Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
October 19 – 20, 2011 Public Meeting
Docket Number: EPA-HQ-ORD-2011-0693
HSRB Web Site: http://www.epa.gov/osa/hsrb

Committee Members: (See EPA HSRB Members List—Attachment A)

Date and Time:	Wednesday, October 19, 2011, 10:30 AM – 5:00 PM Thursday, October 20, 2011, 9:00 AM – 4:30 PM (See *Federal Register* Notice—Attachment B)	
Location:	EPA, One Potomac Yard (South Building), 2777 S. Crystal Drive, Arlington, VA 22202	
Purpose:	The EPA HSRB 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
	Acting Vice Chair:	Rebecca T. Parkin, Ph.D., M.P.H
	Board Members:	Janice Chambers, Ph.D., D.A.B.T. 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 (via telephone) José E. Manautou, Ph.D. Jerry A. Menikoff, M.D. 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.	

Commencement of Public Meeting and Review of Administrative Procedures

Mr. Jim Downing (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor [OSA], EPA [or Agency]) convened the meeting at 10:30 a.m. and welcomed Board members, EPA colleagues and members of the public. He thanked the Board members for their work in preparing for the meeting deliberations.

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 work with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied regarding conflicts of interest; HSRB 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 OSA and the Office of the General Counsel, Mr. Downing has reviewed the reports to ensure that all ethics requirements are met.

Mr. Downing informed members that there were four challenging topics on the agenda for the meeting, and that agenda times are approximate. Copies of the meeting materials and public comments will be available at http://www.regulations.gov under docket number EPA-HQ-ORD-2011-0693. Following the presentations, time has been scheduled for questions of clarification to EPA staff and the principal investigators and sponsors of the studies discussed. This time is to be used for points of clarification rather than Board discussion. A public comment period will be maintained, and remarks must be limited to 5 minutes. All speakers, including Board members and members of the public, should turn on their microphone and identify themselves before speaking as the meeting is being recorded and broadcast live on the Internet. If, during Board discussions, members require additional 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 available on the HSRB website. Meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and certified by the meeting Chair within 90 days. In addition, the HSRB also will prepare a final report as a response to questions posed by the Agency that will include the Board's review and analysis of materials presented. EPA will announce the Board's review and subsequent approval of the report in the *Federal Register*. Mr. Downing turned the meeting over to the HSRB Chair, Dr. Sean Philpott.

Introduction and Identification of Board Members

Dr. Philpott mentioned that this was the first HSRB meeting to be webcast. He noted that the Board worked on a consensus model, and that consensus opinions of the Board would be included in the final report. He acknowledged and thanked Dr. Janice Chambers for her efforts as Vice Chair during the past two years, and for stepping aside to let Dr. Rebecca Parkin serve in her stead as Drs. Chambers and Philpott are entering their last year of service on the Board. They wanted to provide for an orderly transition of responsibilities to the new Vice Chair prior to transition to a new Chair. He then asked Board members to introduce themselves, and members completed their introductions, and invited Dr. Mary Greene (Deputy Director, OSA, EPA) to offer welcoming remarks.

Welcoming Remarks

Dr. Greene welcomed all in attendance on behalf of EPA's Science Advisor Dr. Paul Anastas. The OSA provides the administrative oversight for the Board. The OSA is associated with the Office of Research and Development, but addresses the science and science policy issues within the Agency. She thanked the Board for all of their work before, during and after the meetings, and welcomed them, along with members of the public. She thanked her EPA colleagues and noted that EPA was looking forward to some additional changes in the Board as

time progresses. She then reviewed the agenda and the four topics to be discussed by the Board. Dr. Greene remarked that EPA looks forward to the thoughtful consideration that the Board will give to these topics; the Board's recommendations are used by the Agency in furthering its mission to protect human health and the environment.

Opening Remarks

Dr. Steven Bradbury (Director, Office of Pesticide Programs [OPP], EPA) also expressed his thanks to the Board members and welcomed them to the meeting. He noted that the Board's role in providing advice to the Agency is instrumental in ensuring that EPA is protecting human health and the environment by using the most ethical evaluations and highest quality research possible. The HSRB's work helps to protect the public and ensure that research involving human subjects is reviewed by the EPA in an open and transparent manner. He also acknowledged Dr. Chambers' service as Vice Chair, and noted that EPA appreciated her service. He thanked Board members, Mr. Downing, and his EPA colleagues who were involved in preparations for the meeting. Finally, he thanked the public for their participation in the Board's efforts, as that was an important part in ensuring high-quality science and ethical review.

OPP Follow-up on Previous HSRB Recommendations

Mr. William Jordan (OPP, EPA) stated that he would discuss four topics that the Board had advised on at previous meetings. He noted that EPA had determined that the Agricultural Handler Exposure Task Force (AHETF) research on closed cab and open cab airblast scenarios discussed at the January and April 2011 meetings represented the "best available data" for these exposure scenarios. Therefore, no quantitative changes were made to the data following HSRB review but that additional language was added to the final EPA reviews in response to HSRB recommendations, including limitations on use of the data. The data will be used in future risk assessments to assess risks to workers applying pesticides using open cab and closed cab airblast equipment.

In its review of the Antimicrobial Exposure Assessment Task Force (AEATF)-conducted research, the HSRB had recommended that additional statistical analyses be conducted on the non-detects on some of the samples. It was assumed originally that any sample that was recorded as a non-detect actually contained one-half the level of quantification (LOQ), but two other approaches also were taken: evaluating exposure based only on the residues found on hands, and maximum likelihood imputation methodology for non-detects to estimate values that could be used to calculate exposure. The results differed between the ready-to-use (RTU) wipe results and the spray and wipes. The RTU results for handling the non-detects agreed very closely with all of the clothing scenarios, and hands represented the majority of exposures. With the spray and wipe, the substation of one-half LOQ or substitution of maximum likelihood imputation estimates agreed closely with regard to overall exposure estimates for all clothing scenarios. The hands-only method agreed for the "long" clothing scenario but represented two-thirds of exposure for the "short" clothing scenario. EPA's conclusions were that whole body dermal exposure should be used as the basis for risk assessments. The hand values drive exposure, and the conclusion was that the varying imputation methods for non-detects in the spray and wipe

scenario had minimal impact. In reviewing results of future research, EPA will examine both ways of analyzing the non-detects. The Agency has begun to use the data in its risks assessments.

The *Gulson et al.* study that the Board reviewed in April 2011 presented information inadequate to conclude that the study was conducted in substantial compliance with procedures at least as protective as those in subparts A-L of 40 Code of Federal Regulations (CFR) part 26. EPA has not pursued collecting the additional ethics information, but may do so in the future should there be a regulatory need for use of these data. EPA is currently planning to use the *Moiemen et al. (2011)* study if the Board reviews it favorably at this meeting.

The proposed revisions to the Human Studies Rule were published in April 2011, and only 10 public comments were received. EPA is planning to finalize the amendments as proposed. EPA review has been completed; the next step is interagency review, and the rule has been submitted to the Office of Management and Budget for this reason. EPA has a settlement agreement that commits the Agency to publish the final rule in December 2011.

Session 1: A Completed Carroll-Loye Biological Research, Inc. (CLBR) study (No Mas 003) to Evaluate the Field Repellent Efficacy Against Mosquitoes of a Product Containing 16% Para-Menthane-3,8-Diol (PMD) and 2% Lemongrass Oil

Background

Ms. Kelly Sherman (OPP, EPA) noted that the Board would be discussing a completed study of No Mas, a lotion formulation containing 16 percent PMD and 2 percent lemongrass oil. The protocol was favorably reviewed by the Board in October 2010. The study was conducted in California at two different field sites in July 2011, and the final report was submitted to EPA in August. The sponsors are developing No Mas 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 mosquitoes. The purpose of the present study was to test the product for efficacy against three mosquito genera – *Culex*, *Anopheles* and *Aedes*.

EPA Science Assessment

Dr. Clara Fuentes (OPP, EPA) stated that the Carroll-Loye Efficacy Test of No Mas was conducted in a manner substantially consistent with the study protocol reviewed by EPA and the HSRB. There was one protocol deviation and several amendments.

In terms of consistency with the protocol, amendments were approved prior to study initiation, justification was provided for choice of sample size, and rationale was provided for choice of statistical methods to analyze non-normally distributed data. The deviation from the protocol was that data forms were reformatted to minimize data entry error and enhance accuracy, and the change is expected to improve data quality.

The study's objective were: 1) to characterize the performance of No Mas against wild populations of mosquito species among the genera *Culex, Anopheles* and *Aedes*; 2) estimate the

mean value of complete protection time (CPT) within a 95 percent confidence interval (CI), and; 3) provide efficacy data required to support registration of the No Mas repellent formulation. The standard consumer dose for arms and legs was determined from the grand mean of 10 subject means (five males and five females). The efficacy testing then tested 10 treated subjects (five males and five females) and two negative control untreated subjects per site at two different mosquito habitat sites. The standard consumer dose used for testing was 1.20 microliter per square centimeter ($\mu L/cm^2$) on the arms and 1.04 $\mu L/cm^2$ on the legs. The margin of exposure (MOE) was greater than 583 for arms and was greater than 287 for legs. Those values were calculated on the dose rate of the products and are relative to the no observed effect level (NOEL) of dermal toxicity of the formulation, which is greater than 5,000 milligrams per kilogram (mg/kg) of adult body weight.

The efficacy endpoint was the CPT measured as the interval between first exposure and time of confirmed landing with intent to bite (LIBe). The landing pressure was monitored by the two untreated subjects at each site throughout the test. The threshold for acceptable landing pressure is no less than one mosquito landing per minute. The exposure delays are defined as the interval between application of repellant and time of first exposure. The average exposure delays were 3.2 hours at site 1 and 6 minutes at site 2. Subjects at site 1 applied the formulation before traveling to the site, but subjects at site 2 applied after arrival at the site. The exposure to mosquitoes lasted 1 minute every 15 minutes.

Results show differences between the two testing sites in confirmed landings. Site 1 subjects all had confirmed landings, but only four of the 10 subjects at site 2 did. Therefore, the data collected from site 2 are right censored. The six subjects with no confirmed landing were assigned CPT at the end of the test, ranging from 9.02 to 9.25 hours. At site 1, testing took place in the morning, and the formula was applied to subjects' forearms. At site 2, testing took place in the evening, and the repellant was applied to the lower legs. More mosquito species were collected at site 2 than site 1. At both sites, *Aedes melanimon* was the most abundant species followed by *Aedes vexans* at site 1. At site 2, 3 additional species -- *Aedes nigromaculis*, *Culex tarsalis* and *Anopheles freeborni* -- were collected.

The average testing dose was the grand mean (± standard deviation) across 10 subjects' means. CPT was estimated from the sample size of 10 subjects per site, and statistical methods used to calculate the CPT within 95 percent CI were the Weibull Mean, Kaplan-Meier median and Normal Mean. The Weibull Mean result for CPT was 9.8 for site 1 and 10.1 for site 2; the Normal Mean is irrelevant because the data do not fit the normal distribution. The researcher explained that the Weibull Mean was a better fit for the distribution of the CPT data points. The Kaplan-Meier analysis was not estimated at site 2, and the researchers do not explain why the value was not reported.

EPA posed the following statistical question to the HSRB: Which statistical method is appropriate to calculate the CPT for the No Mas repellent: parametric (with Weibull distribution) or non-parametric (Kaplan-Meier)?

