Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
October 27-28, 2010 Public Meeting
Docket Number: EPA-HQ-ORD-2010-0797
HSRB Web Site: http://www.epa.gov/osa/hsrb

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

Date and Time:	Wednesday, October 27, 2010, 10:30 AM – 5:00 PM Thursday, October 28, 2010, 8:30 AM – 4:00 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 provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.

Attendees:	Chair:	Sean Philpott, Ph.D., M.S. Bioethics
	Vice Chair:	Janice Chambers, Ph.D., D.A.B.T.
	Board Members:	George C.J. Fernandez, Ph.D. Vanessa Northington Gamble, M.D., Ph.D. Sidney Green, Jr., Ph.D., Fellow, ATS Dallas E. Johnson, Ph.D. Michael D. Lebowitz, Ph.D., FCCP José E. Manautou, Ph.D. Jerry A. Menikoff, M.D. Rebecca Tyrrell Parkin, Ph.D., MPH William J. Popendorf, Ph.D. Virginia Ashby Sharpe, Ph.D. Linda J. Young, Ph.D.

Meeting Summary: Meeting discussions generally followed the issues and general timing as presented in the meeting Agenda (Attachment C), unless noted otherwise in these minutes.

Meeting Administrative Procedures

Mr. Jim Downing (Designated Federal Officer [DFO], Human Studies Review Board [HSRB or Board], Office of the Science Advisor [OSA], U.S. Environmental Protection Agency [EPA or Agency]) convened the meeting and welcomed Board members, EPA colleagues, and members of the public.

Mr. Downing noted that in his role as the DFO under the Federal Advisory Committee Act (FACA), he serves as liaison between the Board and EPA and is responsible for ensuring that all FACA requirements are met. The DFO must ensure that all appropriate ethics regulations are satisfied regarding conflicts of interest; Board members have been briefed on federal conflict of interest laws and have completed a standard government financial disclosure report. In consultation with the deputy ethics officer for the OSA and the Office of the General Counsel, Mr. Downing has reviewed the reports to ensure that all ethics requirements are met.

He informed members that agenda times are approximate. Copies of the meeting materials and public comments will be available on www.regulations.gov under docket number EPA-HQ-ORD-2010-0797. Following presentations, time has been scheduled for questions of clarification to EPA staff and the principal investigator and sponsors of the studies discussed. A public comment period will be maintained. Remarks should be limited to 5 minutes. During Board discussions, if members require clarification from the public, they may request such information through the Chair or DFO. All background materials for the meeting will be available in the public docket and most are also available on the HSRB Web site. Meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and must be certified by the meeting Chair within 90 days. The HSRB also will prepare a final report as a response to questions posed by Agency that will include the Board's review and analysis of materials presented. EPA will announce the Board review and subsequent approval of the report through the *Federal Register*.

Introduction and Identification of Board Members

Dr. Sean Philpott, HSRB Chair, welcomed members of the public to the meeting and thanked the Agency and Board members for their service. He noted that Board members Drs. Sidney Green and Linda Young would be participating in the day's meeting by telephone, and that Dr. Vanessa Northington Gamble would be present only on October 28, 2010. He asked Board members to introduce themselves and welcomed Dr. Paul Anastas (Science Advisor, OSA, EPA).

Welcoming Remarks

Dr. Anastas thanked the Board members for the opportunity to speak with them. As the Agency Science Advisor, he has administrative oversight of the Board. The time and effort Board members spend on human studies issues are appreciated by the Agency. The Agency and the Administrator take the issue of human subject research very seriously. When Dr. Anastas was first approached about joining the Agency, he wanted to ensure that scientific integrity would be central to his work and to EPA's work in general. Before he had a chance to discuss the issue with the Administrator, she released a statement that she and President Obama believed that the work of the Agency had to be based in science and must preserve scientific integrity, transparency, and the rule of law. The work of the HSRB is an essential piece of ensuring scientific integrity. The success of the Agency in relying on sound science to achieve its goals requires a foundation of solid science. If the science relied on for regulatory decision-making lacks the rigor and ethical foundation that the HSRB seeks to ensure, then the Agency and its

actions will be undermined. The attention that the Board is paying to these issues represents time well spent. Dr. Anastas expressed his personal appreciation and that of the Agency and Administrator for the Board's work. The Agency has pledged to ensure maximum transparency in all its deliberations, and public meetings such as this are essential to ensuring transparency. The specific issues that the Board is addressing are fundamentally science-based issues that have relevance to daily lives and serious downstream considerations. Regardless of the issue that the HSRB is addressing, the same fundamental questions about science and ethics need to be asked and addressed to ensure that EPA's mission to protect the environment and human health is not put at risk. Dr. Anastas thanked the Board members again and assured them that the Agency takes the HSRB's work extremely seriously.

Dr. Philpott noted his appreciation for Dr. Anastas' comments and for the Agency's work.

EPA Follow-up on Previous HSRB Recommendations

Mr. William Jordan (Office of Pesticide Programs [OPP], EPA) noted that the Board had concurred with EPA's conclusions that the two studies by Carroll-Loye Biological Research, Inc. (CLBR) discussed at the June HSRB meeting were scientifically and ethically acceptable: completed study LNX-002, a field study of repellency of two picaridin formulations to black flies; and completed study LNX-003, a laboratory study of repellency of two picaridin formulations to two species of ticks. EPA has accepted the studies, and the products now are considered fully registered.

Other topics discussed at the last Board meeting included an EPA presentation of the Final Guideline 810.3700 for Performance Testing of Skin-Applied Insect Repellents. The Board offered several comments on the draft document, and some additional revisions were made. EPA published a notice in the *Federal Register* on August 6, 2010 announcing the availability of the guidelines as a final version for comment. The guidelines can be found at http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series810.htm.

Mr. Jordan also informed the Board about the status of the amendments to EPA's rule for the Protection of Subjects of Human Research, 40 Code of Federal Regulations (CFR) part 26, which is the regulation under which the Board operates. EPA and some non-governmental organizations had reached a settlement in litigation on the 2006 version of the regulation. As agreed to in the settlement, EPA plans to propose amendments to the rule. A *Federal Register* notice currently is undergoing interagency review through the Office of Management and Budget. EPA does not expect the review to raise significant issues or to result in major changes to the proposal described at the June HSRB meeting. The Agency is hopeful that the review will end soon and wants to have the Administrator's signature on the proposal by January 18, 2011 with publication of the notice shortly thereafter.

Dr. Philpott acknowledged that Mr. John Carley (OPP, EPA) would be retiring from EPA and that this would be his last HSRB meeting. Dr. Janice Chambers thanked Mr. Carley on behalf of the Board for the balance and clarity he had brought to his work with the HSRB.

Session 1: CLBR Protocol No Mas 003, a Field Efficacy Test of Para-Menthane-3,8-diol (PMD) and Lemongrass Oil-based Repellant "No Mas" Against Mosquitoes

Background

Ms. Kelly Sherman (OPP, EPA) noted that the protocol under discussion for a field study of the repellent efficacy of a lotion formulation containing 16 percent (%) PMD and 2% lemongrass oil (called "No Mas") had been submitted by CLBR in July 2010 before the release of EPA's revised guidelines for skin-applied repellants. The protocol is similar to a previous CLBR mosquito field study LNX-001; the Board reviewed this protocol in June 2007 and reviewed the completed study report in October 2008. The research has been proposed to satisfy EPA registration requirements. The sponsor is developing this product as a low-cost repellent for distribution in developing countries with vector-borne disease, and reports that the product has broad-spectrum efficacy against more than 40 species of mosquitoes, including four of the most important malaria-vectoring anophelines. The present study protocol proposes to test the product for efficacy against three mosquito genera: *Culex*, *Anopheles*, and *Aedes*.

EPA Science Assessment

Dr. Clara Fuentes (OPP, EPA) noted that the protocol contains a dose determination phase, to determine the amount of No Mas a consumer might typically apply and to determine the standard dose (in milliliters per square centimeter [ml/cm^2]) for use in the repellency phase, and a repellency phase to determine the duration and efficacy of No Mas in repelling three mosquito species (*Culex, Anopheles*, and *Aedes*) in the field.

The formulation is of low toxicity. Both acute dermal and acute oral LD_{50} is greater than 5,000 milligrams per kilogram (mg/kg) body weight, and the formulation is neither a skin sensitizer nor irritating to the skin. Based on previous dosimetry studies, the estimated maximum dose for No Mas is likely to be 1,000 mg/subject or less. Assuming a 70 kg subject, the equivalent dose rate is 1,000/70 = 14.3 mg/kg. Therefore the margin of exposure (MOE) is greater than 5,000/14.3, or greater than 350.

In the dose determination phase, it is proposed that 10 subjects self-apply No Mas repeatedly to each arm and each leg, with the dose rate (mg/cm^2) determined from weight of lotion applied and the skin area of the subject's forearm or lower leg. The grand mean of subject means is calculated as the estimate of typical consumer dose, and the grand mean dose is converted to the volumetric dose (ml/cm^2) for use in the repellency phase.

In the repellency phase, the product will be tested once at each of two ecologically different habitats in California's Central Valley. Subjects will receive one treatment consisting of one formulation. There will be five male and five female treated subjects, two untreated control subjects, and two alternate subjects per site. Subjects are exposed for 1 minute at 15-minute intervals, and landing pressure must be at least one landing with intent to bite (LIBe) per minute for untreated controls. The endpoint is the first confirmed LIBe (FCLIBe) for each subject or the end of the test, whichever occurs first. Measurements include the time from application to the

first exposure, the time of each LIBe, and the complete protection time (CPT), the time between application and FCLIBe or end of test.

For the statistical analysis plan, in addition to individual subject data, the study will report mean CPT with standard deviation and 95% confidence interval, the Kaplan-Meier median, and time to 25% failure. To ensure the reliability of the test, the test material will be applied by laboratory technicians; all landings will be verified and recorded by a research technician; mosquito landing pressure throughout the test will be monitored by two untreated subjects; subjects' attractiveness to mosquitoes will be determined prior to testing; and subjects will be trained to handle mosquitoes prior to testing.

EPA believes that the following elements are adequately addressed: available acute toxicity studies with No Mas adequately characterize the toxicological profile of the formulation and support the estimate of acceptable MOE; dose determination; experimental design of the repellency phase; and the statistical analysis plan. EPA did note that care is needed to ensure that the target genera of mosquitoes are present in sufficient numbers at the selected field sites to allow achievement of the study objective, and that justification for sample size in future protocols should not rely on a comparison to the superseded 1999 guideline.

EPA Ethics Assessment

Ms. Sherman explained that the proposed study would be of value to society because it would test the field repellent efficacy of No Mas against three species of mosquitoes and the product could provide a low-cost alternative to other available repellents that could benefit many users.

Participants will be recruited from among a volunteer database of previous subjects of CLBR testing who have expressed interest, supplemented by word of mouth. The database is racially diverse and includes volunteers of different age groups (75% between the ages of 20 and 40 and 25% between the ages of 40 and 55). Inclusion and exclusion factors are well-defined and appropriate. Pregnant or nursing women and children, as well as those who are not in good health and those who do not speak and read English are excluded. Students and employees of the study director are excluded, as are employees of the sponsor. No eligible subjects are expected to be especially vulnerable.

There are five categories of risk for participating in the study: test material will irritate the eyes on contact and may cause skin irritation in some individuals; possible exposure to biting arthropods; possible exposure to arthropod-borne disease; risks of physical stress in the test environment; and breach of privacy (pregnancy testing). Steps were taken to minimize the risks in each of these categories. The study would have no direct benefit to subjects; the primary direct beneficiary is the sponsor. However, if the product is proven effective, indirect beneficiaries will include repellent users who prefer this product to other repellents.

Risks have been effectively minimized and are reasonable in light of the expected societal benefits of the knowledge likely to be gained. Independent Investigational Review Board Inc. (IIRB) in Plantation, Florida reviewed and approved the protocol and informed consent

materials, and IIRB's complete policies and procedures, entitled "Human Research Protection Program Plan," was provided to the HSRB.

In terms of subjects' informed consent, subjects are screened by the study director. It is explained that subjects are not obligated to participate and can withdraw at any time. The description of subject recruiting and consent processes is complete and satisfactory in this case. The consent forms include all elements required by regulations, and the language and reading level of the consent forms are appropriate.

In terms of respect for the subjects, effective methods for protecting subjects' privacy are in place, the proposed level of compensation is appropriate ($20/hour), subjects will be free to withdraw at any time, and medical care for research-related injuries will be provided at no cost to subjects.

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, and therefore the primary ethical standards applicable to the conduct of this research are 40 CFR 26, subparts K and L, and Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) §12(a)(2)(P). EPA found no specific deficiencies relative to 40 CFR 26, subparts K and L, or to FIFRA §12(a)(2)(P), and believes that the CLBR protocol No Mas 003 will meet the applicable requirements of 40 CFR part 26, subparts K and L.

Charge Questions

Ms. Sherman read into the record the two charge questions:

If the proposed field repellency study protocol No Mas 003 is revised as suggested in EPA's review and if the research is performed as described:

- Is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested materials in repelling mosquitoes?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Questions of Clarification

Dr. Dallas Johnson noted that EPA's science review did not state how long the subjects would be exposed to mosquitoes, but he had read that would be 18 hours, longer than studies had been in the past. Dr. Fuentes responded that the 18 hours includes travel to the site, so the actual time of exposure to mosquitoes is less than 18 hours. She believed that participants will be wearing the repellent for as long as 18 hours, however. Dr. Johnson added that one of the issues in past studies is that some of the products never failed, which makes the data hard to analyze; exposure for 18 hours might have more failures.

Dr. Young asked if the purpose of the study is to lead to registration, what types of label claims are expected from this work. For example, do the sponsors hope to state that the product will offer at least 8 hours of protection, or will the study results determine the label? Mr. Jordan

explained that there has been discussion at EPA about developing standard procedures to translate the results of efficacy testing into label language. There is not yet a consensus on the topic. In general terms, what companies have done in the past is to propose label wording. There are a range of views about what labeling language to use to convey information to the prospective user. EPA has been conducting focus groups with pesticide users to see how they perceive labeling language and what they look for in terms of how they use these products. People have different views based on their interests (campers versus casual users, etc.). The task is to determine the best way to state what a consumer can expect in terms of efficacy, and the Agency does not have an answer yet. Products in the marketplace use various language such as "lasts up to x hours" or "lasts at least x hours." EPA is attempting to translate results of the study into something that will be a general indication of the duration of complete protection that a substantial portion of the population can expect to receive. EPA understands that there are numerous variables among people and environmental conditions. It will not be possible to have a single statement that applies to everyone everywhere. The Agency, however, is working to develop a consistent approach that can be used across all products rather than leaving it up to a particular person such as the registrant or EPA reviewer.

In response to Dr. Young's question about the purpose of the study, Mr. Jordan stated that his understanding is that the purpose of this study is not to establish a minimum amount of protection, but this should be confirmed with the investigator. The goal is to run the study to the point where each individual experiences a failure or withdraws or the study is terminated, then data from the protocol will be used to develop statistical values for CPT: the mean of the values of CPT for each individual subject; the mean of the subjects' values for the group, and the Kaplan-Meier median.

Dr. George Fernandez asked, because the product may be used in developing countries, if similar studies will be conducted in developing countries. Ms. Sherman noted that in many developing countries products are approved for use if they are registered in the United States. She is not aware of plans to test the formulation internationally. Dr. Fernandez added that mosquito populations may be different in developing countries than in the test sites. Mr. Jordan stated that EPA has no jurisdiction outside of the United States. If someone wanted to run a study in another country for submission to EPA, the design of the study and human subject use would be reviewed, but this study is designed to be executed in California.

Dr. William Popendorf commented that in EPA's review it was stated that the protocol should be revised to exclude employees of the study sponsor. Ms. Sherman responded that employees and students of the study director are excluded, but that she would check on the other exclusions. Dr. Popendorf noted that studies done to test typical customer level of application likely are conducted for other repellents as well. At some point would the Agency have enough data to use the results from prior studies? Mr. Jordan stated that efficacy studies for insect repellants have changed over time. Until fairly recently with the advent of the HSRB, most studies used a standard dose. When Dr. Scott Carroll (CLBR) brought his first study to the Board, he included a dose determination, which seemed like a good idea because how the repellent is applied varies from person to person depending on whether it is applied to arms or legs and depending on the delivery system. All those variables lead to fairly big differences. EPA now has a fairly limited database including approximately a dozen products. The Agency has

seen some surprising differences between products in laboratories and does not feel that it has enough information to skip that phase in insect repellency testing. In the future, there may be enough data, but issues like the viscosity of the particular material make a difference in the amount an individual will apply.

Dr. Virginia Ashby Sharpe noted a correction on EPA's memorandum on page 24; IIRB now is an accredited institutional review board (IRB). Ms. Sherman thanked Dr. Sharpe.

Dr. José Manautou inquired about the habitats used to conduct the field tests; the susceptibility of vectors to pesticides could vary depending on whether they are carrying a particular microorganism. This could affect the efficacy of the pesticide. Dr. Fuentes agreed that there might be a difference in how they respond to pesticides, but that the test sites have to be vector free. Dr. Manautou inquired about the composition of the habitat, and how it is ensured that the mosquitoes are free of diseases. Dr. Fuentes responded that the sites are tested near the date of the repellency testing. Ms. Sherman added that the research could only proceed if no diseases were present, but the species in the habitat can be vectors for diseases, so they are good species to test for repellency. Mosquitoes are trapped for approximately 2 weeks leading up to the actual research and tested for diseases. Dr. Manautou added that he would like to see a discussion of the susceptibility of disease-free versus infected mosquitoes.

