http://www.regulations.gov*, your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

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

SUPPLEMENTARY INFORMATION:

I. Public Meeting

A. Does This Action Apply to Me?

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

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

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

Docket: All documents in the docket are listed in the *http:// www.regulations.gov* index under the docket number. Even though it will be listed by title in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Copyright material will be publicly available only in hard copy. Publicly available docket materials are available either electronically in *http:// www.regulations.gov* or in hard copy at the ORD Docket, EPA/DC, Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW., Washington DC. The hours of operation are 8:30 a.m. to 4:30 p.m. EST, Monday through Friday, excluding Federal holidays. Please call (202) 566–1744 or e-mail the ORD Docket at *ord.docket@epa.gov* for instructions. Updates to Public Reading Room access are available on the Web site (*http:// www.epa.gov/epahome/dockets.htm*). EPA's position paper(s), charge/ questions to the HSRB, and the meeting agenda will be available by mid March 2008. 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 CONTACT**.

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– 0033 in the subject line on the first page of your request.

a. *Oral comments.* Requests to present oral comments will be accepted up to April 1, 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 email) to the person listed under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern time, April 1, 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, April 1, 2008. You should submit your comments using the instructions in Unit I.C. of this notice. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to the person listed under FOR FURTHER INFORMATION CONTACT. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

A. Human Studies Review Board

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

B. Topics for Discussion

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

- An update on revisions to the EPA document, ''Scientific and Ethical Approaches for Observational Exposure Studies,'' which the HSRB previously reviewed and commented on at the October 24–26, 2007 HSRB meeting.
- Two closely related product-specific reports from a single completed field study by Carroll-Loye Biological Research of the mosquito repellent efficacy of two registered pesticide products containing Deet.
- A research proposal from Insect Control & Research, Inc. to evaluate the laboratory efficacy in repelling stable flies of a registered pesticide product containing picaridin.
- Two research proposals from the Antimicrobial Exposure Assessment Task Force II (AEATF) to monitor exposures of subjects who apply an antimicrobial pesticide by wiping and by mopping. The AEATF proposals will consist of multiple documents including a ''Governing Document'' describing the larger research initiative of which these two studies are a part, a set of ''Standard Operating Procedures'' for the execution of the studies, a ''Scenario Justification'' describing the AEATF's rationale for key elements of each study design, and protocols for the mop study and for the wipe study.

In addition, the Agency will report to the Board on how it has resolved issues relating to the design of sampling strategies for handler research programs proposed by the Agricultural Handlers Exposure Task Force and the Antimicrobials Exposure Assessment Task Force II. Finally, the HSRB may also discuss planning for future HSRB meetings.

C. 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: February 14, 2008.
George Gray,
Science Advisor.
[FR Doc. E8–4583 Filed 3–6–08; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
PUBLIC MEETING
APRIL 9-10, 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-2008-0033

8:30 AM **Convene Meeting and Identification of Board Members** – Celia Fisher, Ph.D. (HSRB Chair)
8:40 AM **Welcome –** George Gray, Ph.D. (EPA Science Advisor)
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, Office of the Science Advisor [OSA], EPA)
9:05 AM **Update on Revisions to the EPA Document "Scientific and Ethical Approaches for Observational Exposure Studies" –** Roy Fortmann, Ph.D. (Office of Research and Development, EPA)
9:35 AM **EPA Follow-up on Pesticide Specific HSRB Recommendations –** Mr. William Jordan (OPP, EPA)

Overview of EPA's Assessment of Proposed Pesticide Handler Research

Sampling Strategies in Proposed Pesticide Handler Research
9:50 AM **EPA Presentation** – Mr. William Jordan (OPP, EPA)
10:30 AM **Break**
10:45 AM **HSRB Workgroup Report on Sampling Strategies in Proposed Pesticide Handler Research –** Celia Fisher, Ph.D. (HSRB Chair)
11:00 AM **Public Comments**
11:15 AM **Board Discussion**
11:45 AM **Lunch**

Antimicrobial Exposure Assessment Task Force (AEATF) Governing Document

12:45 PM **EPA Science and Ethics Assessment of Revisions to AEATF's Governing Document** – Mr. David Miller (OPP, EPA)

1:00 PM **Public Comments**

1:15 PM **Board Discussion**

EPA Review of AEATF-II Mop and Wipe Scenarios

1:45 PM **Background, Context and Sampling Design** – Mr. John Carley (OPP, EPA)

2:15 PM **Science Assessments –** Mr. Tim Leighton (OPP, EPA) and Cassi Walls, Ph.D. (OPP, EPA)

3:15 PM **Break**

3:30 PM **Ethics Assessments –** Mr. John Carley (OPP, EPA)

4:00 PM **Public Comments**

4:30 PM **Board Discussion** (Note: due to similarities of the mop and wipe scenarios, both exposure scenarios will be discussed together)

Science

If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by mopping?

If the proposed research described in AEATF's proposed wipe scenario designs, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by wiping?

5:45 PM **Adjournment –** Celia Fisher, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)

Thursday, April 10, 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)
8:40 AM **Follow-up from Previous Day's Discussion –** Mr. William Jordan (OPP, EPA)

EPA Review of AEATF-II Mop and Wipe Scenarios

Ethics
If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

If the proposed research described in AEATF's proposed wipe scenario designs, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

ICR Protocol: A382
10:00 AM **EPA Science and Ethics Assessment of ICR Protocol: A382 –** Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)
10:45 AM **Break**
11:00 AM **Public Comments**
11:15 AM **Board Discussion**

If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling stableflies?

If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

12:15 PM **Lunch**

Carroll-Loye Biological Research Completed Studies: SCI 001.4 and SCI 001.5

1:15 PM **EPA Science and Ethics Assessment of Carroll-Loye Biological Research Completed Studies: SCI 001 and SCI 002 –** Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)

2:00 PM **Public Comments**

2:15 PM **Board Discussion**

Are these studies sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes?

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?

3:15 PM **Concluding Remarks –** Mr. William Jordan (OPP, EPA)

3:30 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 e-mail: lewis.paul@epa.gov.