The study can be considered reliable because test material was applied by laboratory technicians; alternate subjects were enrolled to ensure adequate sample size; all landings were verified and recorded by a research technician; and pre-training of subjects was conducted on

how to handle mosquitoes. The uncertainty of the mean values is associated with the sample size. The reported mean values for CPT were calculated across all 10 subjects per site assuming a non-normal Weibull distribution within a 95 percent CI. The following elements were adequately addressed in the study: prerequisite acute toxicity research to characterize toxicological profile of the formulation and calculate MOE; dosimetry; experimental design; and verification of subject attractiveness to mosquitoes.

In conclusion, EPA found the study to be scientifically acceptable. The data provide scientifically reliable information that could not have been obtained except by research with human subjects. The study has a defined scientific objective, and the study design generated adequate data to meet that objective.

Board Questions of Clarification—Science

Dr. Sidney Green noted that the final report stated that for acute oral toxicity the "up and down approach" was used. For acute dermal, the limit test was used. For acute ocular toxicity, there are no well-validated studies to substitute for the Draize rabbit eye test. In terms of the dermal sensitization study, he believed that the Interagency Coordinating Committee for the Validation of Alternative Methods recommended that the local lymph node assay could be used as a replacement for the Beuhler method; the latter was used in this study. He asked why the lymph node assay was not used. Mr. Jordan replied that EPA is committed to working with regulatory authorities and specific applicants to reduce the number of animals used in testing. The Agency has actively participated in the work being conducted to develop alternative methods for testing that use non-animal models, but will accept data from both types of tests. He was unaware when the toxicity testing for the compounds in No Mas had occurred. Dr. Philpott suggested that Dr. Scott Carroll of CLBR, the director of this study, could better answer the questions.

Dr. Linda Young noticed a limited number of species in the study, and asked if there had been any comparison with mosquitoes in developing areas where No Mas will be marketed. Dr. Fuentes responded that the most common species were encountered in the test; the *Anopheles* genera is very aggressive, and *Culex* is less aggressive but is a disease vector. The test showed a good representation of mosquitoes.

Dr. Dallas Johnson asked if the control subjects were exposed for a full minute or until a confirmed landing. Dr. Fuentes responded that the threshold was one mosquito per minute. Dr. Philpott suggested that the Board again defer to Dr. Carroll on that point.

EPA Ethics Assessment

Ms. Sherman stated that the recruitment process stated in the protocol was followed such that 32 subjects were selected randomly from a pool of 92 subjects, 10 subjects participated in the dosimetry phase, 22 subjects participated in the field testing at one or both sites and six subjects were enrolled as alternates. Some of the subjects participated in both dosimetry and field testing. The consent process also followed the protocol. Subjects were provided with the Material Safety Data Sheet (MSDS), study synopsis, consent form, California Experimental Bill

of Rights, and other study-related information during the consent process. They later signed the consent form and the California Experimental Bill of Rights prior to enrollment, and there were no reported or unreported deviations related to the consent process. Five males and five females were used during the dosimetry testing and at each site during the study. One male and one female served as untreated controls at each site. Each subject was over the age of 18, and the female subjects were tested for pregnancy prior to each day's participation. The research was conducted without incident. No subjects withdrew from the research, and no adverse events or incidents of concern were reported.

The protocol for the No Mas study was approved by the Independent Investigational Review Board (IIRB), Inc. and submitted to EPA in July 2010, and EPA's science and ethics review found the protocol acceptable with minor changes. The protocol was reviewed by the HSRB on October 27, 2010, and accepted with minor revisions. Amendment 1 dated November 15, 2010, addressed most EPA and HSRB comments, and was approved by IIRB on November 16, 2010. The amended protocol was approved by the California Department of Pesticide Regulation (CDPR) on March 21, 2011. Amendment 1 provided additional justification for the chosen sample size and discussion of data analysis approach; adjusted the wording in the protocol and consent form per recommendations from EPA, the HSRB, and CDPR; and excluded as permissible subjects employees of the sponsor or researchers. Amendment 1 addressed most of EPA's and the HSRB's concerns except that the acronym PMD was not spelled out when first used, and "Child/Minor" was not added to the list of exclusion criteria, although the inclusion criteria specify that subjects must be between 18 and 55 years old. Only one deviation from the protocol occurred, the reformatting of the dosimetry data form, and this did not affect the rights or safety of the subjects or compromise informed consent. The primary study report is complete, and all requirements of 40 CFR §26.1303 for documentation of ethical conduct are satisfied.

The substantive acceptance standards used by EPA when determining whether to accept and rely on a study with exposure of human subjects are: 40 CFR §26.1703, which prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children; 40 CFR §26.1705, which prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 CFR part 26; and Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) §12(a)(2)(P), which makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent. The No Mas study met all these requirements, and Ms. Sherman concluded that if No Mas is determined to be scientifically acceptable, she found no barrier in law or regulation to EPA's reliance on it in actions under FIFRA.

Board Questions of Clarification—Ethics

There were no questions of clarification on the ethics of the study.

Board Questions of Clarification for the Principal Investigator/Study Sponsor

Dr. Philpott invited study researchers Dr. Carroll and Mr. Shawn King of CLBR to the table to address Board questions. Dr. Carroll and Mr. King introduced themselves.

Dr. Philpott asked when the acute toxicity studies for the No Mas product were conducted, particularly because of the use of the Beuhler method rather than the local lymph node assay as recommended by the Interagency Committee. Dr. Carroll responded that the studies were conducted in February 2010 by another scientist consulting for the sponsor. Dr. Green added that the determination that the local lymph node assay could be used as an alternative for the Beuhler method predated February 2010. He asked how alternative tests are considered in the toxicology tests that are conducted by the Agency, and does the Agency give guidance to the testing entity, especially if tests are animal intensive. Dr. Carroll replied that a toxicologist knowledgeable in insect repellant testing was engaged for this work, and this individual was aware of federal policy regarding this issue. Industry often is slow to shift from tests that have worked unless a strong regulatory platform exists for such a change. The fact that these tests are conducted mainly in California makes CLBR more likely to attempt some of the newer tests earlier. The sponsors are generally interested in minimizing deleterious impacts of the studies.

Dr. Philpott inquired whether the limited number of species in the study is generalizable to the wide number of species present in the areas where No Mas will be used. Dr. Carroll replied that this repellent's active ingredient (AI) has been tested against a great number of mosquitoes internationally with very large sample sizes. In the past few years, a tremendous amount of new data had been generated. The principal target for No Mas is malaria, and studies show that formulas with this AI typically outperform N,N-Diethyl-meta-toluamide (DEET) against anopheline mosquitoes, the malaria vectors. For this study, there were low numbers of *Culex* and *Anopheles*, and that was because of the testing schedule and the late, cool spring. Dr. Philpott asked if Dr. Carroll was comfortable stating that the data from the study were generalizable to most of the species present in the United States. Dr. Carroll confirmed that this was the case.

Dr. Philpott asked Dr. Carroll to explain how the untreated control subjects were used to measure biting pressure. Dr. Carroll responded that the protocol gives researchers the option of covering a control subject's arm or lower legs, and in this case, after the first landing, that is what was done. It would be useful from the data quality perspective to have the full 1-minute exposure, but the emphasis on the safety of the untreated controls took precedence. Dr. Johnson asked about other ways that do not require exposure of subjects to determine which species might be present. Dr. Carroll stated that this had not been covered in the protocol, but had been performed haphazardly. A more formal method has not been developed. Trapping would be useful, but trapping data would need to be compared to human exposure data. Trapping data could be collected in a separate study.

Dr. Philpott asked Dr. Carroll and Mr. King to clarify the protocol deviation that was recorded. Mr. King responded that a two-page form had been used traditionally, and CLBR moved to a new one-page form to reduce transcription errors from the two-page form to a single sheet.

Dr. George Fernandez inquired about the use of the product in developing countries. He stated that in Sri Lanka, mosquitoes are very active at night, and asked why the report stated that they were not active at night. Dr. Carroll noted that No Mas was intended for use in developed countries as well, and is cosmetically superior, and appears to have a long duration of efficacy.

Mosquitoes can be active at any time; this varies by species. Dr. Fernandez asked if data were available from developing countries about effective formulations with the same amount of CPT. Dr. Carroll commented that there were studies showing CPTs of similar duration.

Dr. José Manautou asked what was meant by "cosmetically superior." Dr. Carroll replied that based on the use of DEET-based repellants, No Mas had a more pleasant feel and odor, and has excellent vanishing properties.

Public Comments

Dr. Carroll pointed out that this was the first repellent study coming from a public health initiative. He is proud to be involved in such a study, and pleased that the Board was involved. Many countries around the world mirror what happens in the United States, so the approval of this product has very direct relevance. In part because of less risk averse sponsorship for this study, the statistical approaches taken were superior to what had been made available in the past. He hoped that this paved the way for more analyses that might give better characterizations of repellent performance based on inherently small data sets.

Dr. Philpott asked if anyone else present would like to comment on the No Mas study. No further public comments were made.

Charge Questions

Ms. Sherman read the charge questions into the record:

- Is the CLBR completed study No Mas 003 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?
- Does available information support a determination that the study No Mas 003 was conducted in substantial compliance with 40 CFR part 26, subparts K and L?

Dr. Philpott made two points before the Board entered into discussion. He stated that Dr. Michael Lebowitz was present via telephone, and pointed out an error in the final Board report from October 2010 that refers to the mosquito genera present as species.

Board Science Review

Dr. Green stated that the protocol was reviewed by the HSRB in October 2010, and the HRSB indicated that if the study were conducted in compliance with the protocol, that it would yield scientifically valid information. The study has been conducted in compliance with the protocol, so the answer to the charge question is yes, the study is sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent.

Dr. Chambers also answered in the affirmative. This study is similar to those previously conducted by CLBR, MOEs are high, and the only deviation will improve the accuracy of the data and not impact the science adversely.

Dr. Philpott asked Dr. Fernandez to address Dr. Fuentes' question on whether parametric or nonparametric methods were best to calculate the CPT for the study. Dr. Fernandez stated that with right censored data, the approach based on the normal distribution does not work. In the parametric survival analysis for CPT, the researchers are using the Weibull distribution for right censoring and this method is basically used in the literature for predicting the CPT time. The choice of the Weibull distribution has to be validated. The small sample size is always a concern with this type of analysis. The Weibull distribution can be validated using the SAS® software. If the nonparametric approach is used with no distributional assumption, the separate sites can be tested to see if they are significantly different. If statistically different, the sites can be combined to produce a more reliable estimate on the survival time. In this case, the CPT on the sites was very similar. In summary, the parametric method using the Weibull distribution can be used if validated. If not, the nonparametric method can be used as long as the two sites are not statistically different. Dr. Fernandez commented that Dr. Carroll may have been using JMP® software to calculate the statistics.

Dr. Young stated that for these data, the Weibull analysis looks good; however, it is important to use the median instead of the mean with the Weibull because in skewed distributions, the mean always exceeds the median. The median will give CPT for 50 percent of the population.