Dr. Carroll, CLBR study director of the No Mas 003 protocol, and Mr. Shawn King, CLBR Director of Operations, were present to respond to questions of clarification from the Board.

Following up on Dr. Johnson's earlier question, Dr. Philpott asked whether the 18 hours listed as the study time included travel or if there would be 18 hours of direct exposure. Mr. King responded that the exposure duration includes travel time. The repellent is applied at the laboratory before travel and CPT is recorded from the time of application. Dr. Johnson asked what probability of failure might be for human subjects within the 18 hour period. Dr. Carroll responded that he anticipates a long duration of protection based on known active ingredients with a minimum efficacy of several hours. He is hoping to gather some failures to improve the analyses. Dr. Johnson asked if the study time was longer than on previous studies. Dr. Carroll responded that it was and that the Board did not seem strongly opposed to asking subjects to consider close to a 20 hour day. Dr. Johnson responded that the longer duration was an improvement.

Dr. Philpott reiterated Dr. Manautou's question about susceptibility variation among disease-free and disease-carrying mosquitoes and asked the study director to summarize how the vectors are proven to be disease-free. Dr. Carroll noted that there was always a non-zero probability of the presence of diseased organisms, particularly in communities of insects that are of sufficient density that they are suitable for tests of this type. To achieve the minimum ambient biting rate on a single limb, each subject must have several mosquitoes around their body during any given exposure. The principle way the risk is monitored is by sampling mosquitoes and screening for West Nile Virus and encephalitis viruses. The areas where CLBR conducts these studies are areas of low incidence. Using sentinel chicken flocks and collected mosquito pools they conduct weekly analyses and the incidence is exceedingly small. Regarding the question

about susceptibility to repellant action and the infected status of mosquitoes, this is not something that has been examined in detail. Parasites do manipulate host mosquito behavior. The most pertinent data to generate coarse inferences comes from malaria carrying anopheles. Repellants using the same principle active ingredient as in No Mas repellent have shown extended periods of duration, with protection times of 10 to 12 hours.

Dr. Chambers inquired if there would be sufficient biting pressure throughout the duration of the test. Dr. Carroll responded that all of the studies conducted have been susceptible to potential problems with reduced biting pressure during the midday period. These study sites have at least 10 species of mosquitoes present; there are peaks of activity early and late in the day, but there are at least 2 species that are active throughout the day so there are rarely periods with no landings on control subjects.

Dr. Sharpe asked about the use of the term "treatment" to describe the application of pesticides. There is an ambiguity in the informed consent form because of the potential confusion with medical treatment. Dr. Carroll replied that was an excellent point; chances of confusion within the study population are low, but it might be useful to consider alternative wording. Dr. Sharpe suggested the alternative wording be used routinely because not all studies might involve the same scientifically educated study population. In addition, Dr. Sharpe noted that "consent" is an intransitive verb; no one can be consented. She suggested that CLBR's informed consent form explain that the informed consent process would be conducted by x, rather than the subjects "are consented by x." This would increase grammatical accuracy and would explain who the responsible party is. Dr. Carroll stated that he did not have full control of the wording of the consent form, but that he would address the point. Dr. Sharpe further noted that page 2 of the consent form states that subjects are offered the opportunity to participate in the research. The way it is phrased in the California bill of rights is "the subjects are requested to consent to participate." This does not have the same implied benefit as stating it as an opportunity, and CLBR should rephrase the text in a way that does not imply a benefit to study subjects. Dr. Carroll replied that this change could be incorporated. On page 30 of the proposal, the significant expense to the sponsor of the addition of four subjects beyond the initial six is discussed; Dr. Sharpe questioned why this was relevant. Dr. Carroll replied that the decision to propose 10 study subjects was not taken lightly. Given that study sponsors proposing to register a new insect repellent must perform cost-benefit analyses, the number of study subjects was carefully considered. The mention of cost was included to show sensitivity to the real world context which ultimately determines study design.

Dr. Popendorf noted that the stopping rule was based on more than one attempted bite in the same minute and questioned whether this constitutes a confirmed event. Dr. Carroll responded that it did. Dr. Popendorf asked if subjects were prevented from being employees of the sponsor. Dr. Carroll responded that this exclusion was not in the protocol. The California Department of Pesticide Regulation (CDPR) brought that to CLBR's attention as well. This had never occurred to Dr. Carroll as most study sponsors had shown an aversion to mosquito repellant tests. It is an important point from both a scientific and ethical standpoint. Dr. Popendorf added that because CLBR is in a university town, perhaps sponsor employees and dependents should be excluded. Dr. Carroll noted that he would ask EPA to consider granting an amendment to the protocol.

Dr. Manautou noted that the active ingredient is 16% PMD and 2% lemongrass oil. He asked about the composition of the 82% inert ingredients and whether the particular formulation was the one that was going to be marketed. Dr. Carroll responded that that the batch of repellant that would be tested is the final formulation. The formulation is proprietary. Mr. Jordan added that the Agency receives a statement of formula at registration, which usually is Confidential Business Information. The inert ingredients are not new to EPA. Dr. Carroll noted a study conducted a year ago in which 700 households participated for 3 months and showed very high compliance with the daily use of the repellants. There were no reports of skin irritation or other health complications associated with the application.

Dr. Philpott inquired about confirming the presence of the three mosquito genera and asked whether this should be added to the protocol. Dr. Carroll noted that this could be incorporated into the protocol on the test day itself because mosquitoes are captured, specifically those that land on subjects and those that find their way into the screen houses; usually all three genera are represented.

On page 64 of the protocol, there is a table which has length/3 and a footnote stating that the column relates to placing dosimeters in pump sprays and aerosol studies. Since this study does not involve a pump spray or aerosol, Dr. Green questioned if this column was appropriate. If this is a standard table, there ought to be a statement that this data is not applicable for the four areas being studied. Mr. King replied that this is a generic table; it was determined that repeated measurements of subjects that have participated in multiple studies are invasive, so the protocol now stipulates that measurements are not repeated more than every two years unless the subject states that they have gained or lost significant weight. Dr. Green noted that on page 79 of the protocol, in the middle of the page, the rationale for the study is discussed. The first sentence of the paragraph states that this is a study of behavior in applying spray insect repellents; however in this case, a lotion is being used. Mr. King responded that this was an error; the text should state "applying insect repellents" and should not mention the type of product.

Public Comments

Dr. Carroll thanked the Board and EPA for their helpful reviews of the protocol and consent form documents.

Dr. Philpott invited additional public comments on the No Mas 003 protocol; none were received.

Board Science Review

Dr. Green opened the science discussion of the No Mas 003 protocol and stated that the research is likely to generate scientifically reliable data useful for assessing the efficacy of the tested materials in repelling mosquitoes if the proposed field repellency study protocol is revised as suggested in EPA's review and if the research is performed as described.

Dr. Manautou noted that he did not have anything to add; his questions were addressed and the proposal as written should provide relevant information.

Dr. Fernandez presented slides on the statistical design analysis of the proposed study. The 10 subjects represent more than the required historical requirement of six. In an example provided by Dr. Fernandez with 10 subjects and no censoring, the values of mean, median, and Kaplan-Meier estimate were valid. However, if there is a larger variation and censoring, the 10 study subjects may not provide enough data to generate valid estimates. The sample should be large enough to yield a definite answer to the research question and it should be justified statistically for each data point. As Dr. Young suggested, an acceptable lower limit should be established for the CPT. Then, the study should be conducted with the proposed sample size of 10, the 95% lower limit for the 25th percentile should be computed, and if this value is less than the previously accepted limit, then repeat the study with another 10 subjects, combine the data and re-estimate.

Dr. Young noted that Dr. Carroll is making an effort to reduce the censoring and that is commendable; censoring makes analysis of the data very challenging. She agreed with Dr. Fernandez that historical standards should not be referred to any longer to justify sample size. The proposed sample size in the presence of censoring may be insufficient. Therefore, some new ideas about design and analysis are needed.

Dr. Chambers commented that Dr. Fernandez suggested repeating the study if criteria were not met. The logistics of repeating the tests are complicated and she is unsure how the Board would deal with this in recommendations. Dr. Fuentes noted that the study is already repeated at two sites; would that count as two replications? Dr. Young responded that the problem with the two sites is that the mean protection times often are not the same for the two sites. This would also be a problem if the study was repeated. She does not think that it is necessary that the study be repeated, but that initial information could be used to determine exactly how many people are needed in order to make the scientific statements intended with the study. Dr. Chambers noted that regardless of the number of people needed, repeating the study still would be a problem. Dr. Young added that the alternative is to do a much better job in justifying the sample size up front. This requires a measure of how precise the estimate needs to be and a measure of variation. The problem of variation, because of the censoring that has occurred, is understated in almost all of these studies.

Dr. Michael Lebowitz suggested that for the present study, after completion, it could be stated as a caveat that the censoring was too severe or the sample size was insufficient to give a final estimate of the protection time, but it would not prevent the study from determining an estimate that the manufacturer could use. It is wise scientifically to make such statements when presenting results when one does not feel like sample size was big enough.

Dr. Philpott stated that the data will come back before the HSRB as well, and it is possible that the study will yield completely useful data. If it does not, the Board may have some comments for the Agency at that point.

Dr. Johnson noted that it would be impossible to estimate standard deviation, but if there was 100% censoring after 18 hours, the product is likely effective. He is unsure how to deal with this issue. Mr. Jordan responded that Dr. Johnson's comments show a perspective that the Agency tries to keep in mind. How can EPA translate the information from these studies in usable forms for allowing labeling claims on products? The limits of the quality of data that the Agency gets from these studies must be considered. They are conducted in two ecological environments that are diverse from each other but hardly representative of all ecosystems. They are conducted with a small number of subjects which cannot represent the variation across the population. Other factors account for variability. EPA has come to appreciate that the studies provide a rough approximation at best; the question is whether or not it is good enough for regulatory decision-making. If the product lasts for 18 hours on all 10 subjects that gives EPA good confidence that the product is effective. EPA is trying to determine, before asking for more testing, what it needs to know for labeling that informs users about what the product will do. It is a struggle to determine what constitutes enough data and the right way to translate the data. Mr. Jordan is not convinced that a CPT plus or minus a half hour on either side is necessary for EPA to do its job as a regulator.

Dr. Manautou noted that the historical number of subjects was six and asked if there was a current EPA mandate on subject number. Mr. Jordan responded that the historical number was six and that there is not a recommended number in the new guidelines. The number of subjects used in the past few years in several of the protocols and completed studies has been 10.

Dr. Carroll appreciated the comments regarding the statistical issues related to utilizing such a small sample size. Statistics are used to solve ambiguities and sometimes the answers are clear. On the other hand, study directors can do better in interpreting the data that they do collect. CLBR needs to explain more thoroughly how to deal with non-normally distributed results, and with a sample size of only 10 subjects, testing whether there is a normal distribution is unrealistic. A gamma distribution is probably a better assumption. The Weibull distribution is commonly used in studies examining time to an event when that event is inevitable. It is known that the probability of failure increases with time. If in addition to doing a Kaplan Meier analysis, a Weibull fit also is included, the behavior of the confidence intervals would be quite different. As the proportion of censoring increases, the confidence intervals increase, but most of that is on the upper side of the distribution toward longer values. Everyone is censored after 18 hours. The calculation of the Weibull 95% confidence interval expands in that direction with more censoring. The mean also shifts up; CLBR is working to minimize censoring to have the most precise estimates, but a realistic lower 95 confidence interval still can be estimated. In response to EPA's evaluation of protocol, CLBR will be supplying an amendment to the protocol regarding statistical approaches and this is the type of approach CLBR will include.

Dr. Philpott remarked that the Board could create a working group to study alternative study designs if necessary in the future. The accuracy of the data should be discussed once the completed study report becomes available.

Dr. Young noted her support for Dr. Lebowitz's suggestion. Once the data are received, it can be determined if censoring is present.

Dr. Philpott concluded that the consensus of the Board is that the study is likely to generate scientifically reliable data if it is revised in accordance with EPA's recommendations, acknowledging that until the Board sees the data, a complete assessment of its utility in assessing the efficacy of the tested material cannot be known. In the submission of the final study data, the study director should include a detailed explanation and justification of the analysis and how the data might be used for regulatory purposes.

Board Ethics Review

Dr. Sharpe stated that the research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L. The study design takes adequate steps to identify and mitigate risks, satisfies IRB requirements, and assures voluntariness of subject participation. The study would be even more likely to meet the applicable requirements if it includes the changes that were discussed with the study directors on the ambiguous use of the term "treatment," the phrasing in the consent form about being offered an opportunity to participate in the research, and the phrasing in the consent form about participants "being consented."

Dr. Jerry Menikoff agreed that the study meets the applicable requirements.

Dr. Philpott added the following suggestions regarding the consent form: it should include an explanation and symptoms of equine encephalitis as well as West Nile Virus; the symptoms of heat stress should be mentioned; eye irritation does not need to be mentioned as a risk for untreated participants; and for the dosimetry studies, the irritation and sensitivity risks should be described.

Dr. Popendorf commented that the Agency's recommendations should be included. Employees of sponsors and their dependents should not be included in the study.

Dr. Philpott noted that the consensus of the Board is that the research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L if it is revised in accordance with EPA's recommendations and with the Board's suggested changes to the informed consent document.

Session 2: A new scenario design and associated protocol from the Agricultural Handler Exposure Task Force (AHETF) to measure dermal and inhalation exposure to applicators who use backpack sprayers or hand gun sprayers to apply pesticides in utility rights-of-way (ROWs)

Background

Ms. Sherman introduced the AHETF's new scenario design and associated protocol to measure dermal and inhalation exposure to applicators who use backpack sprayers or hand gun sprayers to apply pesticides in utility ROWs. She mentioned several previous AHETF scenarios reviewed by the HSRB and noted that the design objectives, sample size, rationale, and procedures related to ethical conduct of this protocol are similar to the previous AHETF scenarios. Differences from previous proposals include the following: the study is comprised of

two scenarios (backpack application and hand gun spray application); two new surrogates (fosamine and imazapyr) are being used; updates were made to the standard operating procedures (SOPs) and the Governing Document; a new cluster configuration (3 monitoring units [MUs] at 7 different sites, not 5 monitoring areas with 5 participants each as used in previous studies) is proposed; the protocol allows for greater than 1 MU per employer; and the protocol does not include individual product risk statements which previously were an attachment to the informed consent form. The protocol is ready for HRSB review and contained all elements of documentation required by 40 CFR §26.1125.

EPA Science Assessment

Mr. Jeffrey Evans (OPP, EPA) presented EPA's scientific assessment on the AHETF's new scenario design and protocol on utility ROWs. The proposed study involves two non-agricultural scenarios addressing exposure of individuals involved in vegetation control using handheld equipment in utility ROWs: (1) applying ROW sprays using backpack sprayers; and (2) applying ROW sprays using handgun sprayers. Non-agricultural scenarios are an important area for the use of pesticides as existing data are weak. Minimum attire for participants will include long-sleeved shirts, long pants, shoes, socks, and chemical resistant gloves. Other clothing that would likely be worn is permitted, including hardhats, baseball-style caps, eyewear (prescription, safety, or sunglasses) and safety vests, but leggings, chaps, or chemical resistant headgear are not permitted.

Backpack ROW sprayers are worn on back of the applicator and used in areas having difficult terrain or when making spot treatments in integrated vegetation management programs. No mixing will be performed by the participants; however, they typically fill their spray tanks with dilute sprays from truck mounted tanks or other containers. Return to these containers to fill the tanks also can be a source for contamination. Handgun ROW sprayers consist of a handgun (wand) operated from vehicles equipped with 100 to 1,500 gallon tanks; they are connected to the tank by hoses up to 2,000 feet in length.

The proposed surrogate pesticides include four widely-used herbicides requiring the minimum personal protective equipment (PPE): imazapyr (maximum rate 24 pounds [lbs] active ingredient); fosamine (maximum rate 1.5 lbs active ingredient); glyphosate; and 2,4-dichlorophenoxyacetic acid (2,4-D). It is important to have a wide range of applications to accommodate the amount active ingredient handled (AaiH) strata. The pesticides 2,4-D and glyphosate have reliable analytical methods and have been successfully used as surrogates in other AHETF exposure monitoring studies. Fosamine and imazapyr are new surrogates for the AHETF, but they have been successfully used in other human exposure monitoring studies. Confirmation of analytical methods is required prior to study initiation. These surrogates demonstrate low volatility and are stable under the conditions of the study. Analytical methods show 70 to 120% recovery with a coefficient of variation 20% or lower. Field recovery is 50 to 120% with a coefficient of variation 25% or lower. The pesticides show low limits of quantification (dermal: 1 μg/section; inhalation 0.01 μg) and require minimal PPE. No mammalian toxicity has been observed for fosamine and glyphosate.

In the proposed AaiH strata, all exposure durations will be at least 4 hours, each subject will apply at least three tanks of spray, and there will be three strata of AaiH for each monitoring area (i.e., cluster). The strata for the backpack ROW are 0.5 to less than 1.5 lbs, 1.5 to less than 15 lbs, and 15 to 50 lbs. The strata for the handgun sprayer row are 1 to less than 3.5 lbs, 3.5 to less than 35 lbs, and 35 to 125 lbs. The AHETF strives to ensure that no two participants will be in the same AaiH stratum per monitoring area, but believes this may not always be feasible, so for these two scenarios, it is stated that it is preferable that no two participants be in the same stratum per monitoring area. Application rates are based on maximum acres treated per day and maximum volume sprayed per day. For the backpack ROW, EPA assessments generally assume 2 acres treated per day or 40 gallons sprayed per day, and for the handgun sprayer ROW, EPA assumes 10 acres treated per day or 1,000 gallons sprayed per day; these figures have been confirmed by experts interviewed by the task force.

For both scenarios the objective is to design a study that has as many conditions that can influence exposure (directly or indirectly) as possible. This is accomplished in these studies by stratifying the range of AaiH and requiring a minimum of three tank loads to be sprayed; diversifying the number of participants and study sites (monitoring areas), including those with different work habits and sites with different climates, vegetation, and terrain. Both ROW study designs are referred to as efficient configurations (statistically the same) intended to achieve two objectives: a primary objective to have relative fold factors for basic statistics such as the arithmetic mean, geometric mean, and 95th percentile 95% of the time; and a secondary objective of providing the ability to test the data to determine if exposure is proportional to AaiH. For agricultural scenarios, the AHETF typically relies on a study configuration having 5 sites with 5 participants monitored per site (n=25), but for these two scenarios the AHETF has 7 sites and 3 participants per site (n=21). The efficient configuration for both scenarios is 7 monitoring areas with 3 participants per area (per scenario) focusing on the eastern portion of the country requiring more vegetation treatments and having areas large enough to treat so that they can find a sufficient pool of participants. Additionally, many utility companies contract out the spraying of ROW, and many contract companies operate in several regions throughout the country. For the agricultural scenarios and through consultation with the Board, the AHETF allows only one participant per company/employer, but because of the smaller pool of employers the AHETF is proposing to allow only one participant per company per site (monitoring area), but to permit more than one participant per company per scenario as long as the participants are in different monitoring areas.

In the study, dermal exposure will be measured with cotton union suits which act as a skin surrogate and are worn beneath participants' typical work clothing. After the monitoring period, the garment will be cut into six sections, and socks also will be included for measurement of exposure to the feet.

Regarding existing data, EPA currently relies on the Pesticide Handlers Exposure Database (PHED) for both backpack and handgun sprayer exposure assessments. Backpack studies include those having measurements to coveralls only (requiring estimates of clothing penetration) or studies that do not have measurements of hand exposure for participants wearing gloves. None are based on individuals making ROW treatments. Handgun sprayer studies include a wide variety of studies, many of which are not specific to ROW treatments; one ROW

handgun spray study does not have measurements of hand exposure for participants wearing gloves.

In conclusion, EPA agrees with the AHETF's definition of and approach to diversify these two scenarios. The AHETF's proposal for 21 subjects collected in seven different monitoring areas having three participants each is appropriate for each scenario as it ensures a wide variety of vegetation, terrain, and worker habits. All attempts should be made to measure participants applying AaiH from each of the three strata per monitoring area. EPA is mindful of the AHETF's ability to achieve all AaiH strata in all regions with respect to achieving primary and secondary objectives. Diversity will be achieved—randomly or purposively—in the course of assigning AaiH strata within each cluster. While the field and laboratory quality assessment (QA)/quality control (QC) aspects for glyphosate and 2,4-D are robust, confirmation of analytical methods are required for fosamine and imazapyr. The scenarios are well-defined and are likely to produce reliable applicator data for these ROW application methods.

EPA Ethics Assessment

Ms. Sherman presented EPA's ethics assessment. She stated that the proposed studies will be of value to society because current data on exposure to workers applying pesticides in ROWs using these types of equipment do not meet contemporary standards. The data resulting from this study will constitute the entire exposure data set for these scenarios in the Agricultural Handler Exposure Database (AHED®), and the data will be used to estimate dermal and inhalation exposure for a wide range of pesticides.

Study subjects will be recruited from eligible and amenable companies that make pesticide spray applications to utility ROWs. Potential subjects must have experience within the past year applying liquid sprays to ROWs and meet the other subject eligibility criteria. Employees are protected from potential employer coercion.

The consent process will include private consent interviews and equivalent processes for Spanish and English speakers, relying on bilingual investigators. The consent form contains all elements required by 40 CFR §26.1116, with acceptable organization and thorough presentation of risk information. Surrogate product-specific risk information from the label and material safety data sheet will be provided to each worker prior to monitoring, and participants will be advised that they can drop out of the study at any time.

In terms of respect for the study subjects: payment to the subjects is reasonable; they are free to withdraw at any time and for any reason; they have the opportunity to request their individual exposure results; and medical care for research-related injuries will be provided at no cost to the subjects. The protocol allows for equitable subject selection, fully informed and fully voluntary choice to participate, and proper procedures for protecting and respecting the subjects.

Risks of the protocol include heat-related illness (there is a stopping rule at 105 degrees heat index), scripting of field activities (possibly longer days than usual), psychological risks, and exposure to surfactants. EPA believes that the risks have been fully identified and effectively

minimized. Although there are no direct benefits to subjects, the risks to subjects are reasonable in light of potential societal benefits.

In response to previous EPA and HSRB recommendations, the AHETF improved the accuracy of Spanish translations through comments of six Spanish speakers and improved the method of providing individual exposure information to subjects who request it. In an analysis of representativeness the AHETF identified important characteristics, sent characteristics associated with each monitored worker to experts, and was asked by experts if characteristics of monitored workers are representative of workers who operate in the areas where the monitoring occurred.

An independent ethics review was conducted by IIRB of Plantation, Florida, which reviewed and approved the protocol and informed consent materials. IIRB is independent of the sponsors and investigators, registered with the Office of Human Research Protection, and accredited by the Association for the Accreditation of Human Research Protection Programs, Inc.; its Human Research Protection Program Plan is on file with EPA and has been provided to the HSRB.

As 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 the conduct of this research are 40 CFR 26, subparts K and L and FIFRA 12(a)(2)(P). EPA has determined that the protocol meets the applicable ethical requirements of 40 CFR 26, subparts K and L and notes no deficiencies.

Charge Questions

Ms. Sherman read the charge questions into the record:

If the proposed AHETF ROW application scenario and field study proposal AHE400 is revised as suggested in EPA's reviews and is performed as described:

- Is the research likely to generate scientifically reliable data, useful for assessing the exposure of workers who apply pesticides in utility ROWs using backpack or handgun sprayers?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Questions of Clarification

Dr. Lebowitz noted that the use of seven by three (seven clusters with three monitoring units each) versus five by five reduces the sample size, and if the same individual is used in more than one stratum, this also reduces the sample size. He questioned how it is determined that the sample size is adequate. Mr. Evans responded that there will be no repeat measurements of the same person, but there may be two representatives of the same company at two different sites. The question is whether there are correlations within companies, such as training programs, that may impact the exposure of individuals employed by those companies. Mr. Evans stated that although it is preferable not to have individuals from the same company, the Agency recognizes that it may be a possibility. In terms of the 3 x 7 design, the task force did a number of

simulations, and 5 x 5 design is in theory similar if not the same statistically as the 3 x 7. EPA believes that the 3 x 7 design will achieve the study objectives, but it is a trust and verify situation; the Agency will be able to determine that objectives were met once the data are collected. Dr. Lebowitz mentioned that the strata of active ingredient would seem to be very different for the four different herbicides used. He asked if EPA is confident that the three strata will be achieved for each of the herbicides. Mr. Evans responded that all of the four pesticides are already used in some capacity. They have a very wide range of active ingredient, and EPA is confident that the investigators will be able to achieve the research goals. Dr. Lebowitz commented that if handlers are loading their own tanks, contamination may occur, and the minimum requirement may change the active ingredient, and the participant could end up in higher strata than intended. Mr. Evans replied that the participants would be using dilute sprays, but EPA is interested in the amount of exposure per AaiH. No concentrated solution is handled. Dr. Lebowitz stated that he assumed EPA carefully examined how the investigators would do the dermal sampling. Mr. Evans responded that for dermal measurements, the outer clothing would not be sampled in this case. For this study, the interest is in the individual using a single layer of clothing. Dr. Lebowitz confirmed that the stopping rule was 105 degrees heat index, not 105 degrees by thermometer.

Regarding documentation of the analytical methods, Dr. Chambers asked whether the new surrogates also are well documented. Mr. Evans responded yes, but noted that it is a trust but verify situation. The detection limits likely were pushed down lower than they were in some of the older methods. The hand-washing solutions also might be different than in the past. Dr. Chambers noted that the criteria for selecting surrogates in the past had been that the analytical methods were sound. She inquired if the employer would choose which of the four surrogates will be used in the study. Mr. Evans replied that the employers do select the surrogate. The task force representative can discuss this, but Mr. Evans believes a supply of all surrogates is brought to the field. Dr. Chambers asked what would happen if one of the workers has an accident and sprays his leg with the chemical. Mr. Evans responded that it is difficult to know how this would be handled, but the field notes will indicate all incidents. Sometimes incidents such as this result in higher exposure, and sometimes they have little impact. In this case, judgment might be reserved on whether to discard the data from this worker.

Dr. Sharpe mentioned that it seems as if there is a discrepancy in the inclusion criteria between EPA's memo and the eligibility criteria in the informed consent form. On page 36, it is stated that inclusion criteria include being trained in safe pesticide handling procedures, but the informed consent form allows training or verification that training is not required. Dr. Sharpe asked if the group of pesticide applicators is required to take training. Mr. Evans responded that training is folded into a worker protection standard requiring employees to be trained in the use of pesticides. However, this scenario does not fall under the worker protection standard. He suggested that this question be deferred to the task force representative.

Dr. Popendorf asked whether the workers would also be covered under the Occupational Safety and Health Administration (OSHA) hazard communication standard. They should be if the companies have more than 10 employees. Mr. Evans noted that this was a good point. Dr. Sharpe mentioned, for the purposes of the study findings, that either it will be determined how much pesticide a trained or an untrained applicator might get on his body. Clarity on the training

is needed to reach clear endpoints. Ms. Sherman stated that these are workers who are experienced with the work and the equipment. Dr. Sharpe noted that on page 40 of the report, there may be an inaccurate cut and paste because it mentions "the cab." Ms. Sherman confirmed that this was an error. Dr. Sharpe mentioned that on page 44, there is a mention of ethics training that is required for all researchers. Ms. Sherman confirmed that this was accurate, and stated that the AHETF has an SOP about the ethics training.

Dr. Manautou asked what constituted chemical resistant headgear. Mr. Evans responded that it was usually a hat with a flap around the back made of chemical resistant material. Dr. Manautou noted that in the presentation, the absence of mammalian toxicity is mentioned, and asked that EPA be more specific. In addition, Dr. Manautou examined the EPA document and did not see a justification for the 3 x 7 design deviation from the 5 x 5. Mr. Evans responded that the simulations justifying the change are in the governing document. Dr. Manautou asked whether there should be a clearer up-front justification for the Agency to be comfortable with the deviation. Mr. Evans noted that this is something that could be added to EPA's document. With respect to mammalian toxicity, for these chemicals, the Agency receives numerous toxicity studies (neurotoxicity, immunotoxicity, developmental toxicity, reproduction effects). These studies did not find adverse affects. Dr. Manautou suggested that the organs usually analyzed for toxicity be mentioned instead of making a vague statement. Mr. Evans agreed that EPA might be best served if the risk assessment numbers were shown.

Dr. Popendorf noted that the protocol does not state whether the face wash is the same solution as the swab, and whether it is wetted. Mr. Evans stated that it was the same solution, and that it is wetted and washed twice. Dr. Popendorf was concerned about the rationale for the 4-hour study duration. Mr. Evans responded that as long as the strata are achieved and the three tank mixes have been used, a shorter study duration could be considered. EPA had pushed for 4 hours because the Agency was receiving half-hour studies that did not measure anything. Mr. Evans agreed that this point could be reconsidered. Dr. Philpott asked about the average work day for participants. Mr. Evans replied that the 4 hours are on the low side of what the participants do in a day, but days also may be longer because they are participating in the study. Interviews with experts indicated that crews typically work 8 to 10 hours in a day. Dr. Popendorf stated that he would like to ensure that the Board has an opportunity to examine some of the pieces of information that Ms. Sherman discussed earlier: task duration records, work pattern that the participants follow (e.g., do they advance while they are spraying or go out to the end of the area and retreat; are they walking through treated foliage?); height and density of foliage; and hose length. It would be useful to do some kind of categorical analysis, because it might turn out that there are differences between the advancing versus retreating application patterns. This could overwhelm the strata in terms of exposure. In response to Dr. Popendorf's questions, Mr. Evans stated that sometimes there is a foreman that manages the hose to assist the crew and that walking through treated foliage is a possibility and would likely be captured in the field notes. Dr. Popendorf added that this information should be captured and categorized; Mr. Evans agreed.

Dr. Fernandez asked about the purpose of collecting the data; the mean estimate and confidence interval are being computed, but simply to document the mean, or to assess risk at the individual applicator level? If the latter, a control chart showing the data points by clusters and individuals would be useful and more visual. Examining the variation between and within

clusters would be more useful than just reporting the mean and confidence interval. Mr. Evans responded that there would be many plots and analyses of the data. EPA will use the data to assess expected potential exposures of individuals applying pesticides that may not be registered yet. They will provide a predictive model for a new herbicide. The contact value states that for every pound applied, the applicator will get x milligrams of exposure to his person. Dr. Fernandez stated that the weather data, such as climate and wind velocity, as well as other factors would impact exposure. Mr. Evans agreed that many factors can contribute, and hopefully these factors get pulled into these exposures. EPA can mitigate risks by determining how to reduce the exposure by reducing the amount of pesticide that can be handled, reducing the application rate, or perhaps the pesticide should be banned because there is no way to mitigate exposure. Dr. Fernandez asked if the Agency could consider recommended limits when the pesticide is applied under certain conditions. Mr. Evans noted that the pesticide will or will not be registered based on these conditions (application rate, how much someone might use in a day, etc.), which will be part of the pesticide label.

Dr. Johnson commented that the study should not lose sight of the exposure a typical worker will have during his normal job, because that is what the data should reflect.

Dr. Victor Cañez (AHETF Technical Chair, BASF Corporation) was present to respond to the Board's questions of clarification. Dr. Lebowitz noticed that the AHETF is planning to utilize a number of different herbicides in the study and that the agents actually used will be dependent on what the contractor prefers using for the applications. Dr. Lebowitz asked why the AHETF chose these specific herbicides, and what would be done if the contractor does not use any of those herbicides. Dr. Cañez responded that the AHETF has a set of criteria on how a surrogate is chosen: it must be available for use and used in the field; it must be stable in the field; it must be able to be analyzed on the matrices being used; and it must be recoverable off the matrices. There must be trust that what is pulled off the dosimeter will give a good measure of the exposure. When the contract applicators first were contacted, they were asked if they use any of the four surrogates, and if they did not, they were taken off the list. Regarding the strata of active ingredient, Dr. Lebowitz asked what factors would influence them. Because of all the variables, he questioned whether the strata will be filled. He requested the AHETF's rationale for how it will take into account all the potential factors that may cause the lowest strata to be exceeded or the inability to get enough measurements in the higher strata. Dr. Cañez noted that the AHETF did its homework up front and asked people who do this kind of work how much they spray in a day and what surrogates they use. Dr. Cañez stated that he believes that the AHETF will get individuals in every one of the three strata. If a very high amount of surrogate is being sprayed based on the contractor being used, it is possible that the worker will be asked to stop spraying midday, or asked to spray slower. Dr. Lebowitz commented that this was a case of scripting, and Dr. Cañez agreed. Dr. Lebowitz noted concern about the number of MUs in each cluster; what happens if it turns out to be too few? Dr. Cañez responded that in the past with the 5 x 5 scenario, it was difficult to get five people all at one time, and if monitored at different times, this would constitute a different statistical cluster.

Dr. Chambers stated that spraying ROW sounds much less predictable than spraying row crops or orchards, and accidents might be more likely. She questioned if there are criteria for rejecting data if a subject falls and sprays himself. Dr. Cañez replied that if the worker falls down

and is drenched, this is an accident and he is required to undress, shower, and stop work. This information would be collected. This could happen in agricultural settings as well. The individual would be replaced by another worker on that day or on another day.

Dr. Sharpe asked for clarification on training in safe pesticide handling because there seemed to be a discrepancy about whether training was or was not required. Dr. Cañez responded that for products that have a certain toxicology category, certain training is required for handlers. For other categories, training classes are not required. The AHETF would like to have participants who are trained in the safe handling of pesticides by the company that employs them. Dr. Sharpe stated that the eligibility criteria in the informed consent form states that participants must confirm that they have been trained in pesticide safety or that they are not required to take this training. Dr. Cañez stated that in the AHETF's inclusion criteria, this is a slightly different. The AHETF inclusion criteria include handling pesticides as part of their jobs and being trained in safe pesticide handling procedures. If there is something different in the consent form, the AHETF will have to examine that. Dr. Sharpe noted that the consent form with the discrepancy is dated 5/25/2010. Dr. Sharpe asked how the pregnancy test is obtained and reimbursed. The informed consent form states that there will be no cost to the participant associated with this research, but within 24 hours, females must present the results of their pregnancy tests. Dr. Cañez noted that the SOP is descriptive on that; the AHETF will provide the pregnancy test, ensure that it is monitored by a female, and let the subjects know that they can opt out of the study. They will be asked if they want to continue to participate, and if they do, the AHETF will want to see that the result of the test is negative. If they no longer want to participate in the study, they can drop out and the AHETF will not learn the result of the pregnancy test. Dr. Sharpe suggested that this process be stated more clearly in the informed consent form.