Dr. Lebowitz agreed with the statistical comments. He mentioned the lower CI with the Kaplan-Meier analysis; even though the medians might be similar, the CI is much lower than the Weibull. Dr. Young responded that in this case, she is comfortable with the Weibull because the fit of the distribution to the data is good. If it had not been as good a fit, she would want to use the Kaplan-Meier because it is not making a distributional assumption. Dr. Johnson commented that the tables that were shown used the Weibull mean instead of the median. Mr. Bayazid Sarkar (OPP, EPA) stated that the report EPA received did not include the median of the CPT using the Weibull. Dr. Young commented that the median for the Weibull was needed. Dr. Philpott stated that the answer to the question about the parametric or nonparametric approach is that in this case, the Weibull is acceptable, but the median should be used rather than the mean.

Dr. Philpott stated that the Board had reached consensus that the study was conducted as designed and yielded scientifically valid information that can be used to calculate the CPT for this product against the three genera of mosquitoes tested. The recommendation is that the Weibull would be acceptable in this case but that the Weibull median and 95 percent CI should be calculated and taken into account as the Agency makes the decision regarding CPT.

Board Ethics Review

Dr. Philpott asked Dr. Jerry Menikoff, as lead ethics discussant for this study, to address the charge question that asked whether the No Mas 003 study was conducted in substantial compliance with 40 CFR part 26, subparts K and L. Dr. Menikoff stated that the study was conducted in substantial compliance with those provisions. He thanked Ms. Sherman and other EPA staff for their analysis, and noted that this was a clean study. Dr. Carroll has conducted many of these studies and has taken account of the recommendations of this Board over time. Dr. Philpott agreed with Dr.

Menikoff, and also thanked Ms. Sherman for her review of the study and CLBR for responding to Board concerns during the past 5 or 6 years. The two previous Board recommendations that were not addressed did not substantially compromise the consent process or place participants at risk. Reporting requirements were completed, and IIRB has been responsive to the reporting requirements as well. Minors and pregnant women were excluded, the product has a low risk of adverse side effects, there were clear stopping rules, and a study design was used that minimized the likelihood of mosquito bites. The mosquitoes were in an area screened for vectors of pathogens and showing none for 2 weeks. Dr. Philpott agreed that the reported deviation from the protocol did not affect the quality of the research negatively or affect the participants.

Dr. William Popendorf expressed concern that not providing an indication of effectiveness of the formula within the CPT has both ethical and scientific implications. He recommended that the Agency examine whether it would be useful to inform consumers of the effectiveness of the repellent within the CPT. He noted that he was not commenting on the study currently under review. Because this recommendation was beyond the scope of the charge questions before the Board, Dr. Philpott suggested that Dr. Popendorf draft a separate memo to the Agency on the subject.

Session 2: A New Scenario Design and Associated Protocol from the Antimicrobial Exposure Assessment Task Force II (AEATF-II), Describing Proposed Research to Monitor the Dermal and Inhalation Exposure of Workers While Pouring Liquid Antimicrobial Pesticide Products from Both Conventional and Reduced-Splash Containers

Background and EPA Science Assessment

Mr. Tim Leighton (OPP, EPA) noted that the Board had reviewed completed studies for mopping and wiping with antimicrobial products. The AEATF has submitted a new liquid pour study design and protocol. He introduced Dr. Jonathan Cohen who served as statistician for the review and who was available via telephone.

In terms of the regulatory context, this proposal under review is for research involving scripted exposures to the disinfectants Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) and Didecyl Dimethyl Ammonium Chloride (DDAC). Because the exposures are intentional, review of the protocol by EPA and the HSRB is required.

The main reason to conduct this study is to address the limitations in the data for the pesticide handler exposure database and also the Chemical Manufacturers Association's data. The study design has been improved through consultation with the Board and the FIFRA Scientific Advisory Panel (SAP). The new studies use whole body dosimeters, and data on complete body parts will be generated. The new studies also include some random elements. The generic principle for getting these new data is that exposure depended more on the use pattern and individuals' behaviors rather than on the AI. This is true when there are stable chemistries, low vapor pressure, and corrections for the field recoveries to account for losses in the field.

EPA had categorized the AEATF's studies into 12 use categories, including agricultural premises, residential public access, drinking water systems, and material preservatives. With help from the Joint Regulatory Committee, which is based on Health Canada's and CDPR's input, the AEATF analyzed the different application techniques. These factors were placed into the matrix shown on slide 6 of EPA's presentation.

This study is on manual pouring of the liquid product, with monitoring of the dermal and inhalation exposures. It will exclude any application of pesticide after it has been poured. The liquid will be poured from both conventional and reduced-splash containers. The AEATF will use DDAC for all the conventional pours and ADBAC for all the reduced-splash. Eighteen people will conduct the scenarios, and each person will conduct both tests. This way, the residues can be distinguished and will relate to the type of test that was done, and the number of people exposed in the study will be minimized. It will reduce resources and it will reduce the number of people actually exposed. Within each scenario, there will be three groupings based on the size of the containers. Within each one of the groups, there are six participants or monitoring events (MEs). Surrogate chemicals have stable chemistry, low vapor pressure, and sensitive analytical methods for good recoveries.

Pesticide labels are not based on the size of the containers; the goal is to have exposure at the high end, so large containers for pouring and large receiving containers also are being used. The study also will be able to show if reduced-splash containers significantly affect exposure. The amount of active ingredient handled (AaiH) also could affect dermal and inhalation exposure. Both of the surrogate chemicals will be poured at 0.2 percent AI because that is not high enough to require the use of gloves, but high enough to avoid non-detects. Both ADBAC and DDAC are dermal irritants at the low concentrations, but EPA believes that the predicted dermal and inhalation risks for these studies will not be of concern.

The study will be conducted in two identical rooms in one laboratory, and it was not thought that the building or geographic location would matter because of the nature of the study. The rooms are 12 by 24 feet, and the ceiling will be measured to get a room volume. Professional janitors or maintenance workers will populate the study because they typically use more product than consumers when cleaning. The same study subjects will be used for both conventional and reduced-splash container scenarios. The source containers will range from ounces to a typical half-gallon to gallon containers up to 5-gallon buckets. The receiving containers will range from a spray bottle, similar to the 32-ounce trigger spray pump bottle for the spray and wipe study to 10-gallon basins or larger. Two pouring heights were selected: floor level and chest level. From 40 ounces up to 30 gallons will be poured by each study subject, selected randomly and recorded, so the volume for each ME will be known. In the conventional scenario, Group 1 and 2 subjects will pour 10 containers randomly selected from a fixed size of 24, 32 and 64-ounces. The third group will pour four 5-gallon buckets. The small group will be pouring them into 32-ounce bottles or 2-gallon buckets. The medium group will be using 2- and 4-gallon buckets, plus the 10-gallon basin. The reduced-splash scenario will be similar, but subjects will pour 15 containers, rather than 10, and the large group will pour six 5-gallon buckets.

The MEs will be stratified by AaiH, with the constant concentration of 0.2 percent AI but varying volume; therefore, the total AI handled, concentration multiplied by volume, will be varied

with each ME. The subjects' behaviors will vary by individual. It is anticipated that the pouring will take from 10 to 60 minutes.

Many variables in this study will be randomly selected. Eighteen study participants and four alternates will be chosen, and they will be recruited through advertisements in local newspapers. The first 22 people who respond and sign the consent forms will be the subjects. It is not a true random selection of 300 million people in the country who can potentially pour, but this method injects some random element within the study design.

The source containers, the pouring height and the order of conventional and reduced-splash tests performed will be assigned to the MEs randomly, as well as the allocation of subjects into Groups 1, 2 and 3. All participants in Group 1 and one-half of the participants in Group 2 will be using a measuring cup. There is some controversy around this fact because using the measuring cup might get more residues on the hand itself, which would mean more AI to get normalized and a dilution of the unit exposure. This will be captured, however, by the spray bottle MEs which are only using the measuring cups and not pouring the rest in the container.

Researchers will take air temperatures and relative humidity in the two rooms within the laboratory. They also will examine the characteristics of the heating, ventilation and air conditioning (HVAC) system. Airflow will be documented, but there is no target airflow for this study. The standard laboratory has air exchange rates of 10 to 12 air exchanges per hour. The researchers will monitor how long it takes a study subject to do the pouring, and this will be photographed and videotaped. To measure the dermal residues, whole body dosimeters inside and outside will be used, with hand washes and face and neck wipes at the end of the task. To measure inhalation, Occupational Safety and Health Administration (OSHA) Versatile Samples (OVS) tubes will be used. They will be worn by each study participant on the worker's lapel.

The collected samples will be analyzed. Researchers will conduct method validations plus standard recoveries of the field, storage, and breakthrough analysis. The study is compliant with EPA's Series 875 Group A. It also meets Health Canada's rules. The study will be conducted under Good Laboratory Practices.

EPA has reviewed many iterations of this protocol and is now satisfied, with the following recommendations. The order in which the source containers will be poured could be randomized, as could the order of measuring cup use for Group 2. The protocol proposed to first fill the spray bottles with product and then fill them the rest of the way with water, but the workers should be allowed to fill the bottles as they normally would. EPA requested more detail on how the airflow in these rooms will be measured. This recommendation is not in the review, but if there are spills, the workers should clean them as they normally would and be monitored while doing so. The researchers will allocate the receiving containers equally among MEs.

EPA's summary conclusion was that this protocol, performed as per the above recommendations, is likely to yield scientifically reliable information that will meet the Agency's regulatory needs.

Board Questions of Clarification—Science

Dr. Popendorf asked, regarding the use categories listed on slide six of EPA's presentation, if the ones listed without 'X's had no uses. Mr. Leighton responded that uses were unlikely, but could be possible. Dr. Popendorf stated that this proposal to monitor the two scenarios using the same person and set of clothing is unique, and asked if there was any precedent. Mr. Leighton responded that there may have been one study in the Pesticide Handler Exposure Database that used more than two or three chemicals. Dr. Popendorf asked if there should be any provision to respond to the effect of spills that saturate the dosimeter and change the behavior of that dosimeter for the second scenario. Mr. Leighton responded that if the researchers were using fortifications, perhaps the low, mid, and high fortifications could be switched to have a low fortification with add-back and then the high fortification with add-back on the same dosimeter.

Dr. Manautou explained that he had struggled with the study design and asked for elaboration. Mr. Leighton responded that it was confusing, but if the conventional scenario, Group 1, is taken as an example, the study subjects will be given 10 containers consisting of three different sizes, so each subject will have to fill some sizes multiple times. The containers each subject receives will be selected randomly; the subjects will not be able to choose them. Each subject will enter the study room and only be provided with the set amount of containers. If subjects are in Group 1 and 2 of the conventional scenario, they will be presented with ten containers. If in Group 1 and 2 of the reduced-splash container scenario, each subject will be presented with 15 containers. Group 3, however, will only be presented with four 5-gallon buckets in the conventional scenario and six 5-gallon buckets in the reduced-splash scenario. Dr. Manautou asked if the containers would have lids, and Mr. Leighton replied that they would, and the subjects would have to remove them. If the subjects are using a receiving container that is a spray bottle and are assigned a one-gallon source container to pour, they would pour four ounces into the measuring cup and then that measuring cup into the spray bottle. If using the 2-gallon receiving container, subjects would pour in two measuring cups and then pour in the rest of the original one-gallon source container.

Dr. Lebowitz asked about the AEATF's acceptance of such a high air exchange rate within the rooms. It is much higher than might be encountered in normal janitorial chores. He also stated that having the subjects use measuring cups and pour the rest of the surrogate into the container without the measuring cups is a non-standardized procedure. Mr. Leighton noted that the protocol is silent on the air flow in the rooms. Mathematically, it could be shown whether it might pose a problem, and perhaps EPA should examine this. Alternatively, the AEATF could be asked to reduce the air exchanges for the study. The second point about standardization is one that EPA has debated internally. It likely will affect dermal and inhalation exposure, but the other half of the MEs will be using the same containers without a measuring cup. Dr. Philpott suggested leaving this topic for Board discussion.

Mr. Leighton added that Dr. Lebowitz was correct that there are few replicates to be able to discriminate between use of measuring cups, no use of measuring cups, different size containers and so on. Once a pesticide label is on a product, however, it could be poured into something large, such as a swimming pool, or poured into a small spray bottle with a measuring cup. EPA wanted to see a large range of uses covered.

EPA Ethics Assessment

Ms. Sherman noted that this study is valuable to EPA because there are consumers and workers who pour these types of products on a daily basis, and reliable data to allow more accurate and realistic risk assessments and exposure assessments is important. The knowledge likely to be gained from the study would be usable in exposure assessments for both consumer products and professional products.

The subjects for this study will be recruited through newspaper advertisements targeting janitorial workers rather than recruiting through employers, which proved to be ineffective. The study will be conducted in Concord, Ohio, and advertisements will be placed in newspapers in that town or in the surrounding county, Lake County, Ohio.

Responders to calls from the advertisements will use an institutional review board (IRB)-approved script to talk to potential subjects. The script addresses different screening factors and other eligibility requirements. Callers meeting these requirements will be scheduled for an informed consent meeting with the study director. The exclusion and inclusion criteria in the protocol are appropriate. Pregnant or nursing women and those under 18 years of age are excluded. To be included participants must speak and read either Spanish or English. The subjects must be experienced janitorial workers and their job duties must include pouring antimicrobial products. Also excluded are people who might be sensitive to the test materials and those who have skin conditions or cuts on their hands. The AEATF also is excluding employees or spouses of an employee of any company represented by the AEATF, or anyone with a relationship to the American Chemistry Council or the research organization that is conducting the study. The recruitment materials are in both English and Spanish.

The consent process will involve a one-on-one meeting between the interested candidate and either the principal investigator (if the potential subject speaks English) or a bilingual researcher (if the subject prefers Spanish). In that meeting, the study design and eligibility criteria will be discussed. The researcher will review the consent document and provide the subject with the pesticide label and a copy of the MSDS. At that time, researchers will tell the subjects about their freedom to withdraw and will answer any questions the candidate might have. At that point, the researcher will ask the subject to sign the consent form.

There are four categories of risk in this study that the Agency believes are properly minimized. The first is the risk of irritant response, which is minimized by excluding subjects who might be sensitive to the products used or who have cuts on their hands. Second is the risk of heat-related illness due to wearing an extra layer of clothing and the air pump. This may be a lower risk than normal because the research will take place in a temperature-controlled setting and is not expected to last more than 2 hours maximum. This risk is further minimized by having a standard operating procedure (SOP) on managing heat stress and through stopping rules; additionally, subjects will be able to take a break between the two scenarios. The third category is risk of embarrassment while changing into the dosimeter, which is minimized by providing private changing areas and same sex technicians to assist. The fourth category is risk related to unwanted disclosure of the pregnancy test results, which is minimized through use of a discreet and confidential testing procedure. A subject may withdraw discreetly after taking the test.

There are no direct benefits to the subjects in this study. The sponsors will benefit from improved exposure and risk assessments of their products, and there is a likely benefit to society in terms of higher quality exposure risk assessments for antimicrobial products. Ms. Sherman believes the overall risks to be low and reasonable in light of the large societal benefit possible.

Ms. Sherman stated that the protocol provides procedures that afford appropriate respect for the study participants. Observations will be as unobtrusive as possible, and the privacy of the participants will be maintained. The payments that are proposed to subjects are reasonable, at $20 for attending an informed consent meeting and $100 for subjects who report to be monitored. Participants are free to withdraw at any time for any reason, and that will be made clear to them in both the consent meeting and in the consent documents. This protocol was reviewed by IIRB, which approved the protocol and the supporting documents in both English and the Spanish translations. 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 are 40 CFR part 26, subparts K and L.

Ms. Sherman has requested a few minor revisions to the protocol before the research proceeds. Newspapers in which the advertisements will be placed should be identified, and these papers should be chosen to target different groups. The AEATF has identified five different newspapers, two Spanish circulars and three English language newspapers as possibilities. Additionally, any reference to a second language should be changed to specify Spanish. She asked that a statement be added to the consent form, noting that within 24 hours after the study, subjects should call the study director if they feel they are experiencing any reaction related to the study. The AEATF agreed to that. Ms. Sherman further noted that the AEATF should develop some procedures and add them to an SOP on how such a call should be handled. Finally, for future protocols, she asked that the AEATF develop and implement a process for improving and verifying the accuracy of regional Spanish translations. The AEATF has determined a process for this, and it likely will be present in the next protocol that EPA receives for review. Finally, she noted that if the guidance coming from the HSRB's working group is produced before the study is conducted; it should be incorporated into how individual exposure results are provided to the subjects.

Ms. Sherman stated that if the revisions and corrections suggested are made, the scenario and protocol will meet the applicable requirements of 40 CFR part 26, subparts K and L.

Board Questions of Clarification—Ethics

Dr. Johnson asked an additional question on EPA's science review. The proposed statistical model for these data differs from the mixed effects modeling used in the earlier mop and wipe studies because the group variable represents a fixed effect rather than a random effect. He asked what was meant by a "fixed effect" in this case. Dr. Cohen responded that for the mop and wipe studies, there was a variable called the cluster, which essentially was the building where the mopping and wiping occurred. These buildings were selected randomly, so the cluster can be viewed as random variable. For the liquid pour study, however, the number of sizes of containers is fixed, so the container size is not randomly selected. He believes it is better to treat the container size as a fixed effect with three possible values. Dr. Johnson agreed that this was reasonable if no

statistical analyses were being conducted. Dr. Popendorf asked for clarification that the Agency, not the AEATF, would conduct the statistical analysis. Mr. Leighton responded that this was correct. Dr. Johnson commented that data are not being collected to determine if there is a difference between the three groups, the three different sizes of containers. Mr. Leighton stated that this was correct, because EPA cannot regulate based on container size. He added that the data would be normalized by pounds of AI. Dr. Popendorf added that this was a surrogate for the size of containers.

Dr. Virginia Ashby Sharpe inquired if the participants would be provided with the MSDSs. Ms. Sherman confirmed that they would.

Dr. Philpott asked why Ms. Sherman concluded that no potential subjects would be from a vulnerable population. Ms. Sherman responded that the subjects would not need extra protections beyond what was provided. Dr. Philpott suggested that a better interpretation may be that Ms. Sherman concluded that the protections in place were adequate, even if a particular subject could be considered vulnerable. Ms. Sherman agreed, and added that the AEATF was not recruiting through employers where the potential for coercion might exist. Dr. Philpott noted that he did not disagree, but that observers might question whether janitorial workers might be vulnerable because of their lower socioeconomic status.

Dr. Parkin commented that the language in the protocol about protecting individuals from being identified in photographs and videos was not included on the list of risks. Ms. Sherman agreed that perhaps it should be added to the categories of risk. Dr. Sharpe noted that the language was in the informed consent form. Ms. Sherman stated it was mentioned in the review under "Respect for Subjects." Dr. Parkin suggested that such a slide be added to EPA's presentation in the future.

Dr. Young noted that there is no plan to test for proportionality, but rather a plan to use a conservative approach when selecting the unit exposure. Mr. Leighton responded that if it is less than a proportionality of one to one, EPA still will use that unit of value and extrapolate it linearly to the high sum.

Board Questions of Clarification for the Principal Investigator/Study Sponsor

Dr. Philpott invited the Task Force members to the table to make public comment and answer Board questions. Ms. Leah Rosenheck, study director for the AEATF Liquid Pour Study, introduced herself.

Dr. Popendorf asked if Ms. Rosenheck had been to the laboratory and asked for a description. Mr. Leighton responded that the rooms were 12 by 24 feet. Ms. Rosenheck added that the ceiling height was 10 feet. The two laboratories that are being considered as the test rooms are vacant, with benches along the walls and a fume hood on the side; the middle part of the room is open. With respect to the question about the airflow rate, the laboratory has its own industrial hygienist who takes the airflow measurements on a regular basis, but Ms. Rosenheck was not sure of the hygienist's ability to regulate or alter it. That may be something she should follow up on.

With regard to the sequence of events, Dr. Sharpe asked why the pregnancy test was to be conducted before the examination of the hands. Ms. Rosenheck responded that the pregnancy test would be conducted as one of the first activities when the subjects come to the site. Dr. Sharpe noted that if someone were to be excluded because of their hands, they would not need to take a pregnancy test at all. Ms. Rosenheck agreed that this was a good point. Dr. Sharpe further stated that the informed consent form states that if you cannot read or understand English, a Spanish-speaking member of the research team will read the Spanish translation to you and answer your questions, but one of the inclusion criteria is English or Spanish literacy. Ms. Rosenheck agreed that she needed to check that and ensure that the statements are consistent.

Public Comments

Dr. Philpott offered Ms. Rosenheck the opportunity to make a 5-minute public comment regarding this study. Ms. Rosenheck commented that analyzing for two different AIs on the dosimeter and conducting the sequential monitoring is novel for antimicrobial studies. There is at least one agriculture exposure monitoring study in which three ingredients were analyzed from the workers' dosimetry. But analyzing for multiple ingredients is not novel, for example, in drug testing. The two AIs have analytical methods that have been independently analyzed and verified, and before the start of the study, the laboratory will validate the combined methods on each of the matrices.

Dr. Popendorf noted that it sounded like the studies Ms. Rosenheck mentioned involved multiple chemicals or AIs in the same product versus two different events. Ms. Rosenheck agreed that was that case.

Dr. Philpott asked if anyone else in the audience wanted to make a comment about the AEATF liquid pour study. Dr. Michael Bartels from Dow Chemical introduced himself. He is the analytical monitor for this study for the AEATF. Dr. Bartels commented that the utility of this methodology, which uses multiple test materials in the study design, has been shown in a variety of study types. Several agricultural studies have used multiple test materials within the same product. Many pharmaceutical and general residue methods, however, do not specifically expect that residues come from the same source. The DDAC is one chemical with a molecular weight different than the ADBAC test material being used in this study. The detection method will be a highly specific mass spectrometry technique, which will differentiate clearly between two chemicals based on the chemical structure and molecular weight. Full validation will be conducted on the combined method, and fully validated methods exist for each chemical in all of the dosimetry types that will be used in this study.

Dr. Popendorf noted that he was more concerned about the physical, rather than chemical, interaction of localized impacts of one pour in one scenario, and then a second impact in that same location, should that occur. If a splash deposits on a sleeve in one scenario, and then another splash occurs in the same place with a different chemical, the dosimeter could behave differently in terms of how much of the deposit would be retained. Perhaps the dosimeter should be changed after a spill. Dr. Bartels responded that he believed the recovery would not be affected.