Dr. Philpott asked, regarding the IRB review process, whether the IRB had access to and reviewed AHETF SOPs as part of the specific review process for this protocol. Dr. Cañez stated that IRB has the SOPs; as they are changed, the IRB is provided with the newest version.

Dr. Popendorf asked Dr. Cañez for any comments about the 4-hour limit. Dr. Cañez responded that one of the things criticized in the PHED studies was that often times there would be a 30-minute work day with no detects. The AHETF did not want to risk this and wanted to have quantifiable residues. When EPA examines these data, if the exposure is based on a 4-hour work time, EPA will double it and make it an 8-hour work time. The AHETF wanted something that represented a whole day's work so that the numbers would not be doubled. The AHETF, however, does not instruct the workers on what to do, but asks them to do what they normally do and takes notes on all activities. Dr. Popendorf added that perhaps some categorical variables could be analyzed, but agreed with Dr. Cañez's stated approach.

Since the handlers could travel quite a distance with the backpack sprayers on, Dr. Philpott asked if they walk a mile out and how they are monitored for heat stress and other risks. Dr. Cañez responded that the workers always are monitored by an observer, and a medical professional also observes the workers to ensure their safety.

Dr. Lebowitz asked when the clothing is cut into six sections, if the thorax section is divided between front and back to account for possible contamination by the backpack. Dr. Cañez replied that the six sections are the arms, front and rear torso, and legs.

Public Comments

Dr. Philpott called for public comments on the proposed AHETF ROW application scenario and field study proposal AHE400; no public comments were presented.

Board Science Review

Dr. Lebowitz led discussion on the science charge question. He noted that the study will provide new information on dermal and inhalation exposures from the herbicides tested with the two types of sprayers. EPA stated that once these studies were reviewed, and if AHETF primary and secondary objectives of relative accuracy and proportionality, respectively, are substantiated, the two scenarios will be added to the AHED database. Dr. Lebowitz pointed out that the SOPs and QA/QC continue to be good. EPA stated that the protocol meets applicable scientific standards, but Dr. Lebowitz questions that, at least in terms of strengths and weaknesses. He brought up the issues about two employees being in different clusters. It concerns him, and it will have to be determined whether it has an effect or not. It is an obfuscation to say that the samples can be selected randomly, especially since it is difficult to obtain the number of subjects needed; it is a convenience sample. Representativeness may not be able to be addressed. There are numerous assumptions that need to be analyzed and deviations from these assumptions should be determined and the effects on the final estimates stated in the results. This is something that the HSRB partially addressed in the past, but that is an issue in this study.

The AHETF is going to script some of the approaches and exposures to achieve the active ingredient strata that they want to obtain. Dr. Lebowitz stated that there will not be any statistical summary of the data in terms to which he is accustomed. In terms of sample size, when the benchmark accuracy requirement is not met, there may not be sufficient power to permit users of the database to perform a limited examination of the relationship between the normalizing factor, AaiH, and exposure. There is a real issue when it comes to proportionality of exposure to active ingredient, and it does not appear to be proportional in most cases. Justification of these sample sizes, number of MUs, and number of clusters may continue to be a basis for discussion and may in the future be subject to criticisms that the AHETF has provided for PHED scenario 34. It will be necessary to compare AHETF data with PHED data, specifically scenarios 18 and 19 as well as 34.

Dr. Lebowitz had the impression that the baseline hand-wash samples were going to be discarded, and instead he believes they should be analyzed to provide baseline exposure information because the removal factor is not 100%, so there is residual remaining. The wipe samples are even less accurate in getting the amount on the skin, and there must be a better approach to that as well. The issues that have not yet been raised in terms of diversity and variability include specific issues of vegetation that may make a difference in terms of exposure, differences in spray volume and pressure and nozzle configuration. The study is dealing with 21 data points, and there are more than 21 variables. Uncertainty is discussed in exposure

assessment, and this does not mean confidence intervals or standard deviations. Uncertainty has to do with a number of different factors that affect the estimates of the distributions and the actual values, and these are not provided by the fortified samples or blank samples. Further work by the AHETF in analyzing such uncertainties is necessary. This study can be generalized, EPA states, within the limits imposed by the purpose and design of the study. The study is not random or representative, however. This study will provide a partial answer to the question: what dermal and inhalation exposures are likely for handlers making backpack (BP)/ROW and handgun (HG)/ROW applications. Dr. Lebowitz concluded that the study will provide useful data; however, he expressed concerns about whether the study will generate scientifically reliable data given the reduced sample size and greater variability than in past studies. Once the data are collected and the results are obtained, a determination as to whether the data are scientifically reliable can be made more efficiently. Dr. Lebowitz concluded that EPA needs useful data, and this study may provide it and will certainly provide more data than the Agency currently has for these types of applications.

Dr. Chambers added that the methods for handling the dosimeters are similar to what the HSRB has seen before. The work the task force conducted in terms of surveys and questionnaires was quite extensive and provided insight into the variables in this type of scenario. Dr. Chambers believes that a tremendous amount of variability will result from this scenario because the terrain is so variable. The underlying hypothesis for the other scenarios is that the amount of exposure will be proportional to the AaiH; this study may not show that proportionality. As the data come back, the Board and EPA do not need to be disturbed by it; they may just reflect the fact that it is an extremely unpredictable environment. The data will be more useful than what is presently available and gathered in a scientifically valid way. If they do not show the proportionality of the AaiH, that should not reflect badly on the study.

Dr. Johnson noted that there has been discrepancy as to whether to call this a 3 x 7 or a 7 x 3 scenario. Statisticians would prefer it 7 x 3 (cluster x MU). Data will be useful and better than any data currently available. Dr. Johnson agrees that the data may or may not be scientifically reliable or reproducible. With this qualification, the answer to the charge question is "yes."

Dr. Popendorf agreed with Dr. Chambers that the study will have a lot of variability and therefore good notes and categorizing some of the variables will be valuable. It is possible that information other than AaiH might appear in statistical analysis of categorical variables which might be useful to the Agency.

Dr. Philpott summarized that the Board's consensus to the charge question is yes, particularly with respect to the usefulness of the data. Some concerns exist about how reliable and reproducible the data will be, whether or not the basic hypothesis of proportionality between exposure and the amount of AaiH is valid given the nature of the scenario and the variability of the terrain, and whether or not the 4-hour requirement is necessary given that the amount of AaiH is being stratified. However, the Board's recommendation is to proceed with the study pending the suggested changes the Agency has noted in its review, and those changes noted from the Board.

Board Ethics Review

Dr. Menikoff provided an assessment of the study in response to the ethics charge question. He highlighted the issue that he believed EPA should assess, which is the exposure to surrogate pesticides. Quoting from the protocol, he stated the "AHETF does not consider the risk of toxicity from pesticide handling to be strictly due to study participation. Therefore the risk of surrogate toxicity will not be listed in consent forms for this protocol." His problem with this characterization is that this is an intentional exposure protocol. In the original version of the proposed rule EPA noted that occupational exposure studies did not fall under the rule. In the final version of the rule, it was noted that if a person was exposed to a substance for research purposes without control over it, that is intentional exposure. This risk needs to be included on the consent form. It is true that as part of their jobs, the study subjects are exposed to some pesticide, but on the day of the study, what happens to them has been manipulated in a number of ways. The AHETF has negotiated what products are going to be applied. Participation in the study led to an individual participant being exposed to a chemical for research purposes. The rule does not mention that it is all right to expose subjects to chemicals as long as the exposure is not more than in their daily lives.

Mr. Jordan stated that from EPA's point of view there is a distinction between what studies the Agency ought to be examining (studies involving intentional exposure of human subjects to pesticides) and what the risks of those studies might be. It is obvious from the Board's work that there are a wide variety of tests involving intentional human subject exposures. Those studies differ from each other in terms of the risks to the subjects who participate. In this instance, the scripting characteristic places this study into the domain of intentional exposure. Subjects have lost control over their ability to control their exposure. In the ethics assessment, is it appropriate to look at the risk to subjects whether the exposure pattern in the protocol represents a qualitatively or quantitatively different kind of risk to the subjects than their daily work or not? In the view of the AHETF and Ms. Sherman, the degree of scripting was so limited that they regarded the risk of exposure as no different from that which the subjects would encounter otherwise. If the Board's advice is to see EPA address specifically how the scripting affects the risks of the subjects compared to the risks that they would encounter absent the study, the Agency can do this. Dr. Menikoff added that the participant, for research purposes, is being exposed to a pesticide on that day. The rule requires EPA to enumerate the risks of the study. It is irrelevant whether it is a greater risk or a lower risk than the participant's daily work. Exposure to the pesticide is a risk of the study. It can be argued that it is not a high risk, but taking the position that it does not have to be mentioned does not follow the rule.

Dr. Sharpe stated that part of the problem may be with the way greater than minimal risk is defined in the regulation. Minimal risk cannot be defined as relative to ordinary non-agricultural groups and then be defined differently relative to some occupational groups for the purposes of this protocol. Dr. Philpott asked EPA what minimal risk standard was being used; he questioned whether it is relativistic for agricultural handlers or related to the risks that an average person experiences in daily life. Mr. Carley stated that the only place in subparts K and L where the phrase minimal risk appears is in the second section in the list of topics that belong in the consent document. None of the distinctions that are made in medical research about minimal risk appear in subparts K and L; therefore, minimal risk is not a factor. He asked Dr. Menikoff if it

would satisfy his concern if the consent form stated that while a subject participated in the study, he would face the same risks from the pesticides that he would on a normal work day. Dr. Menikoff replied that was an improvement, because a risk of being in the study is acknowledged. Mr. Carley noted that these vegetation control pesticides are registered pesticides being used consistently with their labeling, and they have been determined to have an adequate margin of safety in order to get registered. Dr. Menikoff suggested putting some information about the pesticides in the consent form.

Dr. Philpott explained that the issue was not whether these individuals are at any greater risk from exposure to the pesticide than they would be in their daily lives, but the fact is that the Final Human Studies Rule and the Board exist because of concerns about deliberate exposure of human participants in research on pesticides. It makes sense to acknowledge that in the informed consent document.

Dr. Popendorf requested clarification on whether or not the study would be scripted. As he understood it, the only portion of scripting was the 4-hour requirement. His understanding was that for a subject to participate in the study, he had to be scheduled to use that pesticide on that day. Dr. Menikoff commented that the pesticide to be applied was determined by negotiations between the AHETF and the employer. Dr. Philpott asked if there was a possibility that the workers in this scenario may be using a pesticide that they would not normally handle but may be experienced with. Ms. Sherman responded that a company was called and asked if they used any of the four surrogates. As the study date approaches, there may be some discussion about which surrogate the company wants to use. Dr. Cañez clarified that contractors are asked if they use the products, and if they would be willing to participate in the study. They are then asked when they spray, and whether the crew can be recruited. The investigators must participate on the days that the employer planned to spray. The AHETF does not dictate the product, but if there is a need for something in the lower strata and one of the compounds that the employer uses fits that lower strata, then the AHETF may ask the employer to use a specific compound. Dr. Philpott summarized that there is a possibility of scripting what surrogate compound will be used.

Dr. Lebowitz stated that the exposure in the study is intentional, and has some risk to it. That has to be stated in the informed consent. It does not matter how much scripting occurs. The idea is that because it is a study, it is an intentional exposure.

Dr. Chambers asked whether the worker would be deciding what kind of pesticide is used on a normal workday. Dr. Cañez responded that the company would make that decision. Dr. Philpott added that there is concern about scripting of compounds, and that the risk of exposure to the pesticide should be included as a risk in the informed consent form to recognize the intent of the Final Human Studies Rule. Dr. Chambers added that it was not risk of accidental exposure. Accidents happen anyway, so that is not a unique risk of research.

Dr. Manautou noted that there are risks associated with the concentrations that would be used in the study.

Dr. Popendorf agreed that this does appear to be a scripted study. If it was not scripted, and the workers were monitored doing what they normally did, does that constitute a study that would trigger the concerns the Board is addressing? Ms. Sherman responded that if there was no scripting, that is observational research and would not be covered by this rule.

Dr. Philpott stated that the Board's general consensus is to include a statement that there is a risk from surrogate pesticides in the informed consent document.

Dr. Sharpe noted that she was pleased with the resolution of the discussion, and wanted to add a comment about enhancing the informed consent form with information about the pregnancy test to match the SOP.

Dr. Philpott suggested consideration of adding hand-washing before smoking to the informed consent form. Robert Parks (whose name was included in IRB correspondence) is listed as a bilingual researcher. His curriculum vitae lists human subjects training certification, but documentation of that should be provided. Certificates have been provided for all of the other researchers. In addition, the AHETF may want to confirm with the IRB that it reviews all the referenced SOPs during a study review.

The Board's consensus opinion in response to the charge question is yes pending the revisions suggested by EPA in its review and with the suggestion of reinserting the exposure to the surrogate compound as a risk of study participation, some clarification of conduct of the pregnancy test in the informed consent, and consideration of smoking in addition to eating as part of the hand-washing recommendation.

Adjournment of Wednesday, October 27, 2010

Thursday, October 28, 2010

Follow-up from Previous Day

Mr. Jordan stated that EPA found the Board's comments on the CLBR and AHETF protocols helpful and does not have any questions. He would like to inform the Board that Laura Parsons, a scientist who has worked with the Agency for 17 years, will be joining him and Ms. Sherman on human subjects' research issues for the next several months. Ms. Parsons has a science degree and has worked as an exposure assessor for 7 years, and for 10 years following that in risk assessment. She brings a wealth of experience to the area of human studies for pesticide registration. She will be helping Ms. Sherman and Mr. Jordan to prepare for a fairly heavy agenda for the January meeting and to complete work on the proposed amendments to the Human Studies Rule.

Session 3: Completed scenario monograph and study report from the Antimicrobial Exposure Assessment Task Force II (AEATF II): Dermal and Inhalation Exposure of Professional Janitorial Workers Applying Liquid Antimicrobial Products to Indoor Floors Using Bucket and Mop

Background

Mr. Carley introduced the AEATF study on dermal and inhalation exposure of professional janitorial workers applying liquid antimicrobial products to indoor floors using a bucket and mop. He noted this is the first task force handler exposure study to come to the Board as completed work after the Board previously reviewed it as a proposal. The proposal was reviewed by the HSRB in April 2008. The Board and EPA have learned a number of lessons in the time since then from other reviews, and given that this study was written up first in the series, it should not be too surprising that this study was not performed with perfect smoothness.

Different questions are asked about a completed study than a protocol, including: Was the proposal appropriately amended after review? Was the protocol faithfully executed? What were the results? Were the objectives achieved? Was the research conducted ethically?

The mop scenario is 1 of 17 AEATF II antimicrobial handler exposure scenarios and includes mopping floors with a dilute solution of antimicrobial product in water and emptying each mop bucket. It excludes pouring concentrated product into mop buckets and mixing with water. The study was conducted in three randomly selected vacant buildings in Fresno, CA: an office building, a retail space (Rite Aid®) and a meeting space (Retired Teacher's Memorial Building). To ensure diversity of individual exposures, at each site one enrolled subject was assigned to each of six monitoring events (MEs) defined by the planned duration of mopping (ranging from 30 to 90 minutes). In older studies, data points were closely clustered; this is a much better data spread and the intended diversity was achieved.

The study monitored dermal and inhalation exposure of six subjects at each of three sites (N=18) to didecyl ammonium chloride (DDAC) formulated as Buckeye Sanicare Lemon Quat. Subjects wore outer/inner dermal exposure dosimeters (long pants, long-sleeved shirt, shoes, socks, and no gloves; whole body dosimeters (WBD) underneath clothing; and personal breathing zone air samplers, with pump on belt) and mopped floors using a string mop and a bucket with wringer, and emptied spent mop water.

The initial protocol was reviewed by the IRB in 2008 and extensively revised in early 2009. Recruiting began at the end of April 2009. Field monitoring occurred in August and September 2009. A few days after the initial field testing the sample analysis began, and roughly a year was spent on the report which was submitted August 31, 2010 and supplemented several times, and is now in review by the HSRB. EPA review of the study included the primary document, both supplements, and the demographic spreadsheet, the science and ethics reviews of the original protocol, and the June 2008 report of the April 2008 review.

The protocol revisions of February 26, 2009 addressed most EPA and HSRB comments. The protocol was amended to refine criteria for site selection, clarify details in the protocol and

revise the consent form, permit enrollment of subjects one-by-one, add newspaper advertisements, randomize assignment of enrolled subjects to MEs, revise specification for analytical phase, change field study coordinator and associate, and revise consent form to conform to the change.

EPA Science Assessment

Mr. Leighton (OPP, EPA) presented EPA's science assessment of the AEA03 completed study. He stated that EPA will use the data from this study for many things, including new chemicals. The antimicrobial division is working on the registration and use scoping documents; the division is going through each chemical and identifying where it thinks it needs additional data. His hope is to get this data into EPA's next round of risk assessments. For the mop study, he acknowledged statistician Dr. Jonathan Cohen from ICF International, an EPA contractor, who spent significant time on the review. Mr. Leighton mentioned that the Joint Regulatory Committee of Health Canada and the CDPR have been working with EPA and also plan to use the data. From EPA's antimicrobial division, there are two more wipe scenarios that will be presented to the Board for review in January 2011, and the designs are similar to this study.

The study objective was to collect mopping exposure data in which the upper and lower 95% confidence limits will be no more than 3-fold (K=3) higher or lower than the geometric mean, arithmetic mean, and 95th percentile of the unit exposures. In response to EPA comments, the investigators redefined the scenario to include disposing of spent mop water in the revised protocol of February 2009 and provided data on recovery efficiency of hand-wash/face-wipe methods for DDAC in the form of an existing study on efficiency of DDAC residue removal from hands.

In response to HSRB comments, the AEATF II responded as follows: in response to the suggestion to consider repeat measurements, the AEATF II decided to focus on more samples of between-worker variability; in response to the suggestion to use longer monitoring duration, the AEATF II produced additional industry information indicating that 90 minutes of mopping per day represents the reasonable upper range; in response to the comment to consider defining ME by AaiH versus duration, AEATF II found that the best information available for mopping is based on duration; and in response to the suggestion to review proportionality between exposure and AaiH, AEATF II deferred to EPA.

There were 22 reported protocol deviations, including air sampling related issues, light levels not monitored at sites, a participant re-mopped an area previously mopped, and the chain of custody documentation was lost for one sample. There was one unreported deviation (change in type of mop bucket), but none of the deviations negate the use of the exposure results. The bucket was changed from one with an EZMT foot pedal that permits users to empty the bucket into a floor drain without lifting it to one with baffles to prevent sloshing.

The DDAC residue removal efficiency study involved fortifying the hand (pipette to palm) with 5 or 100 microgram (μg) per 50 microliter (μL) per hand; n = 10 for each fortification level. The hand was allowed to dry for 30 minutes, and then was washed/rinsed with 50% isopropyl alcohol (IPA) in water. Residues remaining after the initial hand-wash were wiped from the hand using dressing sponges moistened with 50% IPA in water. The mop study hand-

wash and face/neck wipe procedures were similar. Removal efficiencies were: hand-wash = ~90% (used to correct mop hand residue results); hand wipes = ~60% (used to correct mop face/neck residue results).

Whole body dosimeters were used and sectioned into eight pieces. Inner dosimeters acted as the skin, and the outer dosimeters could be used to mimic short-sleeved shirts. Study participants wore long pants, long-sleeved shirts, shoes/socks, and no gloves over WBDs. For each ME, residues were analyzed from both outer clothing and inner WBDs sectioned by body part. Clothing configurations that can be estimated for each ME include: (1) long pants, long-sleeved shirt [shoes/socks and no gloves]; (2) long pants, short-sleeved shirt [shoes/socks and no gloves]; and (3) short pants, short-sleeved shirt [shoes/socks and no gloves]. Estimates for shorts are obtained by adding the inner and outer lower arm (short-sleeved shirt) or by adding the inner and outer lower leg (short pants).

Mopping duration was scripted, and DDAC concentration was the same for each. On average, subjects used 20 gallons, but only 2 gallons were applied to the floor. All laboratory and field blanks were less than the limit of quantitation (LOQ). In the laboratory, the range for mean ±standard deviation for all 3 clusters was 95±4% to 113±3%; in the field, the range for mean ±standard deviation for all 3 clusters was 91±8% to 109±8%. Field recoveries were used to correct field samples (dosimeters). Results were: air = 10 nanograms (ng); neck/face = 50 ng; hands = 1 μg; WBD sections = 3 μg; and socks = 1 μg.

Three methods were used to estimate unit exposure; empirical estimates; simple random sample (SRS); and mixed model. The mixed model was selected to best represent the unit exposure results.

The benchmark objective of three-fold relative accuracy (K $\leq$3) was met for the mixed-model results using the 3 cluster x 6 ME study design. Relative accuracy (K) ranged from 1.3 to 1.7 for the mixed model results. K less than 3 indicates enough samples (n=18) were collected to satisfy EPA's needs. No additional mop MEs are needed; the sample was large enough.

Based on comparison to earlier studies for similar tasks, an estimated Intra-Cluster Correlation (ICC) of 0.3 was used to determine the number of clusters and MEs in the study design. The ICC calculated from this mop study is zero, which indicates that individual behavior affects exposure more than building type or floor configuration.

Proportionality between exposure and AaiH is an assumption EPA uses in handler exposure assessments. The mop study provides evidence of proportionality between dermal exposure and AaiH with no evidence of proportionality between inhalation exposure and AaiH. Minimal exposure was expected from this mopping scenario (low vapor pressure and low potential for aerosols) and monitored exposure was very low (mean 0.000263 mg/cubic meter [m^3]). EPA did not learn anything that would lead us to abandon the assumption of proportionality.

The potential for data generalization is limited because the mop study population is not a true random sample, and statistical inference from these results to the universe of moppers is not

justifiable. However, EPA plans to use the mop study data in the following manner: unit exposure data can be used generically to estimate potential exposure to low-or moderate-volatility pesticides used in mopping scenarios; the string mop is worst-case and can be used to represent all mops, including RTU, sponge, or microfiber mops; dermal unit exposures are available for various clothing configurations; unit exposures are normalized by AaiH; chemical-specific hazard and dermal absorption data can be used to estimate internal dose and risk.

If it is assumed that a new product has these characteristics (acute toxicity profile is consistent with short-sleeved shirts with long pants, no gloves; 10% active ingredient in concentrated product; dilution rate 0.5 ounce per gallon water, from automatic dispenser) then the estimate of daily exposure = unit exposure x AaiH. The dermal unit exposure can be determined from the long pants/short-sleeved shirt, socks, no gloves results. Inhalation unit exposure = air concentration (mg/m^3/pound active ingredient), and AaiH = 0.5 fl oz * 1 gal/128 fl oz * density 8.34 lb/gal * 5 gallons/day * 0.1 active ingredient in concentrated product. AaiH = the volume of concentrated product in fluid ounces, converted first to gallons, and then to weight, multiplied by the number of gallons mopped per day, multiplied by the concentration of active ingredient in the product.

In conclusion, the study results are sound enough to support estimates of dermal and inhalation unit exposures in the mopping scenario; enough samples were collected so that no additional mop MEs are required; and data limitations must be acknowledged in assessments.

EPA Ethics Assessment

AEATF II responded to EPA comments to provide a better provision for interviewing and consenting Spanish-speaking subjects by replacing references to translator with references to bilingual investigators in the February 2009 protocol. In response to the suggestion to express normal business hours in local time, the times were changed to Pacific Time in the revised consent form and the flyer. In response to HSRB comments to use a tracer rather than a pesticide, the investigators used a pesticide per EPA advice. In response to HSRB comments to ensure that the consent form is readable, the investigators found the change created a negligible change in readability. In response to the HSRB's suggestion to explain how the community will be engaged/involved, the AEATF II revised the section in the protocol, but planned meetings with employers did not take place. In response to HSRB advice to ensure that Spanish translations are in the appropriate dialect, all translations were done by a California translator who was part of the research team.

The initial protocol was reviewed by IIRB in January 2008. All subsequent IIRB reviews were conducted under expedited procedures, without minutes or other records, but investigators complied fully with IIRB procedures and requirements, and this cannot be seen as a deficiency on part of the investigators.

Recruitment was initially conducted through contact with janitorial companies, but was completed successfully with newspaper advertisements. The recruiting process was equitable and free of coercion or undue influence and was conducted consistent with the protocol at each stage of amendment. Subject recruiting and selection processes were consistent with EPA's policy

direction to incorporate random elements whenever feasible. Of the 32 enrolled subjects, just under half were male, and that ratio was slightly different in the group of monitored subjects. Three-fifths of the whole pool and monitored pool were English speakers. The person who reported 40 years of experience was 47 years old. The principal investigator accepted her self-reporting. The age range was 18 to 53; the upper bound of the eligibility criteria was 65. The subjects self-reported their general state of health: 18 claimed excellent, 12 good, and 2 fair. The criteria for eligibility stated that they had to be in good general health. Roughly 80% would like to see their individual results.

Deviations of ethical significance included reported deviations: omitted/shortened rest breaks and photos showing subjects' faces at one site. Unreported deviations included enrollment of two subjects with self-described fair health, and creation and retention of additional records linking subject names to identification codes.

The initial final report showed significant omissions (including a protocol with tracked changes and lack of documentation of IRB approvals), and Appendices Q and R were full of irrelevant, duplicative material, and were completely unindexed. Supplement 1 was substantively complete and irrelevant and duplicative material was deleted from Appendices Q and R. Additionally, both appendices were fully indexed. Other deficiencies were addressed as follows: the rationale for defining MEs by duration was provided in Supplement 2—MRID 48231901; subject demographics were provided in a spreadsheet submitted on September 30, 2010; accounting for the pre-enrollment recruiting process was provided via e-mail on October 18, 2010; and IIRB procedures and roster was provided by IIRB. Therefore, the requirements of 40 CFR §26.1303 were substantially satisfied.

Substantive acceptance standards are as follows: 40 CFR §26.1703 prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children; 40 CFR §26.1705 prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 CFR 26; and FIFRA 12(a)(2)(P) makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent. In this study, all subjects were at least 18; pregnant or nursing women were excluded; and all females were tested for pregnancy. No noteworthy deficiencies were found in the ethical conduct of the research. The protocol was faithfully executed and amended when needed; minor deviations did not compromise the safety or consent of subjects. Subjects were fully informed and their consent was fully voluntary, without coercion or undue influence.

Therefore, available information indicates that the AEATF II mop study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Charge Questions

Mr. Carley read the charge questions into the record:

- Was the research reported in the AEATF II completed study report AEA03 and associated supplemental reports faithful to the design and objectives of the protocol and governing document of AEATF II?

- Has the Agency adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply antimicrobial floor-cleaning products with mop and bucket?
- Does available information support a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26?

Board Questions of Clarification

Dr. Rebecca Parkin noted that the study has gone through a great deal of review and consideration. It was mentioned that the mopping study was performed at the same time as the wipe study; she questioned whether the people participating in the wipe study were in the waiting area while people were mopping. Mr. Carley responded that the wipe study has two scenarios. These two scenarios and the mopping study scenario were designed to be conducted in three randomly selected buildings, but they were not conducted simultaneously. A lot of the lessons learned in the field apply to both the mop and wipe studies. Dr. Parkin looked at the floor plans and was not clear for clusters 2 and 3 about the movement of the subjects. She questioned whether there were concerns about what was happening in waiting area when mopping was being conducted. Mr. Carley noted that this question should be deferred to the investigators. Dr. Parkin noted that there was no mention of heating, ventilating, and air conditioning (HVAC) in Mr. Leighton's presentation. Another factor to be considered was volume of space and this also was not in the report. Mr. Leighton stated that two of the three clusters did not say much that was useful, but one did send air exchange rates. The HVAC would not have too much impact on the mopping studies in terms of the results of the aerosol inhalation samples. Dr. Parkin commented that it might be helpful to have had some points of reference on what is acceptable. Finally, she mentioned that the observer did not take the light measurements, and she requested the rationale for the lack of light measurements. Mr. Leighton suggested that this be deferred to the investigators. Mr. Carley stated that on advice of the Board, EPA encouraged the task force to minimize the number of people following subjects around. Dr. Parkin stated that it would be helpful for the Board to have explanations as to why there were some losses of data.

Dr. Green noted the additional data submitted on October 18, 2010. Mr. Carley stated that the information that arrived on that date was an e-mail that contained the accounting for pre-enrollment recruiting. Dr. Green mentioned that a conclusion stated that statistical inference to the universe of moppers was not justifiable. He asked if this weakens the ability to conduct a risk assessment. Mr. Leighton stated that it was not feasible in these studies to conduct a true random sample. EPA justified the study because it would monitor high end exposure due to longer timeframes and use of a string mop, which they believe would result in higher exposure than use of other types of mops.

Dr. Manautou asked about inhalation and air handling capacity. The studies are developed to determine potential dermal and inhalation exposure in an occupational setting, and it is a weakness that there is not more information on potential differences in air handling capacity and ventilation at the testing sites. Dr. Manautou reemphasized Dr. Parkin's point.

Dr. Fernandez commented on the statistical analysis in the report. He was able to reproduce the results using the data provided. Mr. Leighton noted that Board members were given the Statistical Analysis System (SAS) program and some directions on Excel spreadsheets. Dr. Fernandez thought the presentation of the data was fine. He suggested that it might be better to display the results of the study in a chart. The variability can be seen in the slide Dr. Fernandez presented. By displaying the confidence interval more information can be determined from the data. Mr. Leighton noted that this could be done for the next study report.

Dr. Johnson asked about whether the arithmetic mean listed on slide 26 was adjusted. Mr. Leighton responded that the mean was normalized by the amount of AaiH. Dr. Johnson asked if in this mixed model analysis the ICC equaled zero. Dr. Cohen responded that it was zero for dermal exposures and 0.5 for inhalation. Dr. Johnson asked what the SAS degrees of freedom correction does when the ICC is zero and wondered if it overestimates the degrees of freedom associated with the way the confidence intervals are calculated. Dr. Cohen responded that he would have to research that.

Dr. Young appreciated the effort EPA made to provide the statistical programs and data so that Board members could review the details of the analyses. She noticed that a parametric bootstrap was used, and assumed that was based on a log normal distribution. Dr. Cohen responded that it was based on the fitted mixed model that was used for all the parametric bootstrap calculations. He used the fitted model to simulate new data that came from the fitted distribution. Dr. Young also asked about proportionality. When the data are presented in graphs, she questioned what happens if a line does not adequately describe the data. Mr. Leighton responded that when EPA examined proportionality, they examined the three clothing scenarios and a dermal (no clothing) scenario, and the results were not consistent. Some showed proportionality and some did not. EPA then assessed why the slopes were not the same for all three clothing scenarios when the residues were on the same person. Dr. Cohen went through repeated measures for the dermal scenario. Dr. Young asked if any thought had been given to the lack of fit of the model; perhaps the line is not correct, and it might be a curve. Mr. Leighton responded that this scenario is something EPA can continue to examine. Dr. Young asked if this had been done to date, and Mr. Leighton responded that it had not.

Dr. Popendorf mentioned the correction for the face and neck residue. He clarified that the 60% correction was based on tests of the residues remaining on the person's hands after they were washed. Dr. Popendorf noted that may be an overcorrection. Mr. Leighton was interested in hearing opinions on this because a new study on hand-washing may have to be conducted. Dr. Popendorf recommended that given a choice, a wipe would be used separately from the wash and not be used to wipe someone that had already been washed.

Dr. Lebowitz mentioned interest in the statement that between subject variability was greater than the between cluster variability, which is true for the dermal data but is not true for the inhalation data. This raises questions about the ventilation, but also raises questions about how volatile the material is, or how the lack of volatility is represented. Dr. Lebowitz questioned whether the surrogate used is of lower volatility than the actual disinfectants used for mopping in normal practice. Mr. Leighton responded that the product used (Buckeye Sanicare Lemon Quat) has a big market share among disinfectants. This product is typical of the chemistries used, but

there might be some other products that have higher volatility. Dr. Lebowitz asked whether the study focused on high-end exposures. He suggested that EPA address that issue because the Agency does not currently have the data to indicate that it is or is not generalizable. Mr. Leighton mentioned that with higher volatility, EPA would be asking for a chemical-specific study using generic data or going to air chamber tests. Dr. Lebowitz noted that milligrams per cubic meter were used as measurements, but stated that it was more appropriate to use micrograms or nanograms in inhalation studies. Mr. Leighton responded that the results table is reported in micrograms.

Dr. Gamble raised the issue of inclusion of people who self-identify as in fair health in the study although one of the inclusion criteria is good health. Two people in the group identified themselves as in fair health; however, after speaking with them, the investigators decided subjects were in good health. Dr. Gamble questioned why these subjects were included if the health assessment was supposed to be based on self-identification. There are some studies where there are specific guidelines in terms of heart disease, for example, but in this case, there are serious concerns about the inclusion of those two people in the study. Another concern is the expedited review by the IRB with no minutes. Dr. Gamble did not have a problem with expedited review, but with the fact that there were no minutes taken. Dr. Sharpe noted that this was discussed in IRB rules in 40 CFR, and there does not seem to be an exclusion from the requirement for minutes for expedited review. Mr. Carley stated that there was not a meeting held, so the threshold for that provision was not crossed. Dr. Philpott suggested that this was a discussion point. Dr. Gamble stated that the majority of people wanted their test results back but that has not happened, and it would be useful to know what mechanism is in place to ensure that these results are given back to the people who requested them. Mr. Carley responded, regarding the first question, that eligibility criteria did not tie specifically to self-reporting. The procedural sequence was that the consent form told candidates that they needed to be in good general health. They were asked to fill out the self-description form, but he did not see that their self-appraisal was the defining interpretation. If the study director thoughtfully concluded that they were in good health, then the criterion in the protocol was satisfied. Dr. Gamble added that in the protocol there was no discussion about what it meant to be in good or excellent health. Dr. Philpott commented that it may be another point for discussion or recommendation for future protocols to develop some clearer criterion procedures for determining how the general state of health will be established. Mr. Carley agreed.