Charge Questions

Ms. Sherman read the charge questions into the record:

If the AEATF liquid pour study proposal 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 exposure of individuals who manually pour liquid antimicrobial products?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Science Review

Dr. Philpott asked Dr. Popendorf, as lead science discussant for this study, to address the first charge question. Dr. Popendorf noted that although the liquid pour protocol is complicated and highly scripted, the proposed plan seems to be a feasible way to generate reliable data that include the effects of source container size, size and type of receiving container, and so on. He did not know what the use of the measuring cup would affect, so at this point, the inclusion of measuring cups seemed to be a policy decision rather than a science decision. He suggested that one-half of the participants in Group 2 use the measuring cup to pour the whole volume. This way, the AEATF would be more likely to see any effects of using measuring cups. The other alternative is to not use any measuring cups but to compare Group 1 to Group 2 after adjusting for the AaiH. The second proposal concerned filling the spray bottles from the source and then with water versus letting participants choose the order. Participants should be able to do what they normally do, but they should follow label instructions. All the instructions say, however, is "mix product with water." The third recommendation had to do with the randomization of the source containers. He suggested applying some statistical constraint to the randomization of the distribution of those source containers to avoid unnecessarily rare events and some unusual distribution. The fourth recommendation dealt with room ventilation, which had no effect on applicators while mopping. The protocol should stress the handler's position, however, related to the airflow direction so that no one is oriented in a draft. He agreed with Dr. Lebowitz's comment about air exchanges. The door on the fume hood could be closed, which could reduce total air flow to create a more typical room in which a janitor might be pouring liquids.

Dr. Popendorf noted two limitations to the protocol. The distinction made between the AaiH by consumers and professionals may be true over time, but it is possible that a consumer would handle more than a professional in a single event. Experience may be helpful in minimizing exposure, so the impact of this should be considered. The second limitation is measuring airflow only indoors. At least three of the 12 use categories are likely to occur outdoors, and outdoor conditions will be more variable. Including those would complicate the study. This limitation should be recognized. These aside, he believed that the data will generate scientifically reliable information, so he answered yes to the charge question.

Dr. Manautou stated that he understood that the solutions to be used in the two different scenarios will be diluted antimicrobial preparation, and asked who would be handling the dilution

from the original stock. Mr. Leighton responded that the laboratory staff would dilute the product. Dr. Manautou commented that the label would be on the original container, so it would not be available to participants during the study. Mr. Leighton noted that if there is a label, it is from the original label and would address higher amounts of AaiH than in the liquid to be poured. Dr. Manautou asked if the selection of containers to be used would be based on previous use and familiarity of the selected subjects. Mr. Leighton replied that few designs are available for antimicrobial products. Dr. Manautou mentioned a statement in the review that discussion with regulatory agencies might indicate the need for additional data about a given scenario, and requested elaboration. Mr. Leighton responded that in the beginning of the process, EPA went to the FIFRA SAP and the HSRB and discussed the relative accuracy goal, the K factor, and picked the goal of three. The AEATF built that into its governing document. EPA wants this study to be able to characterize the full range of exposures. Dr. Manautou noted that this was not based on deviations from the study design, and Mr. Leighton confirmed that was correct.

Dr. Young noted that it has to be clear in all of the analyses that have been proposed that the assumption is proportionality. Exposure over the number of units handled is constant, which is an important assumption because all analyses are on these normalized values. Assessing the linearity of the relationship between exposure and number of units handled is absolutely critical. The value of the slope does not matter as much as the fact that there is a linear relationship. When the three sizes of containers for the three groups are examined and allowances are made for differences in intercepts, EPA will need to assess the differences in that proportionality constant. The hope would be that the slopes are not significantly different.

Dr. Young noted that the analysis was of the normalized data, and there may be some confusion in the governing document on the true distribution and then that from this study. If the assumption of proportionality is true, these two distributions should be the same. Some thought needs to be given to the value of exposure over the AaiH. Another relevant fact is that the same person will handle both types of containers, which means that there are two studies in one, and there may be a way to leverage the data to provide improved analysis for each study.

Dr. Philpott asked if Dr. Lebowitz had a response to Drs. Young, Popendorf and Manautou. Dr. Lebowitz added that the additional impact of spills would be hard to measure.

Dr. Johnson commented that there was nothing in the documents that addressed randomizing the order in which the conventional and reduced-splash containers were used, but EPA requested that they be randomized. EPA may have more interest in the former than the latter, however, and perhaps the order should not be randomized.

Dr. Popendorf responded to Dr. Lebowitz's comment, stating that he was attempting to clarify the affect of one large spill on clothing followed by a similar exposure with the other chemical in the second scenario. There likely will be less absorption following the second exposure to a given dosimeter or more breakthrough if two dosimeters are used. The observer should watch for an egregious splash or spill and perhaps have the subject change dosimeters. Mr. Leighton commented that if Dr. Popendorf had a recommendation on the subject, it could be suggested to the researchers. Dr. Popendorf stated that the spill would have to be observable. Dr. Philpott added that the recommendation may be to conduct some experiments to determine if there is saturation in the

physical barrier. Dr. Manautou commented that the researchers wanted to interfere with the subjects as little as possible, and asked if the researchers would interfere if a subject was covered in the solution. Mr. Leighton agreed that the changing of dosimeters might add a bias to the subject's subsequent behavior. Dr. Popendorf stated that the change might be made before pouring the second chemical.

Dr. Philpott stated that the Board seemed to be in general agreement that this study is likely to generate scientifically useful data for assessing the exposure of individuals who manually pour liquid antimicrobial products, but there are some concerns or limitations that the Agency and sponsor should consider. The effect that measuring cups will have on study is unclear, so perhaps options should be considered, such as having one-half of Group 2 use the measuring cup to pour full volume, or alternatively not using the measuring cups at all in Group 2 but comparing them to Group 1. Perhaps there should be some constraints on randomization of the source containers to prevent rare events. The room ventilation question should be considered, because it is not likely to be representative of the situations in which mostly janitorial professionals will be using these products. Additionally, there is an assumption that because janitorial professionals use greater quantities of product, they are likely to have greater exposure than the average consumer, which may be true. In a single event, however, non-familiarity with the use of a concentrated product by a consumer actually may lead to higher acute exposures. Additionally, airflow patterns are measured indoors, but some pour categories likely occur outdoors.

In the statistical analysis, a major concern is that there is an assumption of proportionality, and Dr. Young pointed out that her definition of proportionality seems to differ from EPA's. Exposure over the number of units handled is being viewed as constant, but there is a concern that this may vary within the scenarios. An additional concern was raised that although the governing document is explicit about the use of log normal or other approaches, the end users of the data may not use these approaches. Additionally, each individual will be in two studies, one using the conventional containers and one using the reduced-splash containers, and perhaps the data can be leveraged to improve the analysis.

Finally, there is the question of the additional impact of splashes and spills, and this should be considered, as should ways in which observers can make note of them while limiting the amount of interaction that they have with participants.

Board Ethics Review

Dr. Philpott asked Dr. Sharpe, as lead ethics discussant for this study, to discuss her consideration of the question of whether the research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L. Dr. Sharpe thanked Ms. Sherman and her EPA colleagues for the organization of the materials for the meeting. She agreed with EPA's suggested revisions to this protocol to identify the recruiting newspapers, to specify Spanish language rather than a general statement about a second alternate language, and also to clarify steps that participants should take if they have a perceived reaction within 24 hours.

Dr. Sharpe will pass along edits to the informed consent form to the Agency, but had four recommendations about modifying the informed consent form. They were: (1) to make the language

about reading a Spanish translation to a participant consistent with literacy as an inclusion criterion; (2) to change the sequence of steps so that inspection of the hands comes before the pregnancy test; (3) to change the language that discusses the risks associated with the chemicals because it was based on the concentrated product; and (4) to revise the language consistent with the protocol to clarify that participants who withdraw from the study after exposure monitoring has begun still will be paid.

In the benefits section of the protocol in the informed consent form, a line states "you may also benefit if you ask for your own results from this study so you can learn how much product you got on you compared to other workers doing the same job." Dr. Sharpe asked, because there is not yet workgroup guidance on communicating research results, would the Board still recommend mentioning the returning of results to participants. If so, does the HSRB believe this belongs in the benefits section of the informed consent form, or that it would be best to have it in a separate section to provide a more comprehensive explanation of what the participants could expect? The statement might ask participants how they would like to be informed, or have them check a box if they want to be informed.

Dr. Menikoff agreed with Dr. Sharpe on most points, and believed that the study would be likely to meet the applicable standard. He did not agree that the sequence of pregnancy test and hand examination should be changed because he was concerned about IRBs or ethics reviewers micromanaging research, and he did not believe that ethics reviewers should be restructuring aspects of protocols. In terms of the disclosure of results, there is no real evidence that this is beneficial to subjects. His preference would be that this not be addressed in the consent form and that no letters be sent to participants. He suggested removing the sentence that Dr. Sharpe had mentioned.

Dr. Sharpe agreed with Dr. Menikoff that ethicists should not micromanage research protocols, but there is an ethical rationale for suggesting that the AEATF reconsider the ordering. A pregnancy test is more invasive than a hand examination. Dr. Menikoff commented that a urine test was not particularly invasive. If the concern is about someone learning that she is pregnant, that is a different issue that was not stated as a risk, and may actually be a benefit to the participant. Dr. Philpott asked if Dr. Menikoff would be amenable to a report that states that some Board members were concerned about the sequence of events and suggested that the sponsors consider the order in which the inclusion-exclusion-related procedures were followed. Dr. Menikoff agreed if it could be added if it included the statement that not all members were in agreement. Dr. Philpott noted that this stipulation would be added.

Dr. Philpott noted that the field of bioethics as a whole has been struggling to address the issue of the benefits of returning individual research results. He agreed with Dr. Menikoff that it ought not to be mentioned in the consent form at this time. It may be prudent to wait for the working group to devise some guidance and recommendations. On the point of reordering the sequence of events, a suggestion could be made that reordering be considered rather than a recommendation that the pregnancy test be moved after the hand examination. With these changes and EPA's recommendations, the study meets the applicable requirements of 40 CFR part 26, subparts K and L.

Dr. Popendorf asked if the statement on the value of returning results was general or specific to the study. Dr. Philpott responded that it was general, because the field of bioethics is wary of returning individualized research results unless there is a clear rationale for doing so. Dr. Popendorf agreed with that policy for this study. Ms. Sherman asked if the AEATF should remove any statement concerning providing results to participants. Dr. Philpott said that he would try to address this question when summarizing the Board's consensus. Dr. Sharpe commented that the general questions about the topic would be addressed by the workgroup. In terms of this particular protocol, she agreed with Dr. Philpott that the reference to returning the results should be removed. Dr. Parkin questioned whether it was the Board's prerogative to remove a sentence rather than let the sponsor and the Agency decide.

Dr. Philpott stated that the general consensus was that the answer to the charge question is yes and that the Board is in agreement with all of EPA's revisions. He commented that Dr. Sharpe had made a number of recommendations regarding the informed consent document, and there seemed to be a broad consensus. Consensus has not been reached on whether the study procedure sequence should be a concern, but the HSRB's recommendation might be that sponsors should consider the sequence in which they examine participants as to whether or not they meet inclusion and exclusion criteria, noting that not all Board members believed that there were concerns. Additionally, the Board did not find it objectionable should the Agency and the sponsors elect not to return individualized exposure results to study participants nor did the Board find it objectionable should the Agency and sponsors elect to continue the precedent of returning those results.

Mr. Downing concluded the meeting for the day at 4:54 p.m. He announced that the next day's public meeting would begin at 9:00 a.m.