Dr. Sharpe stated that she was curious about how results are communicated. Opportunities exist for them to be obscure rather than clear. Mr. Carley responded that the Board would soon see what the task force has proposed to do to communicate results. Dr. Philpott noted that the next protocol the Board would review contained a suggested method for communicating results, and that perhaps the AEATF II could use the advice offered for that protocol as well.

Dr. Gamble asked about the use of the terms Spanish language and English language in the demographics table. She requested clarification on whether this specifies the way the subjects received the consent forms and discussion. Mr. Carley responded that this could be asked of the investigators, but his understanding was that it specified the subjects' preferred language for communicating with investigators.

Dr. Parkin commented, regarding the 47-year old that claimed 40 years of experience, that perhaps the Agency could check on the reported age of the subject, which may have been the error. Mr. Carley responded that one of the requirements for participation is a government-issued identification card, which could be used to verify self-reported age.

Dr. Fernandez mentioned the PROC MIXED procedure in SAS used for normally-distributed data analysis; when conducting a data transformation, this procedure is used. SAS has a new procedure called PROC GLIMMIX in which the distribution can be specified, which may be another way of conducting the analysis. Dr. Philpott asked whether that procedure was performed. Dr. Cohen responded that he had used PROC MIXED for the analysis, but agreed to examine other possibilities, such as the NLMIXED procedure. Dr. Cohen stated that EPA would like to have a model that makes physical sense as well as statistical sense. If there is a complicated function relating the exposure to the amount of active ingredient, it will not be as useful to the Agency as a simple unit exposure type model.

Dr. Sami Selim, study director, joined the Board to respond to questions of clarification. Dr. Philpott noted the Board's questions for the investigator, beginning with the question of the interdigitation of the mopping and wipe studies. Dr. Selim stated that the investigators were concerned about the issue of cross-contamination so in every cluster, each day there were two wipers and one mopper scheduled at different times. There was no overlap among the subjects who went into separate isolated areas that were not in contact with any of the treated areas. In addition to that, another area was used for taking samples to ensure that there was no cross-contamination. Background levels were taken every day for the air concentration before the subjects entered the facility. Air samples were collected at the height of 3 feet to ensure that the levels were below detection. An extremely sensitive liquid chromatography tandem mass spectrometry method was used, and the LOQ was 10 mg of total compound for the length of exposure. Dr. Parkin asked, regarding cluster 2, whether subjects had to walk through the treated area to get to the changing area. Dr. Selim responded that the investigators ensured that the area in the middle was not mopped so that subjects could get to the dressing area without crossing a treated area. Dr. Parkin asked if the mopping was conducted before the wiping each day. Dr. Selim replied that the sequence depended on when the subjects could be scheduled. Dr. Parkin asked whether the time between moppings on two days could have been as short as 12 hours. Dr. Selim noted that the last mopping was at 5:00 p.m. and the first mopping in the morning was at 8:00 a.m., but that air samples were collected in the morning to ensure that there was no compound present in the air.

Dr. Philpott asked what the observer's role was in the collection of data. Dr. Selim replied that the observer had a cart holding a device that measured temperature, and followed the subjects so the temperature could be determined at the subject's location. In one instance, that device did not function properly, but other temperature data were available from the facility itself. Dr. Philpott noted that light levels were not measured although they were mentioned in the protocol. Dr. Selim responded that the compounds used in the study were stable and should not be impacted by light; light was not measured because a device to measure it was not available. Dr. Lebowitz added that a question remained about the HVAC system and what was measured in terms of air exchange. Dr. Selim responded that the temperature inside the facility indicated that the system was working. The HVAC specifications are reported in the study. Dr. Manautou

clarified that the ventilation of the HVAC system was operational at the time of the study even though the facilities were vacant. Dr. Selim confirmed that before renting the facilities, the investigators checked that the HVAC systems were operational.

Dr. Philpott asked, regarding the reporting of the demographic data, whether the listing of Spanish versus English was a language preference or self-reported language. Dr. Selim responded that Mr. Carley's answer was correct; the language listed was the choice of the subject for the informed consent form. Dr. Selim interviewed every subject that enrolled in the study, and cosigned every informed consent form. Dr. Philpott confirmed that the age recorded was the age listed on the government-issued identification.

Dr. Philpott asked about Dr. Selim's plans for the return of the exposure results to the subjects who requested them. Dr. Selim shared a possible letter to subjects on this topic with the Board. The investigators hope to avoid sending a letter that includes the subject's identification number as well as name and address. The letter that Dr. Selim shared contained a chart presenting information comparing the subject's result to the average exposure, highest value, and lowest value. Dr. Philpott suggested that Dr. Selim submit a procedure and letter that the Board can review with ample time. Mr. Leighton noted that he liked the idea of using relative comparisons rather than absolute numbers. Dr. Parkin commented that she had provided results to study participants in the past, and they need to have some way of interpreting their results; for example, is the exposure too high? Dr. Selim responded that the last sentence of the letter states that exposures were all low and within the safe range for skin and inhalation exposure. Dr. Philpott noted that the Board members would be willing to review the letter and procedures for sending the letter to subjects, so Dr. Selim might want to work with the Agency to submit the letter to the Board. Dr. Manautou noted hesitation to include graphics for a population who might not know how to interpret them; very simple explanations of the results and how they compare with the other test subjects might be a better approach.

Dr. Gamble asked for further clarification of the use of the terms good health and fair health. Dr. Philpott asked what the investigators' expectations were regarding those terms, and asked that Dr. Selim address the two individuals who identified themselves as in fair health but were included in the study nonetheless. Dr. Selim confirmed that the protocol states that subjects must be in good health. The two subjects in question were interviewed about their health and were very healthy. Dr. Gamble queried whether the subjects were asked why they specified that they were in fair health. Dr. Selim stated that he did ask them, and noted that he believed that the Spanish translation for "fair" was "*normal.*" Board members reported that this was not an accurate translation. Dr. Selim believed that the form listed "*normal,*" but would need to check. Dr. Philpott stated that Dr. Selim did ask the subjects, but there seems to be some uncertainty about why they said they were in fair health, and Dr. Selim made a personal assessment based on specific questions that were asked that the subjects were in adequate health for the study. Dr. Selim added that he described the tasks to these individuals as well.

Mr. Roogow, Chief Operating Officer of IIRB, joined the Board to respond to questions of clarification. Dr. Gamble asked about the procedure for expedited review and why there were no minutes taken. Mr. Roogow responded that per IIRB's SOPs, expedited review is conducted by one IRB member appointed by the Chair. The expedited review is a full review; once the

review is complete, the documentation of that review is an approval letter that is reported to the convened IRB on the agenda of the next meeting. Dr. Gamble noted that there does not seem to be any documentation in the record. Mr. Roogow commented that there is no requirement to have minutes for that review. Mr. Carley mentioned that he had not seen any report describing the expedited review; only a summary report stating that IIRB had "approved this after expedited review" was in the record. Dr. Philpott asked if a written report was provided from the individual reviewer to the full IRB. Mr. Roogow responded that there was not. Dr. Philpott added that the regulations do not require that for expedited review. Dr. Menikoff commented that the regulations do not apply in terms of expedited review. Mr. Carley asked if under IIRB procedures, any documentation exists on a decision that a case is eligible for expedited review. Mr. Roogow replied that the expedited reviewer makes the determination that the case is eligible for expedited review and completes a form. Mr. Carley clarified that the expedited reviewer screens all incoming reviews, and Mr. Roogow confirmed that this was correct. Dr. Gamble noted that the Board did not have the documentation that the amendment was eligible for expedited review. Dr. Philpott confirmed that a documentation deficiency had been identified.

Dr. Gamble asked Dr. Selim whether the participants who reported themselves as in fair health were Spanish speakers. Dr. Selim noted that one spoke Spanish and one spoke English; the Spanish speaker was the one who participated in the study.

Public Comments

Mr. Has Shah (AEATF manager) thanked EPA, the HSRB, CDPR, and the Canadian Pest Management Regulatory Agency for their valuable input in designing the mop study. He thanked EPA for responding to the AEATF's questions during conduct of the study in a very timely manner. He also thanked Dr. Selim and staff for their efforts in conducting the study. Many lessons were learned in this study that will be used in presenting the wipe study report to EPA and the HSRB next year.

Mr. Roogow thanked the HSRB and EPA, and noted that IIRB's main concern is the safety of human subjects and they are proud to be a part of this process. He also stated that IIRB is willing to take recommendations from the HSRB to improve the process.

Board Science Review

Dr. Parkin noted that in terms of the first charge question, neither the final report nor the original protocol includes an explicit summary statement of the study design. Instead, descriptions of the study conducted and completed were provided. The final report contains a number of sections which offer more detail than in the protocol. Some of the issues raised by the Board in 2008 were not addressed; some were. Supplement 1, section 8, provides discussion of study design including detailed justifications for the various design elements. Although the importance of HVAC was noted on page 28, it was not given equivalent attention in the conduct of the study. Supplement 2 provides a rationale for changes in key elements in the study design. Modifications to analytic procedures were noted in section 7.2.2 of the final report and it was stated the laboratory and field data were validated. Deviations from protocol and SOPs were briefly stated but not explained in the final report. It was disappointing not to find rationales or

evidence-based support for those deviations, but some were explained in more detail. HVAC operations and air exchange rates were indicated as a study metric in the protocol but the actual data during the study was not documented. This lack of information places potentially important limitations on how the data should be interpreted and used for exposure estimation. In summary, the study conducted was largely consistent with the study design and was reasonably well described.

In the final report, the objective was stated as to determine potential dermal and inhalation exposures to professional janitorial workers when mopping floor surfaces with a liquid antimicrobial pesticide product containing DDAC. Although faithful to its objectives, the final report discussed the dermal exposure estimates more completely and effectively than the inhalation exposure estimates. Although less specific, the Supplement 1 objectives are consistent with the final report. In Supplement 2, a benchmark objective was stated. In summary, the stated objectives were met and documented in the final and supplemental reports but because of the lack of some expected data it is difficult to determine whether the goal of characterizing high end exposures was met.

Dr. Parkin stated that Section 3 of the Agency's scientific review discusses the limitations of the dermal and inhalation exposure data. In terms of dermal exposure, the Agency has adequately considered the interpretation and estimation of dermal exposure data. Regarding inhalation exposure, the Agency discussed some but not all of the limitations that need to be considered when interpreting estimates. In its 2008 comments, the Board noted several factors that are important to inhalation data interpretation: (1) room temperature – the Agency commented that the temperatures do not appear to compromise the participants' activities, but more detailed information about the air monitoring equipment was not provided; (2) HVAC data limitation – EPA's conclusion was that the air exchange data is not a significant factor was based on rationales related to the low vapor pressure of DDAC and the low LOQs observed. In Dr. Parkin's opinion this is an incomplete argument; (3) total area mopped – the final report noted that the available space for mopping was limited in clusters 1 and 2, but the Agency did not comment on whether this limitation compromised the design or should be considered in interpreting the inhalation exposure data; (4) duration of mopping – the Board sought more detailed consideration of duration, which was found in the Agency's review. (5) volume of the enclosed space – the Agency's review makes no comment on the potential impact of this factor or how it should be considered in evaluating the air concentration data; (6) respiration rate of the study participants – the Agency does not note this omission or comment on the value of using respiration rate averages or assumptions to interpret the air concentration data. The six factors that the Board raised in 2008 were not fully addressed in the Agency's report.

Dr. Green thanked Dr. Parkin for her excellent review. He agreed with all of her comments.

Dr. Young commented on the parametric bootstrap; the approach used relies heavily on the model being correct and with 18 data points, it is hard to assess that. In some of the graphs presented, she questioned whether the model is correct. In addition, she felt that the test for proportionality did not make sense. With the short pants/short-sleeved shirt scenario, it seems that the line does not fit at all. To test for proportionality when there is not a good fit of the

model is questionable. Dr. Young appreciated the fact that members were provided with the data and statistical programs.

Dr. Popendorf noted that he had three points focusing on the inhalation side of the study. Inhalation doses are smaller than dermal, but concentration multiplied by time must be considered. His three concerns regarding the airborne data from the mop exposure study include: (1) inhaled dose is more equivalent to dermal dose than airborne concentration, and thus airborne concentration should be the hypothesized correlate with lbs AaiH; (2) despite the limitation of airborne concentration, it should be measured; (3) given the lack of correlations between either airborne concentrations or inhaled dose and lbs AaiH, the Agency should reconsider its plan to continue applying a unit exposure value to inhalation exposures.

Inhaled dose can be calculated by using concentration and duration of the task, and if EPA is going to look for correlations between active ingredient and exposure. A good way to consider AaiH is simply what fraction of what is handled gets on the subject's skin or into their respiratory system. Dr. Popendorf would like to make it a recommendation of the Board that form of airborne exposure should be examined. Mr. Leighton mentioned that EPA had two Scientific Advisory Panel meetings on the inhalation risk assessments. EPA is moving toward specific inhalation risk assessment; from a rat toxicity study, the human concentration is being calculated. From there, the Agency is intending to examine the air concentration. Dr. Popendorf suspected that different outcomes likely were being examined. For the purposes of looking for a correlation between AaiH and exposure, concentration, particularly the averages during the mopping activity, should be considered. The time and concentration represents a fraction in the air of what was used; if there is a correlation that would be the one to examine.

Dr. Popendorf added that the report negated the fact that the material has low volatility and no aerosols were produced. It is possible that material spritz could get into the air sampler. If this did occur, there would be a correlation between front torso and air concentration. Another possibility is data entry; Dr. Popendorf did not see a QA/QC on data entry and was concerned with subject M24. This subject used more than twice the amount of active ingredient as others, and mopped one of the smaller floor areas. This subject is an outlier, and Dr. Popendorf hoped it was not an error. He included an equation for examining saturated vapor concentration using vapor pressure, material weight and material to get a concentration for DDAC (0.4 ng/m^3). Air concentrations are 0.2 μg, so that is saturated at the mop area. This is three orders of magnitude below measured levels of vapors. If it is assumed that the aerosol is generated as a mist by the mop and if the concentration of the product is known, a prediction of the aerosol concentration right around the mop can be made – for DDAC this is 0.6 mg. As the aerosol leaves the mop, the water will evaporate. Dr. Popendorf examined other predictors such as square feet per minute mopped; mopping faster did not seem to produce more aerosols. Active ingredient used per minute did not seem to correlate. Ventilation data are missing, but if the rooms varied in their flow rate on the order of a factor of two, this would mean the range of aerosol concentration would be a range of six. Dr. Popendorf stated he did not think differences in ventilation among the buildings were a significant contributor. Discussions on air changes per hour illustrate a common misconception; how long it takes to reach a steady state does not indicate what the steady state would be. That depends on the cubic feet per minute flowing in and out of the room. From the scientific perspective, there is no justification for using AaiH as a predictor of airborne

exposure. When he ran a correlation between AaiH and inhaled dose time concentration, there was an insignificant but slight negative correlation.

Dr. Philpott noted that the general Board consensus is that the research as reported is faithful to the design and objectives of the protocol, but sometimes those are not clearly articulated. The Board felt that although the dermal exposure data are accurate, it raised issues about inhalation data. Some concerns remain about the HVAC unit, air exchange and flow, and volume of the enclosed space. Additionally, some statistical concerns remain, including confidence intervals that were too narrow, and use of the parametric bootstrap based on a model that may not be correct. Concerns also were raised about the test for proportionality, specifically the fit of the model.

Dr. Johnson was uncertain about the degrees of freedom of the mixed model analysis. Dr. Philpott noted that could be a recommendation to look at some of the other methods that could be applied to analyze the data. Dr. Johnson added that when there is an ICC of zero, the degrees of freedom may be too large and confidence interval may be too narrow.

Board Ethics Review

Dr. Gamble thanked the Agency staff for putting the materials together for the Board to review. Getting the ethical concerns in better order has been a long process. None of this research involved intentional exposure of pregnant or nursing women or of children, and there was voluntary informed consent. Some deviations from the protocol were made, and need to be noted although they did not have ethical significance. One was a lack of a break for enrollees in the study, and the other was photographs taken of the faces of people at one site, and it needs to be determined whether they were informed of the breach of privacy. The other issue the Board should address is adequate documentation of IIRB's expedited review. The Board does not have documentation that an expedited review was warranted or of the expedited review itself. The inclusion in the study of those who reported fair health also is a concern. In the protocol, it is not clear how health status would be determined. Regarding the reporting of the results to participants, investigators are making efforts, but attention must be paid to how the results are communicated and translated. Dr. Gamble believes that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26, but there are some deficiencies that need to be addressed.

In response to the charge question, Dr. Menikoff stated that the study is in substantial compliance. Given the level of risk involved in this study, an extraordinary amount of attention was given to ensuring that appropriate care was taken of human subjects.

Dr. Sharpe stated that it would be helpful for future studies to more specifically define if there are health criteria that could be used to gauge subjects' health. When it is up to the investigator to make the ultimate determination, there could be conflicts or bias if recruitment had been difficult. In terms of IRB records, she reads the regulations to mean that documentation of IRB activities should be included.