Thursday, October 20, 2011 – Introduction and Identification of Members

Mr. Downing welcomed attendees and members to the second day of the HSRB meeting and turned the meeting over to the Chair, Dr. Philpott. Dr. Philpott asked members to identify themselves, and members completed their introductions. He invited Mr. Jordan to give a follow-up from the previous day.

Follow-Up from Previous Day

Mr. Jordan noted that EPA wanted to follow up on the matter raised about spills in the AEATF protocol. Mr. Leighton commented that the previous day the EPA discussed this issue, and one of the options mentioned was that if the observer sees dripping from a dosimeter, he/she should stop the ME and have the test subject change his/her dosimeter. However, this might change the behavior of the study participant. Another option discussed is stopping that ME and employing an alternate to continue the study. The problem is that EPA still would want that data from the subject who had made the spill, but then it would stand as an outlier. Another option was that if someone observes breakthrough of the dosimeter at the end of the ME, a rinse similar to the face/neck wipe could be employed. This may be overkill, because the residues on the skin may round out compared to what is on the two layers of clothing. Finally, it may be acceptable to have breakthrough, as it will not underestimate exposures. Dr. Popendorf thanked the Agency for starting the thought

process on the topic. Mr. Jordan added that the Agency will better understand what they need to learn once they have the results of this research.

Dr. Young asked why putting in an alternate would result in an outlier. Mr. Leighton responded that if it appeared that data from a spiller was driving the exposure assessment and the participant was pulled from the study and did not complete the monitoring, there would be a cloud of uncertainty over the results.

Session 1: A New Scenario Design and Associated Protocols from the Agricultural Handler Exposure Task Force (AHETF) Describing Proposed Research to Measure Dermal and Inhalation Exposure to Workers Who Use Closed System Equipment to Load Liquid Pesticide Products from Returnable and Non-Returnable Containers

Background

Ms. Sherman noted that the matter to be discussed was a new protocol that had come to EPA in August 2011 from the AHETF. It proposed to measure exposure of workers as they load liquids using closed systems into either pre-mixed tanks or application tanks. Closed systems are designed to prevent the pesticide from contacting the handlers. The study examines two scenarios: loading from non-returnable containers, and loading from returnable containers, because there may be different patterns of exposure from the different containers.

The returnable containers are larger, and there will be more loading events in the study if the containers are smaller, so there are more events with non-returnable containers. Rinsing will be monitored as part of this scenario, and non-returnable containers usually are rinsed by the handler, whereas returnable containers are rinsed by the manufacturer after they have been returned. There are additional differences in the way the material is moved from the container into the equipment. This protocol appears similar to other AHETF studies that have come to the Board recently in design objectives, rationale and ethical conduct procedures. There will be three clusters and three monitoring units (MUs) per cluster, and some existing data will be incorporated.

EPA Science Assessment

Mr. Jeff Evans (OPP, EPA) reiterated that there were two separate studies representing two different scenarios that are governed by a common protocol. This is the same approach chosen by the AHETF for the rights-of-way spraying scenarios that the Board reviewed last year. The scenarios address mixing and loading; are distinct by container type, returnable and non-returnable; and are closed systems as defined by EPA's Worker Protection Standard (WPS).

The scenarios are defined by clothing and personal protective equipment (PPE). The clothing and attire shall consist of long-sleeved shirts, long pants, shoes and socks, and the PPE shall consist of chemical-resistant gloves. Aprons will not be required, as the surrogate chemicals used in this study are low toxicity. If a person normally wears an apron with chemicals of this nature, he/she will not be considered for participation in this study. Closed systems under pressure require protective eyewear, and this will be worn as its use will not significantly affect the exposure measurements.

There are some potential exposure scenario differences. For the non-returnables, the container size is small, and there is the function of rinsing containers and many more options for removing the pesticide from the container. In this scenario, there are no available data to add to the studies that will be conducted. Returnable containers are larger and rinsing is very unlikely. Mainly suction extraction is used for removing pesticides from the containers. This scenario is complicated by the presence of two pre-rule studies that the AHETF intends to use to support this scenario. Mr. Evans showed photographs of the various types of equipment to the Board. All of the systems involve dry coupling to keep the liquids away from the handler. Most of the exposure involved comes from dealing with coupling. The couples connect the container breach system into a holding tank or the application tank; if a holding tank, it will be transferred to the application tank by more dry coupling. The AHETF intends to diversify the MUs in any cluster to incorporate different systems of moving from a holding tank, a holding tank to application tank, and to an application tank.

The non-returnable scenario will consist of seven clusters with three MUs per cluster. The AHETF has defined the cluster as an entire state, and each individual will load the pesticide in the amount determined by one of three strata. For the returnable study, there are two pre-rule studies. One was conducted in California and one in Texas. The new protocol will provide an additional 15 MUs to the existing MUs, provided that they are configured as five clusters with three MUs per cluster. The California study consisted of seven MUs, but only two participants. One participant was measured on four separate occasions, and the other was measured on three separate occasions. Likewise, for the Texas returnable study design there were 15 MUs utilizing seven participants. Some individuals were monitored three times and others only one time. WPS post-rule AHETF studies differ from the pre-rule studies by imposing similarity restrictions, including not having repeated measures of the same individual, not working on the same farm, having a different employer, and ensuring a wide range of AI being applied in those previous studies. The AHETF asserts that the existing data for the returnable study do not represent true variation, but the AHETF also wants to see if the data are consistent with the assumptions used in their reference model: a geometric standard deviation of 4, and an intra-cluster correlation of 0.3. The AHETF determined that the assumptions are consistent and that 15 additional MUs are needed provided that they are configured as five clusters with three MUs each. As in the non-returnable scenario, the cluster will be the entire state. Each participant will apply a different amount of AI. EPA expects that this configuration, along with existing data, will result in achieving the primary objective of relative fault accuracy of 3 for geometric and arithmetic means, as well as the 95th percentile, and 80 percent power to test exposures proportional or independent to the AaiH.

A wide range of surrogates are available in non-returnable containers, with fewer options for the returnables. The returnable scenario, however, has fewer MUs. The surrogates have low toxicity and do not require aprons. They represent a wide range of application rates that should help to fill the AaiH strata, they can be used safely under the conditions of the proposed studies, and there are acceptable analytical methods for all of the dosimetries. This protocol will use whole-body dosimeters, upper and lower sections, hand rinse, face and neck wipes, and the OVS tubes. It will be difficult to find study participants and to diversify the MUs within each cluster by equipment type and transfer system. Additionally, not all systems are closed. It also may be difficult to find participants who are willing to forgo the use of their apron if one is normally used.

EPA agrees with using the entire state as a cluster; these are states that have high use of closed systems, and there may be more states used with fewer MUs per state. The AHETF should consider all closed liquid systems, provided that they are consistent with the WPS, and should try to diversify MUs by equipment types and transfer systems.

In terms of the recruitment, the AHETF has developed employer lists from such sources as Farm Market ID and Triple A. The eligibility list will include growers and commercial application firms, and the lists will be used to identify employers using returnable and non-returnable containers. The resulting list may be randomized by the AHETF contractor or the call center, and if the list is large, it will be sub-sampled. Potentially eligible employers will be referred to the AHETF. Often, however, by the time the MUs are identified, the application window for the pesticide application has expired. Therefore the AHETF plans to utilize an MU as soon as recruited. EPA finds this approach acceptable and agrees with the AHETF study design approach of having more clusters and fewer MUs per cluster for the 15 new MUs, provided they have a five by three configuration. Diversity should be achieved randomly or purposively in the course of assigning mixer/loaders to the AaiH strata within each cluster. EPA's conclusion is that the scenarios are well-defined and this study likely will produce reliable mixer/loader data to assess the potential exposures of handlers using closed system liquid loading with non-returnable and returnable containers.

Board Questions of Clarification—Science

Dr. Chambers mentioned that the closed systems do not require gloves but that the study participants will be wearing them. Mr. Evans noted that some closed system products require gloves and some do not. Hand rinsing will be performed once the gloves are removed. Dr. Chambers asked whether rinsing the containers would be part of the activity of the workers. Mr. Evans responded that it would be part of the non-returnables scenario. Dr. Chambers asked whether the analytical techniques used to collect the 20-year-old data set were valid, if the limits of detection were the same, and if the observations EPA is recommending were conducted. Mr. Evans responded that any study purchased by the AHETF was likely to have good analytical methods. Mr. Evans was not overly familiar with the California study, but the Texas study contained many observations of participant behavior.

Dr. Popendorf noted that the Board had not received the existing data, and asked how the unit exposure values compared to the traditional mixing/loading exposures. Mr. Evans replied that one study was in the Pesticide Handler Exposure Database. In the other, the unit exposures for the mixing/loading are an order of magnitude lower than open mixing/loading. Dr. Popendorf commented that the upward limit was 2,400 pounds and, of the existing data, only two of the 15 were less than 2,400 pounds. Most range from 24 up to 9,600 pounds. For the ongoing studies, the upper limit must be strict. Mr. Evans responded that it would be possible to measure up to a certain point and then stop. Dr. Popendorf stated that the non-returnable scenario upper limit was lower, and asked if in that scenario people would be likely to apply more than 800 pounds. Mr. Evans responded that the main idea of having bands of strata was to ensure proportionality, but EPA could consider modifying the upper limit. Dr. Popendorf commented that there are gradations of closed

systems, and Mr. Evans agreed that EPA was attempting to settle on the definition of a closed system; it may be that it is closed and not leaking.

Dr. Chambers asked if the scripting is designed to stop the participants in the highest stratum at a particular point rather than going above 2,400 pounds. Mr. Evans confirmed that it was.

Dr. Lebowitz noted that the protocol calls for four coatings, with three as the minimum, and in fact it may be restricted to fewer than three. This would call for a change in the protocol. Additionally, he was pleased that the prior data were used to examine the same worker-day correlation.

EPA Ethics Assessment

Ms. Sherman stated that EPA believes that there is value in gathering improved data to support EPA risk assessments for these types of uses.

The first step in recruiting subjects is to contact growers and commercial applicators that have the right types of equipment and are in the target areas. The eligibility criteria include experience within the past year using the same type of equipment; those who routinely wear aprons are excluded. Once a candidate is identified, a one-on-one meeting is held with the study director or a Spanish-speaking researcher, and the study, procedures, and risks and benefits are explained. The meetings are held in a hotel or vehicle away from the site to ensure that there is no coercion from the employer involved. The employers that allow their employees to be approached have signed an agreement not to coerce employees.

The consent form contains all of the required elements. Both the protocol and the consent form specify five categories of risks:

1. The risk of heat-related illness from wearing two dosimeters and the air sampling pump; there is an SOP for managing heat illness and a medical professional will be on site, so that risk is minimized.
2. Exposure to surrogate chemicals.
3. Exposure to surfactants used for hand and face wipes are minimized by excluding subjects who have sensitivities to chemicals, selecting experienced handlers and selecting subjects who identify themselves as in good health.
4. The risk from scripting of field activities to achieve diversity, such as additional working time, or mixing or loading more or less than participants might during normal activity is minimized by selecting experienced subjects and by the procedures for protecting against heat-related illness.
5. Psychological risk, including embarrassment from changing into dosimeters or disclosure of pregnancy tests, is minimized by private changing areas and same-sex assistants, and by discreet and confidential pregnancy testing and subsequent discreet withdrawal from the study if needed.

There are no benefits to subjects from participating, but the sponsors benefit from improved risk and exposure assessments. The likely benefit to society is higher than the risks to subjects, because the risks are fairly low.