Mr. Jordan, regarding informing the participants of the study results, asked whether the Board would recommend that the results not be sent to participants until after it has reviewed the material. It could be put on the agenda for the January 2011 Board meeting, but Mr. Jordan questioned if it is more important to send the results sooner. Dr. Philpott suggested that the Board may want a small working group to address this. Dr. Menikoff noted that the letter seemed reasonable. Dr. Gamble stated that the letter may have been benign, but was not useful, and she supports Dr. Philpott's suggestion to form a working group. Dr. Lebowitz agreed that a working group can help resolve that issue.

Dr. Philpott proposed, because the working group needs to present its recommendations to the full Board, that it can be done in the teleconference currently planned for mid-December.

In response to the ethics charge question as to whether the available information supports a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26, the Board's consensus is yes, noting some concerns and giving some recommendations for future studies in this area, including trying to define objective health criteria for inclusion and noting the documentation concern regarding the IRB review of the protocol.

Session 4: Revised scenario design and associated protocol from the AHETF describing proposed research to monitor exposure of workers who mix and load pesticides formulated as wettable powders in water-soluble packaging

Background

Ms. Sherman noted that the protocol was reviewed favorably by EPA and the HSRB favorably reviewed the protocol in June 2009. At that time, carbaryl and acephate were the surrogates. In late 2009/early 2010, it became apparent that different surrogates may be needed because carbaryl was no longer being sold in water-soluble packaging and there is not much use of acephate. AHETF membership confirmed the need for the data and identified other suitable surrogates. Three additional surrogates – dithiopyr, imidacloprid, and thiophanate-methyl – were added to the protocol; acephate is still included as a surrogate, but carbaryl no longer is included. The change in the surrogates resulted in a change to AaiH strata, which in turn resulted in revised monitoring areas.

In addition to these revisions, the AHETF addressed comments from the EPA and HSRB reviews. In response to suggestions, the AHETF took the following actions: improved the accuracy of Spanish translations; specified a method for providing individual exposure information to subjects who request it; and detailed the procedure for analyzing representativeness of the monitored subjects. In addition, the AHETF updated several SOPs and made minor revisions to the Governing Document and ceased use of Individual Product Risk Statements.

The proposed procedures governing the ethical conduct of this research have not changed, so Ms. Sherman will not conduct an ethics review of this revised protocol. Many comments from the ROW study will apply, as the ethics procedures are similar.

EPA Science Assessment

Mr. Evans noted that the scenario definition is unchanged from the original proposal, which is the mixing and loading of soluble or wettable powder pesticides enclosed in water soluble packets (WSPs) for many crops under three sub-scenarios: mixing of WSPs directly into the tank used for the pesticide application; mixing of WSPs into a "pre-mix" tank at the same concentration to be applied to the crop; and mixing of WSPs into a tank as a concentrated solution/suspension that must be further diluted and transferred to the final application tank. All three sub-scenarios must be performed at each monitoring area, and the design is a 5 x 5 study design.

WSPs are used to reduce exposure to the powder. They can be placed directly into sprayer tanks, or placed into a variety of holding tanks either fully diluted for use or as concentrated solutions for further dilution and transfer to spray tanks at a later time. Portable mixing stations also may be set up.

Three of the proposed surrogate pesticides are new to the AHETF, however they have been successfully used in other studies reviewed by EPA: dithiopyr, imidacloprid, and thiophanate-methyl. Dithiopyr was used successfully in a post application monitoring study conducted by the Outdoor Residential Exposure Task Force. Imidacloprid was used successfully by Bayer CropScience in a post application monitoring study, and thiophanate-methyl successfully was used in residue studies relying on similar surfactants and cotton collection media.

An important part of having a suite of surrogate pesticides is having a wide range of application rates, and in this case dithiopyr and imidacloprid have low application rates and are critical for collecting exposure measurements of participants using the lower AaiH strata. Florida and California were included to address the use of these pesticides. Thiophanate-methyl has a high application rate and is useful for collecting exposure measurements of participants using the higher AaiH strata; it is widely used in North Dakota on high acreage crops such as dry beans.

The AHETF acknowledges that collection of exposure measurements for all AaiH strata may not be possible in all monitoring areas. Collecting data for the lowest stratum may be an issue because for each MU, the participant must perform at least three mix/load activities during the monitoring period. This is the reason that dithiopyr and imidacloprid were selected, and Florida and California, which have a high numbers of acres of turfgrass grown for sod, were included.

EPA accepts the AHETF's selection of three additional surrogate pesticides provided that confirmation of analytical methods is required prior to initiation of field studies. EPA recognizes, however, that in some monitoring areas measurements of participant exposure using all AaiH strata cannot be achieved. The AHETF therefore will need to ensure that primary and secondary benchmark objectives are achieved (three-fold accuracy for the arithmetic mean, geometric mean, and 95th percentile).

For the proposed AaiH strata, all exposure durations will be at least 4 hours, and each subject will mix/load at least three tanks of spray mixture. The five strata of AaiH in each cluster are: 3 to 7 lbs AaiH; 8 to 21 lbs AaiH; 22 to 56 lbs AaiH; 57 to 150 lbs AaiH; and 151 to 400 lbs AaiH.

Proposed monitoring areas are in varied climates and include a wide variety of crops. EPA is reasonably assured that success can be achieved in the study. Not all strata may be applied in each cluster; EPA has concerns about achieving the lowest stratum (3 to 7 lbs AaiH). Dithiopyr and imidacloprid were selected specifically to achieve this range, however, and monitoring areas of California and Florida were selected for having large areas of turfgrass for which dithiopyr and imidacloprid are registered.

EPA calculated the exposures and risks for maximum AaiH (400 lbs) for all of the surrogates and found no issues. EPA agrees with the AHETF plan to diversify these general equipment types. The Agency believes that each of the three sub-scenarios must be monitored at least once within each monitoring area, and stresses that all attempts be made to measure participants applying AaiH from each of the five strata per monitoring area, keeping in mind the AHETF's ability to achieve all AaiH strata in all regions with respect to achieving primary and secondary objectives. EPA notes that diversity will be achieved either randomly or purposively in the course of assigning mixer/loaders to AaiH strata within each cluster, and concludes that the proposal for 25 subjects collected in 5 different monitoring areas having 5 subjects each is appropriate for this scenario.

The analytical methods for acephate are robust, but confirmation of analytical methods is required for dithiopyr, imidacloprid, and thiophanate-methyl. Overall, the scenario is well-defined and the study is likely to produce reliable mixer/loader data to assess the potential exposure of handlers using WSPs.

EPA Ethics Assessment

Ms. Sherman noted that she planned to discuss the ethics points raised for yesterday's ROW study which were the same as for this study. She noted that the revision was reviewed by IIRB under the expedited review process, so minutes or other documentation of the review is not available. The four comments received from the Board on ethics included the following: Dr. Sharpe asked that there be some clarification in the eligibility requirements in terms of training; Dr. Sharpe asked that the description of the pregnancy testing procedures be copied from the SOP into the informed consent form; Dr. Menikoff suggested that the risk discussion in the consent form and the protocol should acknowledge the risk of exposure to surrogate chemicals; and Dr. Philpott suggested that it be included in the informed consent form that subjects should wash hands before smoking as well as before eating. These comments all apply to the current study as well as the AHETF study discussed on the previous day.

Charge Questions

Ms. Sherman read the charge questions into the record:

If the revised AHETF scenario and field study proposal AHE120 is revised as suggested in EPA's reviews and if the research is performed as described:

- Is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who mix and load soluble or wettable powder pesticides in water-soluble packaging?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Questions of Clarification

Dr. Philpott commented that it was important to note the HSRB was reviewing a revised protocol, the original of which had been favorably reviewed in June 2009. He suggested that the Board focus on the impact of the changes to the protocol such as the new surrogate compounds and new study sites.

Dr. Chambers noted that Mr. Evans had mentioned that there were six data monitoring sets already available; this study will provide 25 more. She questioned whether the data sets will be combined or if the original six will be rejected. Mr. Evans responded that the six data sets that EPA has include many non-detects because of the short monitoring period, and they will likely not be considered at all.

Dr. Popendorf commented that he examined the clothing that the applicators are going to use and it included a chemical resistant apron. He asked if the chemical resistant apron was required for all WSPs, and if use of the apron would have an effect on the generalizability of the data. Mr. Evans responded that the reference to aprons was a mistake on his part and no aprons would be used in the study.

Dr. Popendorf questioned what will be done with the data if insufficient data are collected on the lowest strata. Mr. Evans responded that investigators anticipated that there would be greater success at the lower strata in California and Florida, and then in other locations (such as North Dakota and New York) they would focus more on the higher strata.

Dr. Popendorf mentioned that in the review, it was stated that being an employee of the sponsor was an exclusion criteria. Ms. Sherman confirmed that sponsor employees are excluded.

Dr. Sharpe asked for clarification as to why this study is considered greater than minimal risk; the implication is that it is because agriculture is a high-risk profession. She suggested the wording be changed to state that it is a greater than minimal risk because it is an intentional exposure and there is a risk of heat-related illness.

Dr. Manautou asked for clarification on the Agency's statement regarding duration of exposure, that the MUs will be monitored during their entire work day since many other known factors might contribute to exposure. He asked what those known factors might be. Mr. Evans responded that these activities include tractors pulling up and interacting with personnel; EPA wants to ensure that a typical day is captured.

Dr. Fernandez asked what types of analysis plans are proposed; the locations are selected, the crops are different, and the active ingredients are different. The sites will not be considered as random as those in the mop study. He questioned whether the AHETF will be conducting any comparison hypothesis testing to see if any significant differences exist among the locations. Mr. Evans replied that this is a mixing and loading study, so the variety of tanks is more of a concern; it has less to do with the person's exposure treating an apple orchard compared to treating sod or a row crop. The study is centered on the activities putting the product into the tank. Dr. Fernandez asked whether this was the case even though a wide range of crops were being covered. Mr. Evans replied that the variety of crops provided a way to involve more tank types.

Dr. Philpott commented that the additional surrogates are being incorporated because carbaryl packaged in WSP was out of production, and it also seems as though acephate is being phased out of production. He asked why acephate is still being used as a surrogate. Ms. Sherman explained that the active ingredients in carbaryl are not being phased out, but it is no longer being produced in the WSPs. For acephate, the question may be better asked of the task force. Dr. Philpott added that one of EPA's concerns is getting confirmation of method results for thiophanate-methyl. Given that this appears to be a technical restriction, he asked why this surrogate was chosen. Mr. Evans responded that it was chosen to be able to achieve the upper strata on crops such as dry beans, canola and apples. Dr. Philpott mentioned the shift to hotter climates, which means that more participants may be facing a risk from heat. Mr. Evans responded that EPA agreed with that assessment, but the sites were chosen for longer growing seasons, and therefore there may be more time to conduct the studies.

Dr. Cañez (AHETF technical chair) joined the Board again to respond to questions of clarification. Dr. Popendorf asked about the effect of task duration and the AHETF's plans for reporting task duration. He asked if only the total duration would be recorded, or if the duration of the active task would be recorded as well. Dr. Cañez responded that the monitoring time is recorded from when the air pump turns on until it turns off. Everything done during this time is monitored by someone; whether the subjects are actually mixing and loading or cleaning up the area, the monitor will write down whatever they do.

Dr. Johnson asked how the subjects got to 4 hours of mixing and loading because it seemed as though it would be a relatively quick process. Dr. Cañez responded that the subjects may not be mixing and loading for the whole 4 hours, but from the time they start and finish three loads, the entire duration will be 4 hours. If the subject is mixing a large amount of slurry, it may take a significant amount of time.

Dr. Manautou commented that not all of the scenarios are continuous exposures, but intermittent exposures because of the waiting for new trucks, and so on. Dr. Cañez replied that the same thing is true with an applicator. Dr. Manautou noted that in a scenario of a higher volume of work, a potential worker would be mixing for a longer period of time than in an operation with fewer trucks. He asked if this could lead to different scenarios of exposure. Dr. Cañez stated that this may be one of the variables, and it would be written down, but to tease that out of the data would be difficult. Basically the AHETF is attempting to normalize the exposure to lbs AaiH, and whether the lbs AaiH is in three half hour segments or a 1.5 hour segment will be unclear.

In response to a comment by Dr. Philpott, Dr. Cañez stated that acephate is not going away; its popularity in agricultural settings is decreasing, but it is used quite a bit in minor crops.

Dr. Popendorf stated that if total time was monitored, as was time on task, it would be fairly easy to tabulate that, and the difference between the two would be the time between tasks. It could be potentially useful to have this information, and it seemed like it would be available in the study notes. Dr. Cañez noted that the observations of when the subjects are on task are recorded. Dr. Philpott noted that one of the discussion points was that intermittent versus continuous exposure may be a variable that the AHETF should consider; it may affect the proportionality of AaiH to exposure. Dr. Manautou stated that the AHETF's level of confidence would be based on the total lbs AaiH, but in toxicology the type of exposure, even to the same amount of AaiH, could have different effects, and the exposures are clearly different.

Dr. Lebowitz noted that all these operations are intermittent. If the study were on health effects, far more samples would be needed to determine what effects different degrees of intermittency can have. The AHETF must figure out how to approach these variables in terms of trying to relate the amounts used to the exposure.

Dr. Chambers agreed with Dr. Lebowitz because the granularity the AHETF might try to get in trying to record the intermittencies of these exposures is probably going to be almost impossible with any degree of accuracy. It seems it is quite reasonable to normalize to the AaiH.

Public Comments

Dr. Cañez noted that it had been a pleasure coming before the Board and that he always learns something.

Board Science Review

Dr. Popendorf noted that the science behind the protocol is still largely the same as it was during the review of the original protocol by the HSRB in June 2009. The changes that were discussed in active ingredients and geographic regions were justified, agreed to by the Agency, and still seemed to provide good probability of achieving the primary goals. The only additional recommendations would be to review the need and impact of the 4-hour restriction and to possibly include the task duration time in the data that is planned to be collected. Dr. Lebowitz stated that he did not have anything to add to EPA's review.

Dr. Manautou noted that his comments and concerns were addressed by the Board, the Agency and the AHETF.

Dr. Johnson clarified that on page 5 of the review, it was stated that mixers and loaders would wear chemical resistant aprons, but he understood that was an error. Mr. Evans indicated that it was. Dr. Johnson noted that chemical resistant gloves and footwear would be worn. On page 8, the fourth bullet states: "requires the grower to have sufficient acreage that the minimum AaiH can be mixed and loaded." Mr. Evans confirmed that this stipulation was made to ensure

that the study was not conducted at too small a site. Dr. Johnson added that the next bullet still mentioned carbaryl. Mr. Evans responded that this was an error.

Mr. Carley stated that all of the scenarios have some degree of intermittency and exposure, but that not only the task activity can lead to exposure. When an applicator has taken his tractor back to the base to get reloaded, if he gets out of the tractor and leans against the tank, he could be getting more exposure from that than from anything that happens while he is actually applying the compound. The same thing could happen with the mixing and loading. Therefore, the time on task is not equal to the time of potential exposure. Dr. Lebowitz commented that differentiating what the subject is doing then may be important in interpreting the results and calculations.

Board Ethics Review

Dr. Philpott concurred with the conclusions and observations regarding the ethical strengths and weaknesses as Ms. Sherman noted in her review, and believed that the proposed study is likely to meet the applicable ethical requirements of research involving human subjects based on the following criteria: there is an acceptable risk/benefit ratio with five risks to participants enrolled in the study, including heat-related illness, exposure to the study surrogate chemicals, injury associated with scripted field activities, allergic reaction to the surfactants used for hand-washing and wipes, and psychological stress and breach of confidentiality associated with the pregnancy test results. Heat-related illness is the greatest risk because of the addition of the WBD. Changing to an additional hot climate changes the number of subjects exposed to risk, but this risk is properly minimized by stopping rules.

He suggested that the AHETF examine the language in the informed consent document about how they inform participants about the symptoms and the medical monitoring plan. The surrogate materials used consist of very common pesticides which have been extensively tested and subjects will only be exposed to concentrations at the accepted exposure thresholds. Participants who have experience handling these and similar compounds in WSP loading scenarios will be selected for the study. The participants are reminded about safe handling practices and procedures, will be wearing appropriate PPE, and will be monitored for any accidental or unintended product exposure. Because there is the desire not to enroll participants that use PPE more than the average worker, the language that is currently in the informed consent document is slightly directive and may lead workers to use less protection than they normally would to participate in the study and receive financial compensation. He suggests reframing that language in a non-directive manner that asks what PPE they normally use for that compound; if they list PPE beyond what is normally worn, they can be excluded. Allergic reactants to surfactants are usually mild and can be treated with over-the-counter steroidal creams and subjects who have a history of severe skin reactions to such detergents are excluded.

Minors and pregnant or lactating women also are excluded, with pregnancy being confirmed by the use of an over-the-counter pregnancy test on the day of the study. The potential stigma of study exclusion because of pregnancy is minimized through enrolling additional participants in confidentiality. He agrees with Dr. Sharpe that a better description of the pregnancy test should be included in the informed consent form. There is clear voluntary consent

of all the participants. He admitted that the requirement to engage the growers first and the resulting potential for coercion cause him concern. Good procedures exist to try to minimize that potential. He asked whether the grower will still receive the surrogate compound if he agrees to participate but none of his workers volunteer for the study. If he does not, he may overtly or covertly pressure his workers to volunteer if that is a substantial benefit to him. Ms. Sherman noted that the product is not provided to the growers, but they are reimbursed for the cost of the product used in the study. Her understanding is that the reimbursement is not a significant inducement to the grower in comparison to the inconvenience of having the research conducted on their property.