In terms of respect for subjects, the payments proposed are reasonable at $20 for a consent interview and $100 for reporting to be monitored. Subjects are paid if they decide to withdraw after they appear at the study, and that is explained in the consent document and the protocols. The consent form clearly states that medical care for research-related injuries will be provided at no cost to the subjects. Additionally, to protect subject privacy, identification numbers are used, with no use of names, and subjects' faces or distinguishing marks are not shown in photographs or videos. The protocol was reviewed and approved by IIRB. This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide with the intention of submitting the data to EPA under the pesticide laws. The applicable ethical standards are 40 CFR part 26, subparts K and L, and FIFRA §12(a)(2)(P).

Ms. Sherman requested two revisions. In future protocols, she asked the AHETF to develop and add an SOP on the criteria that a medical professional would use to determine whether a subject is too sick to refuse medical treatment. The second revision is based on the Board's discussion during the previous day about the questionable value of providing personal exposure results. In conclusion, she believes that the protocol meets the applicable ethical requirements of 40 CFR part 26, subparts K and L.

Board Questions of Clarification—Ethics

There were no questions of clarification regarding the ethics of the AHETF protocol.

Board Questions of Clarification for the Principal Investigator/Study Sponsor

Dr. Philpott invited Drs. Victor Cañez and Richard Collier to respond to questions from the Board. Dr. Cañez is a consultant to the AHETF and Dr. Collier is Chair of the AHETF Administrative Committee.

Dr. Philpott asked how it would be determined that the systems were functioning properly. Dr. Cañez responded that the assessment would be made at the initial site visit to ensure that the equipment meets WPS qualifications for protecting the worker. Photographs of the equipment will be taken as well. Dr. Collier added that the equipment would be inspected on the day of the monitoring event; however, specific criteria for inspection cannot be written because many systems are unique.

Dr. Philpott inquired how the AHETF is addressing the fact that some "closed" systems may not be closed given the wide diversity of equipment. Dr. Cañez responded that this can occur with "stingers" or large containers with inserted probes, which in some cases remain open. These cases will be monitored, but they are not preferable in the selection process.

Dr. Philpott questioned whether the scripting was designed to stop at 2,400 pounds. Is there a plan to restrict this or to change the upper stratum to anything above 311? Dr. Cañez noted that there had to be an upper limit, which was chosen based on the surrogates. The initial study had high

amounts of AI handled that will not be found in the MUs in the future study. The strata are based on what is typical with the surrogates. Dr. Popendorf agreed that this was reasonable for the returnables, but asked if there was a reason to maintain the upper limit for the non-returnables. Dr. Cañez stated that this should be discussed with the AHETF's statistician. Dr. Collier added that the upper limit is needed to complete the design and ensure enough range of AaiH to address the secondary objective, but there is no reason in the performance of the study to reject someone who may be applying above that number.

Dr. Chambers asked if there ever was enough chemical left in a returnable to increase the stratum to a higher level. Dr. Cañez agreed that there was a possibility that there could be some solution left over. Dr. Collier added that the AaiH will be calculated based on the actual amount used, not on how much is left in the container.

Public Comments

Dr. Philpott offered Drs. Cañez and Collier the opportunity to make a public comment regarding the AHETF closed system of liquids mixing and loading scenario. Dr. Collier thanked the Agency and the Board for their time and effort in reviewing the protocol and commented that the AHETF looks forward to conducting the research.

Dr. Philpott asked if anyone in the audience wanted to make a comment on the study. No comments were offered.

Charge Questions

Ms. Sherman read the charge questions into the record:

If the AHETF closed-system liquid loading study proposal 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 exposure of workers using closed systems to load liquid pesticide products from returnable or non-returnable containers?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Science Review

Dr. Chambers stated that her response to the first charge question was yes. The AHETF addressed a number of past Board comments in this protocol. She agreed with EPA that the behavior and the events of the experiment should be monitored. The 20-year-old data causes some concern because the monitoring may not have been as robust. Another issue is the assumption that there will be proportionality. Exposures may be incidental, so monitoring the behavior will be very important. The study is well designed; it will be a challenge to conduct, but it should generate good data.

Dr. Lebowitz agreed that this would be a difficult study and, although the old data appear to fit within the assumptions made, they will have to be questioned when the new data are collected. He queried whether a total exposure estimate will be made from the study in addition to the studies of application because in real life handlers apply the loaded pesticides. He further asked whether the AHETF had results from prior field-fortified samples, and if initial wipes had been analyzed to determine if the background concentrations of the pesticides would affect integrated or cumulative exposure. He responded in the affirmative to the charge question.

Dr. Johnson commented that as a statistician, he was pleased to see clusters and MUs of seven and three.

Dr. Young stated that she saw no value in the second objective of the study, the test for proportionality. What is important is that there be a linear relationship between exposure and AaiH, and that the intercept of the line be zero. If the slope is positive, it will inflate the normalized values. When the normalized values are treated as a distribution, it is assumed that the distribution of exposures at each of the levels of AI is the same. There are not enough data to verify that assumption. She suggested rewording objective two to focus on what is needed to meet objective one.

Dr. Popendorf suggested that the Agency or the AHETF allow higher handling AaiH values for the non-returnables and describe what the study director might observe and use as criteria in the field. Additionally, whether surfaces contaminated by prior applications of material, are outliers, or are causing uniform distribution non-proportionality should be observed. He further suggested adding cotton gloves over the chemical protective gloves as a dosimeter so that protected and unprotected exposure could be measured.

Dr. Philpott stated that the Board's consensus opinion was that the research is likely to generate scientifically reliable data useful for assessing the exposure of workers using closed systems to load liquid pesticide products from returnable and non-returnable containers, but there are some concerns and suggestions that the sponsors and the Agency might want to consider in both the design and the analysis of the study. There seemed to be general consensus that the 20-year-old data may not be as useful as thought. It is unclear whether there may be differences in the analytical methods and the way that the assessments were done. Many Board members raised the concern that, given the level of protection that these systems are designed to provide, there may be a repeat of the closed cab scenario in which most exposures are incidental. The suggestion from the Board is to consider the incidental exposures and determine a standardized approach for the observers to identify when potential incidental exposures occur.

Other concerns raised were related to study objective number two, which is the test for proportionality that relies on a number of assumptions, including the assumption that each level of AI handled is the same. The suggestion was to check for linearity, and a slope of zero; if linearity is present but the intercept is greater than zero, that will inflate the normalized values and give a more conservative estimate of exposure.

Additional recommendations were made around developing criteria for what is meant by proper functioning of the mixing and loading systems. Finally, there was a suggestion about using

cotton gloves or another kind of dosimeter outside of the chemical-resistant gloves to measure unprotected exposures.

Board Ethics Review

Dr. Vanessa Northington Gamble congratulated Ms. Sherman on her excellent review. She agreed with Ms. Sherman that it should be included in the consent form that if subjects experience symptoms related to their participation they should contact the study director, and a phone number should be included. Additionally, she agreed that an SOP for criteria a medical professional would use to make a decision that a participant is too sick to refuse medical attention be included. She further asked that the discussion about participation in the study be conducted away from the work site. She could not comment on the return of results because she was not present at the previous day's meeting. She agreed that the study would meet the applicable requirements.

Dr. Philpott agreed with Dr. Northington Gamble's assessment that Ms. Sherman's review was excellent. He also agreed with all of the Agency's recommendations, and reiterated the need for clearly articulated criteria for when participants no longer are capable of making medical decisions on their own. Additionally, he pointed out that the benefit of returning individual study results is unknown, and the Board's suggestion from the day before that it would not be objectionable if the sponsor chose not to return individual study results to participants at this time applied to this study as well. He reiterated the point that the Board is convening a new working group that will provide the Agency with guidelines as to when it may be appropriate to return individual exposure data to study participants. At this point, however, the HSRB was neither recommending nor discouraging the return of individual study results. Dr. Sharpe added that if results were provided, the working group may be able to suggest the best manner in which this could be conducted.

Dr. Philpott noted that in summary, the Board's consensus opinion regarding the ethics charge question on whether the research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L, is yes, assuming that the study is conducted as described, and also following the recommendations made by the Agency and the Board. These recommendations include: adding contact information for the director on the informed consent documents, drafting an SOP regarding the criteria for the medical monitoring decisions that study participants may have lost the capacity to make medical decisions on their own behalf, and a suggestion that the Board will not find it objectionable should the AHETF not return individual study exposure results to study participants at this time. Should the AHETF so choose, the Board working group that had just been convened will assist in drafting a letter and can provide an example of a letter that was developed for the AEATF.

Session 2: A Published Report by *Moiemen et al* (2011) of an Intentional Exposure Human Study Measuring Dermal Absorption of Silver from the Use of Nanosilver-Containing Wound Dressings to Treat Major Burns

Background and EPA Science Assessment

Dr. Philpott mentioned that the Board had permission from Elsevier to use the study, which is in a copyrighted journal, for the purposes of this review but that it is not publicly available on the website. Because of these copyright restrictions, Board members who do not have access to the

journal *Burn* were asked to delete the document from their hard drives after the Board's final report is completed. Dr. Philpott then asked Ms. Sherman and Dr. Jessica Ryman (OPP, EPA) to discuss EPA's science and ethics review of this published report from *Moiemen et al*.

Dr. Ryman explained that the Agency has registration applications pending for articles such as textiles that are treated with nanosilver and is interested in conducting quantitative risk assessments for these products. These assessments include quantitative dermal assessments to estimate risks from dermal exposure to nanosilver-treated articles and require the Agency to quantitatively estimate dermal penetration of nanosilver. Limited data are available in the literature that quantitatively estimate dermal penetration of nanosilver, and the few studies available are conducted *in vitro*. EPA does not rely on *in vitro* studies alone; they can be used only in a weight of evidence with animal or human data. This study provides human data that will allow quantitative estimation of dermal penetration of silver from nanosilver in human volunteers, and the Moiemen study likely would overestimate any dermal penetration that would be observed from treated articles, because the patients in this study all had major burns. The methods that EPA used to calculate dermal absorption of silver from these data were conservative. The Agency assumed that all circulating serum silver would result from dermal absorption of silver from the wound dressing, or from silver that is deposited in the skin layers, and that these serum levels of silver would not be elevated because of impaired clearance or long plasma half-life, which also are possibilities. EPA proposes to use the Moiemen study, together with *in vitro* studies in a weight of evidence, to quantitatively estimate dermal penetration of silver from nanosilver that is applied to treated articles. This estimate will be an upper bound estimate, so it would reflect a worst-case scenario.

The study was conducted at the Midlands Burn Centre in the United Kingdom (UK), and the objective of the study was to confirm the safety of the use of Acticoat®® wound dressing on burns on 20 percent of the total bodily surface area or more. Previously, Acticoat® had been shown to be safe on smaller burns. The test substance used in this study is the three-layer Acticoat® wound dressing that contains silver nanoparticles called SILCRYST™. An inner core of rayon or polyester is between two layers of nanosilver-coated low-adherent polyethylene mesh that is in contact with skin. Two kinds of Acticoat® were used in the study: one in which the polyethylene mesh is coated with calcium alginate, which extends the antimicrobial efficacy of the wound dressing to 7 days, and one that is uncoated and has 3 days of antimicrobial efficacy.