Dr. Philpott appreciated all of the efforts that the AHETF took to ensure that the non-English documents are in appropriate regional dialects and to use bilingual researchers. Overall, there is equitable selection of study participants. He agrees that this study is well designed and is likely to meet the applicable requirements of 40 CFR part 26.

He added that with respect to reporting results to participants, the task force should examine the guidelines for this study as well, because he has concerns with the language and content. Because enrollees may be functionally illiterate, ways of reporting the information other than a letter must be considered. Finally, he would encourage the task force to incorporate into the informed consent document the idea that this information may be a benefit to the participants because they can use it to identify accidental exposures and provide them with information to help them lower their exposures if they are above the mean range. The participants should be asked in the consent process and on the form if they want the information released to them rather than require the participants to contact the study director. The informed consent document or the protocol for the AHETF should better explain what is meant by the statement "you may refuse medical treatment unless...we believe you are too sick to make a rational decision about getting medical treatment." This statement is subjective, so appropriate criteria are needed in the informed consent form and the protocol, as is an explanation of who will be making this decision.

Dr. Gamble agreed with Dr. Philpott that the study meets the applicable requirements. She stated that he is correct in terms of the evolution of the document for Spanish speakers, but it must be considered that languages other than English and Spanish may be needed in the future. She urges the AHETF to recognize that there is a difference between interpretation and translation; translation involves just language, while interpretation involves cultural aspects as well. The AHETF should think more in terms of interpretation than translation. She shares the concerns of Dr. Philpott in terms of engaging the growers first; this is an area that can have some potential conflict and the HSRB must continue to pay attention to that area to ensure that there is no coercion there.

Dr. Sharpe noted, in anticipation of the discussion of return of results to participants, that there is an assumption made that this would be a benefit to the participants. She questioned whether the basis for returning the results is fundamental ethical principle or respect for persons or reciprocity. It may not be a benefit; there may be risks involved with the return of the information. The information could get into the hands of third parties and thus have a negative impact. In terms of the way that it is characterized in EPA's report, there is an assumption about

benefit that the HSRB should not make. The ethical basis for return of the results can be discussed when guidelines for this are considered.

Dr. Gamble asked Dr. Sharpe if every time there is a study, the question about return of the results should be asked. Dr. Sharpe responded that some IRBs mandate offering to provide results. In every case where the HSRB thinks it would be appropriate to offer to provide results, it needs to be clear about how to characterize that, and the ethical basis for returning the results. Dr. Philpott added that he characterized it as a potential benefit. If someone was shown to have a lower exposure relative to his/her peers, he/she might decide to wear less PPE. These issues need to be considered in terms of how they will be presented to the participants. If participants are below the mean, they might not engage in the same level of self-protective behaviors that they had in the past. This issue can be deferred to the working group.

Dr. Lebowitz noted that this discussion had raised a number of points; he agreed with Dr. Sharpe. It is very different when intentional exposures are examined if medical situations require attention. Intentional exposure studies also differ from what may or may not be done in observational studies. General information obtained in the study may be of great importance to all the workers versus individual ones, and this needs to be determined. Dr. Philpott is correct in his sense that the HSRB needs to consider these issues, but perhaps the working group should address them instead of the HSRB offering comments at this time.

Preview of Upcoming Meetings

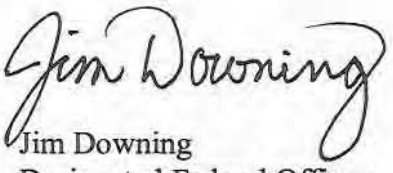
Ms. Sherman stated that the next HSRB meeting would be in late January 2011 and would have a full agenda. The first submission is a new protocol from the AHETF for mixing and loading wettable powders. Next there will be one or two completed reports from the AHETF, the closed cab air blast study reviewed in 2008, and possibly the open cab air blast study. A fourth possible item is the wipe study companion to the mop study from the AEATF.

Mr. Downing reminded Board members to submit their meeting evaluations. The dates for the next meeting will be January 25-28, 2011. The date of the December teleconference for review of the report from this meeting has not been set yet, but may be during the week of December 13, 2010. Dr. Philpott will send a meeting request to the Board members for that week and the week of December 6, 2010.

Adjournment

Mr. Downing adjourned the meeting at 2:50 p.m.

Respectfully submitted:



Jim Downing
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

Sean Philpott, Ph.D., M.S. Bioethics
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	HSRB Members
Attachment B	Federal Register Notice Announcing Meeting
Attachment C	Meeting Agenda

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

*Sean Philpott, PhD, MS Bioethics — Term: 3/27/2006-10/31/2011
Director, Research Ethics
The Bioethics Program
Union Graduate College-Mt. Sinai School of Medicine
Schenectady, NY

Vice Chair

*Janice Chambers, Ph.D., D.A.B.T. — Term: 3/27/2006-10/31/2011
William L. Giles Distinguished Professor
Director, Center for Environmental Health Sciences
College of Veterinary Medicine
Mississippi State University
Mississippi State, MS

Members

*George C.J. Fernandez, Ph.D. — Term: 5/1/2010-8/31/2013
Director, Center for Research Design and Analysis
University of Nevada – Reno
Reno, NV

*^Vanessa Northington Gamble, M.D., Ph.D. — Term: 10/19/2009-10/31/2012
University Professor of Medical Humanities
Gelman Library
The George Washington University
Washington, DC

*Sidney Green, Jr., Ph.D., Fellow, ATS — Term: 10/19/2009-10/31/2012
Department of Pharmacology
Howard University College of Medicine
Howard University
Washington, DC

*Dallas E. Johnson, Ph.D. — Term: 8/31/2007-8/31/2013
Professor Emeritus
Department of Statistics
Kansas State University
Manhattan, KS

*Michael D. Lebowitz, Ph.D., FCCP — Term: 3/27/2006-8/31/2012
Retired Professor of Public Health
(Epidemiology) & Medicine & Research Professor of Medicine
University of Arizona
Tucson, AZ

*José E. Manautou, Ph.D. — Term: 5/1/2010-8/31/2013
Associate Professor of Toxicology
Department of Pharmaceutical Sciences
School of Pharmacy, University of Connecticut
Storrs, CT

Jerry A. Menikoff, M.D. — Term: 3/27/2006-8/31/2012
Director, Office for Human Research Protections
Department of Health and Human Services
Rockville, MD

*Rebecca Tyrrell Parkin, Ph.D., MPH — Term: 10/1/2007-8/31/2013
Professorial Lecturer (EOH)
School of Public Health and Health Services
The George Washington University
Washington, DC

*William J. Popendorf, Ph.D. — Term: 10/19/2009-10/31/2012
Professor
Department of Biology
Utah State University
Logan, UT

Virginia Ashby Sharpe, Ph.D. — Term: 5/1/2010-8/31/2013
National Center for Ethics in Health Care
Veterans Health Administration
Department of Veterans Affairs
Washington, DC

*+Linda J. Young, Ph.D. — Term: 3/28/2008-8/31/2012
Department of Statistics
Institute of Food and Agricultural Sciences
University of Florida
Gainesville, FL

*Special Government Employee (SGE)
^Not in attendance on October 27, 2010
+Participated via teleconference

Attachment B

Federal Register Notice Announcing Meeting

[Federal Register: October 6, 2010 (Volume 75, Number 193)]
[Notices]
[Page 61748-61750]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr06oc10-84]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2010-0797' FRL-9211-1]
Human Studies Review Board; Notice of Public Meeting
AGENCY: Environmental Protection Agency (EPA).
ACTION: Notice.

SUMMARY: The U.S. Environmental Protection Agency (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 reviews of research with human subjects.

DATES: This public meeting will be held on October 27-28, 2010, from approximately 11 a.m. on October 27, 2010 to approximately 5:30 p.m. on October 28, 2010, 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 persons 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 section I., under subsection D., "SUPPLEMENTARY INFORMATION" of this notice.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact Jim Downing, at telephone number: (202) 564-2468; fax: (202) 564-2070; e-mail address: downing.jim@epa.gov, or Lu-Ann Kleibacker, at telephone number: (202) 564-7189; fax: 202-564-2070; e-mail address: kleibacker.lu-ann@epa.gov; mailing address: Environmental Protection Agency, Office of the Science Advisor, (8105R), 1200 Pennsylvania Avenue, NW., Washington, DC 20460. General information concerning the EPA HSRB can be found on the EPA Web site at http://www.epa.gov/osa/hsrb/.

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2010-0797, by one of the following methods:

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

E-mail: ord.docket@epa.gov.

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

Hand 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 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm).

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2010-0797. 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 the disclosure of which is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or e-mail. 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.

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, or to persons who are, or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act (FFDCA) or the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). 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 Jim Downing or Lu-Ann Kleibacker listed under FOR FURTHER INFORMATION CONTACT.

B. How can I access electronic copies of this document and other related information?

In addition to using regulations.gov, you may access this Federal Register document electronically through the EPA Internet 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. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted 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 20460. 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 early October 2010. 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 EPA 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 either Jim Downing or Lu-Ann Kleibacker 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:

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data that you used to support your views.
4. Provide specific examples to illustrate your concerns and suggest alternatives.
5. 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-2010-0797 in the subject line on the first page of your request.

1. Oral comments. Requests to present oral comments will be accepted up to Thursday, October 21, 2010. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to Jim Downing or Lu-Ann Kleibacker, FOR FURTHER INFORMATION CONTACT, no later than noon, Eastern Time, Thursday, October 21, 2010, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Official (DFO) to review the meeting agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation and the organization (if any) the individual will represent. Oral comments before the HSRB are generally limited to five minutes per individual or organization. Please note that this includes 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 the time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, further public comments may be possible.

2. Written comments. Submit your written comments prior to the meeting. 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 this 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, October 21, 2010. You should submit your comments using the instructions in section I., under subsection C., "What Should I Consider as I Prepare My Comments for EPA?" In addition, the Agency also requests that persons submitting comments directly to the docket also provide a copy of their comments to Jim Downing or Lu-Ann Kleibacher listed under FOR FURTHER INFORMATION CONTACT. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

1. Topics for discussion. At its meeting on October 27-28, 2010 EPA's Human Studies Review Board will consider scientific and ethical issues surrounding these topics:

a. A proposal for new research to be conducted by Carroll-Loye Biological Research to evaluate in the field the repellent efficacy against mosquitoes of a registered product containing 16% para-methane-3,8-diol and 2% lemongrass oil. EPA requests the advice of the HSRB concerning whether, if the protocol is revised as suggested in EPA's review and if it is performed as described, this research is likely to generate scientifically reliable data, useful for assessing the efficacy of the tested material in repelling mosquitoes, and to meet the applicable requirements of 40 CFR part 26, subparts K and L.

b. A new scenario design and associated protocol from the Agricultural Handler Exposure Task Force (AHETF) describing proposed research to measure dermal and inhalation exposure to applicators who use backpack sprayers or hand gun sprayers to apply pesticides in utility rights-of-way. EPA requests the advice of the HSRB concerning whether, if it is revised as suggested in EPA's review and if it is performed as described, this research is likely to generate scientifically reliable data, useful for assessing the exposure of those who apply pesticides in utility rights-of-way with backpack sprayers or hand gun sprayers, and to meet the applicable requirements of 40 CFR part 26, subparts K and L.

c. A revised scenario design and associated protocol from the Agricultural Handler Exposure Task Force (AHETF) describing proposed research to monitor exposure of workers who mix and load pesticides formulated as wettable powders in water-soluble packaging. This scenario was previously reviewed favorably by the HSRB in June 2009, but has since been revised to use different surrogate chemicals. These changes forced other revisions in turn; the proposed changes, taken together, are significant enough to warrant a new review by the HSRB. EPA requests the advice of the HSRB concerning whether, if it is revised as suggested in EPA's review and if it is performed as described, this research is likely to generate scientifically reliable data, useful for assessing the exposure of those who mix and load pesticides formulated as wettable powders in water-soluble packaging, and to meet the applicable requirements of 40 CFR part 26, subparts K and L.

d. The report of a completed scenario monograph and study report from the Antimicrobial Exposure Assessment Task Force II (AEATF-II) in which the dermal and inhalation exposure of professional janitorial workers was monitored as they applied liquid antimicrobial products to indoor floors using a bucket and mop. EPA seeks the advice of the HSRB on the scientific soundness of this completed research and on its appropriateness for use in estimating the exposure of professional janitorial workers who apply antimicrobial floor-cleaning products with mops, and on whether available information supports a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26.

2. 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: September 29, 2010.
Paul T. Anastas,
EPA Science Advisor.
[FR Doc. 2010-25126 Filed 10-5-10; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
OCTOBER 27-28, 2010 PUBLIC MEETING

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

October 27, 2010

10:30 AM* **Convene Public Meeting and Review Administrative Procedures** – Jim Downing (Designated Federal Officer, Human Studies Review Board [HSRB], Office of the Science Advisor [OSA], EPA)

10:35 AM **Introduction and Identification of Board Members** – Sean Philpott, Ph.D. (HSRB Chair)

10:40 AM **Welcome** – Paul Anastas, Ph.D., (Science Advisor, OSA, EPA)

10:45 AM **EPA Follow-up on Previous HSRB Recommendations** – Mr. William Jordan (OPP, EPA)

Session 1: **Carroll-Loye Biological Research, Inc. Protocol *No Mas 003*, a Field Efficacy Test of PMD and Lemongrass Oil-based Repellent "No Mas" Against Mosquitoes**

10:55 AM **EPA Science and Ethics Reviews** – Clara Fuentes, Ph.D. (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)

11:25 AM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor

11:55 AM **Public Comments**

12:10 PM **Board Discussion**

Charge to the Board:

If the proposed field repellency study protocol No Mas 003 is revised as suggested in EPA's review and if the research is performed as described:

- Is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested material in repelling mosquitoes?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

12:50 PM **Lunch**

Session 2: **A new scenario design and associated protocol from the Agricultural Handler Exposure Task Force (AHETF) to measure dermal and inhalation exposure to applicators who use backpack sprayers or hand gun sprayers to apply pesticides in utility rights-of-way**

2:00 PM **EPA Science and Ethics Reviews** – Mr. Jeff Evans (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)

2:45 PM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor

3:15 PM **Public Comments**

3:30 PM **Board Discussion**

Charge to the Board:

If the proposed Agricultural Handler Exposure Task Force (AHETF) Right-of-Way application scenario and field study protocol AHE400 is revised as suggested in EPA's review and if it is performed as described:

- Is the research likely to generate scientifically reliable data, useful for assessing the exposure of those who apply pesticides in utility rights-of-way with backpack or hand gun sprayers?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

5:00 PM **Adjournment**

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
OCTOBER 27-28, 2010 PUBLIC MEETING

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

October 28, 2010

8:30 AM	**Open Meeting** – Jim Downing (Designated Federal Officer, HSRB, OSA, EPA)
8:35 AM	**Introductions of Members** – Sean Philpott, Ph.D. (HSRB Chair)
8:40 AM	**Follow-up from Previous Day** – Mr. William Jordan (OPP, EPA)
Session 3:	**Completed scenario monograph and study report from the Antimicrobial Exposure Assessment Task Force II (AEATF–II): Dermal and Inhalation Exposure of Professional Janitorial Workers Applying Liquid Antimicrobial Products to Indoor Floors Using Bucket and Mop**
8:45 AM	**EPA Science and Ethics Reviews** – Mr. Tim Leighton (OPP, EPA) and Mr. John Carley (OPP, EPA)
9:45 AM	**Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor
10:15 AM	**Public Comments**
10:30 AM	**Break**
10:45 AM	**Board Discussion**

Charge to the Board:

In the completed scenario monograph and study report AEA03 from the Antimicrobial Exposure Assessment Task Force II (AEATF–II):

- Was the research reported in the Antimicrobial Exposure Assessment Task Force II (AEATF–II) completed study report AEA03 and associated supplemental reports faithful to the design and objectives of the protocol and governing documents of AEATF-II?
- Has the Agency adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply antimicrobial floor-cleaning products with mop and bucket?
- Does available information support a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

12:30 PM **Lunch**

Session 4: **Revised scenario design and associated protocol from the Agricultural Handler Exposure Task Force (AHETF) describing proposed research to monitor exposure of workers who mix and load pesticides formulated as wettable powders in water-soluble packaging**

1:30 PM **EPA Science and Ethics Reviews** – Mr. Jeff Evans (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
2:00 PM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor
2:15 PM **Public Comments**
2:30 PM **Board Discussion**

Charge to the Board:

If the revised AHETF scenario and field study proposal AHE-120 is revised as suggested in EPA's review, and if it is performed as described:

- Is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who mix and load pesticides in water-soluble packaging?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

3:45 PM **Preview of Upcoming Meetings** – Ms. Kelly Sherman (OPP, EPA)
4:00 PM **Adjournment**

HSRB WEB SITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA-HQ-ORD-2010-0797

Agenda times are approximate and subject to change. For further information, please contact the Designated Federal Officer for this meeting, Jim Downing, via telephone: (202) 564-2468 or e-mail: downing.jim@epa.gov.