The medical history of the patients was obtained, as well as details on the burns, photography of the burns, baseline levels of serum silver, a full blood count and serum clinical chemistry. Both the burns and the grafting sites were dressed with the Acticoat® wound dressing, and the surface area of the wound was estimated by calculating the total amount of the Acticoat® wound dressing that was applied to the wound. The end points that were investigated in the study were blood silver levels, which were measured at the start of the study and every 3 days until the Acticoat® treatment was discontinued, and then at 1, 3, 6 and 9 months after discontinuation. Blood levels of silver were detected by inductively coupled plasma mass spectroscopy (ICPMS), which does not distinguish silver ions from silver nanoparticles.

The detection limits for silver ions by this technique in the blood were not given in the study. The Agency estimates that the detection limits are probably around 0.1 micrograms of silver ions per liter, based on the baseline range observed for patients in the study, as well as instrument

detection limits that were described in a previous EPA publication for the ICPMS method for detecting silver ion. Aside from blood silver levels, the other end points investigated in the study were hematology, clinical chemistry, wound healing and clinical signs.

Study participants were numbered 1.01 through 1.06. The authors noted that the changes that they observed in hematology and clinical chemistry parameters were consistent with what would be expected for patients who had severe burns and were not attributed to the Acticoat®. One adverse event potentially related to Acticoat®, the loss of a graft, was reported, but the authors did not consider it to be a serious event, and EPA did not find it to be indicative of Acticoat® toxicity. Healing was sufficient for all of the participants in the study except for Patient Number 1.04, who unfortunately died during the study. No adverse effects were observed for the remainder of the patients, and the results confirmed the clinicians' view that Acticoat® was safe for use on major burns.

EPA calculated an estimated dermal absorption factor (DAF) for silver from nanosilver based on data in the study. Dr. Ryman showed a graph that compared the preoperative total body surface area of the burn versus the maximum serum levels of silver that were observed during the course of Acticoat® treatment. It showed no apparent relationship between maximum serum silver levels and the total body surface area of the burns. Another graph showed the relationship between serum silver levels on the y axis and treatment duration. Except for Patient Number 1, who was treated with Acticoat® before the start of the study, in most of these patients, serum levels of silver reached a maximum by about 9 days. Once this maximum was reached, the levels stayed at a maximum (they decayed somewhat in one patient) and then remained at a steady state for the duration of the time that the Acticoat® was in contact with the skin. The investigators also measured serum levels after discontinuation of treatment and found that there was a fast phase in which the serum levels of silver dropped within about 12 days after removal of the wound dressing, and a slower phase during which silver was eliminated from the blood. The study authors calculated a median half-life of silver in the blood after removal of the wound dressing of about 46.4 days, which was a loss of approximately 1.5 percent in blood levels of silver per day.

The study investigators found no apparent relationship between silver exposure and maximum serum levels; there was no apparent dose response between dermal exposure to silver and serum levels of silver ion. One explanation posed was that decreased vasculature in areas of the skin that were burned would inhibit systemic absorption. The Agency determined systemic absorption of silver from Acticoat® by estimating the area under the curve (AUC) during treatment. EPA also estimated the AUC after discontinuation of treatment, and the total AUC was determined by adding the AUCs during the treatment phase and after the discontinuation of the treatment phase. The Agency then calculated the DAF, which is the percentage of the total amount of silver in the systemic circulation, by dividing the total AUC by the theoretical maximum cumulative exposure to silver. EPA multiplied this value by 100 to get the percentage of silver from nanosilver that was absorbed into the systemic circulation during treatment: the result was less than or equal to 0.1 percent, which provides a conservative upper bound estimate for dermal absorption of silver from nanosilver, because the 0.1 percent value is the highest value that was observed for the six patients. This value is several orders of magnitude higher than those that have been observed in *in vitro* studies that have been conducted with intact or mildly damaged human skin.

EPA recognized severe limitations to this study. Only six patients were recruited for the study and no statistical analysis of the data was performed. In addition, there was no physicochemical characterization of the SILCRYST nanoparticles that are present in the wound dressing. The detection limits for silver in serum for the ICPMS method were not provided, and there was little detail on how the ICPMS was performed. Finally, the calculation method for the half-life of serum silver elimination was not provided in the study.

The Agency concluded from this study that less than 0.1 percent penetration of silver from nanosilver is anticipated from textile products that are in direct contact with intact skin.

Board Questions of Clarification—Science

Dr. Popendorf asked if data were available to recreate the half-life calculation of the investigators, and if the elimination appeared to be biphasic. Dr. Ryman responded that the study authors did provide the data to the Agency, but she did not have permission to present it. They did not, however, provide information on how the half-life was calculated, and she would have liked to have seen more of that in the paper. The elimination does appear to be biphasic. Dr. Philpott noted, based on his experience with human immunodeficiency virus (HIV) dynamics, that biphasic curves like these often reflect two different half-lives, with the second phase reflecting coming from tissue or cellular reservoirs.

Dr. Popendorf asked why there was silver on both sides of the Acticoat®, and if there was any way the silver on top could be absorbed by the skin. Dr. Ryman did not know why there was silver on both sides of the dressing. Dr. Philpott inquired if the calculation of the total silver exposure was based on the inner layer or on both layers. Dr. Ryman responded that it was unclear in the paper. Dr. Popendorf believed that it was the total silver in the material. Dr. Popendorf further asked about the calculation of the AUC and how that related to the calculated absorption. Dr. Ryman responded that the estimate integrated the total exposure based on serum levels of silver observed at different times and was a conservative estimate because the assumption was that all of the silver in the blood was just absorbed. Not enough detail was available to determine how much silver was coming in and how much silver was being eliminated at a given point in time.

Dr. Green asked if there was a sense of urgency for acquiring these data, and if there was a statutory requirement that meant the information was needed by a certain time. This would help him understand better if the study should be used, or if the HSRB should advise the Agency to wait for better data. Mr. Jordan explained that under the pesticide law, when a company submits an application EPA is required by statute to give a decision within a certain period of time. Several applications currently are pending seeking registration of antimicrobial nanosilver, and the deadlines for making decisions about those pending applications are approaching quickly. Dr. Green asked for more detail on how the weight of evidence approach is employed. Dr. Ryman replied that the *in vitro* studies on absorption of silver from nanosilver in human skin were conducted on isolated human skin. These studies indicate that the penetration of silver from nanosilver likely is around 0.003 percent in healthy skin, and around 0.02 percent in damaged skin. The Agency does not consider *in vitro* studies alone, however, so the goal is to bring in other lines of evidence that can build confidence around that estimate. The study under consideration provides a worst-case estimate

of 0.1 percent, which is very conservative because it is based on damaged human skin and is much higher than what is observed *in vitro*. The Agency did not find any animal data on the issue.

Dr. Philpott noted that Dr. Green's questions were appreciated, but that the HSRB had to focus on the charge questions. Thus, while Dr. Ryman's and Mr. Jordan's answers were helpful in clarifying the Board's understanding of the charge questions, how the study will be used in the overall weight of evidence should not affect the Board's recommendations to the Agency.

Dr. Sharpe asked if it is known that damaged skin is more absorbent than healthy skin. Dr. Ryman responded that it depends on the level of damage. If the skin is burned all the way through, the vasculature is completely destroyed and there is not going to be much absorption. She tried to discern a relationship between the surface area of full thickness burns and absorption, but there were too few patients to do so. In addition, one patient required Integra® (artificial skin) grafts instead of human skin grafts, and there is no absorption through that material. It is difficult to determine; decreased vasculature could be a reason, but there could be other explanations. There was sufficient healing in the patients, however, to provide skin with varying degrees of damage; it would seem that the potential for absorption is higher in damaged skin than healthy skin in all cases, except for cases in which there is a full-thickness burn.

Dr. Lebowitz noted that there often are two layers of treatment in a dressing, because one gets absorbed or damaged in the process of being used to coat the burn. Additionally, epidermis and endodermis are protective, so when those are removed there will be greater absorption. He added that with six patients with differing levels of skin damage, he was not surprised at the lack of a dose-response relationship. He asked how important that fact was. He believed that the Agency's approach of calculating the AUC to get the maximum amount of silver absorbed was an appropriate one. He did not know what was meant by the authors' statement that the dose estimate was consistent with a previous *in vitro* study that showed two orders of magnitude of absorption lower on intact and abraded skin. He believed that EPA's calculation was a useful maximum estimate. Dr. Philpott noted that Dr. Lebowitz had asked how important the lack of a dose-response relationship was in how the Agency planned to use this data in the overall weight of the evidence. Dr. Ryman responded that she would have liked to have seen a dose response. Given all of the variables in the study, however, EPA was not surprised not to see one. Because the study is being used as an upper bound estimate, the lack of dose response does not limit the utility of the study.

Dr. Fernandez asked whether the outlier on slide 14 of EPA's presentation was the patient with 70 percent burn damage. If that outlier is removed, there is a good relationship. Dr. Ryman agreed. She added that Patient 1.01 was treated with silver before the study, and if Patients 1.01 and 1.04 were removed, there was an apparent dose response. Dr. Philpott asked whether Patient 1.01's prior exposure to silver was calculated in the study. Dr. Ryman noted that this was unclear in the study. Dr. Johnson agreed with Dr. Fernandez, and noted that it could not be stated with certainty that there either was or was not a dose-response relationship.

Dr. Manautou inquired how the theoretical maximum cumulative exposure was calculated. Dr. Ryman responded that it was based on the total amount of wound dressing used on each patient. This was multiplied by the parts per million of silver in the dressing. Dr. Manautou asked if this calculation accounted for dressing changes, and Dr. Ryman replied that it would, and would have

taken into account the amount of dressing used each time. Dr. Manautou asked if the authors had the hematological results of kidney and liver function tests for each patient. Dr. Ryman responded that they did, and concluded that the changes that these patients had were consistent with patients with major burns. Dr. Manautou commented that when the authors calculated the half-life at 46.4 days and a median elimination rate of 1.5 percent per day that was a reduction of serum levels daily. He asked what was meant by Dr. Ryman's comments on serum levels after the discontinuation of treatment. Dr. Ryman read from the report that close examination of the elimination data for each patient revealed an apparent pattern of biphasic elimination for most patients, with faster elimination prior to day 12, followed by slower elimination. Urinary excretion of silver was not monitored in the study, so the theory that silver may be cleared by urinary excretion at high silver levels could not be confirmed. She believed that Dr. Manautou's question was on skin-associated silver and she was concerned about the absorption of skin-bound silver residue in this study into the systemic circulation. Dr. Manautou confirmed that Dr. Ryman was suggesting that this residue might contribute to the slower phase of elimination. He did not agree with the investigators' interpretation that there is biliary clearance then renal clearance. He noted that the possibility that both ionic and nanoparticle silver are being absorbed from the skin, and that the rapid decline might be elimination of ionic silver, should be considered. He further suggested that nanoparticles might find a depot from which they would then be released. Dr. Ryman agreed that this was an alternative explanation. Dr. Manautou commented that the report noted the limitation of not knowing the form of silver that had been absorbed. He further noted that to obtain accurate estimates of absorption and blood levels, it is important to understand renal clearance and renal function. Dr. Ryman agreed that urine data would have been useful, but did not find its absence to be a fatal flaw because the AUC estimates were very conservative. Finally, Dr. Manautou noted that combining full thickness and partial thickness burns into a total percentage of burns might mask any potential dose-response relationship. Dr. Ryman responded that in spite of its limitations, the study provides a conservative upper bound estimate. Dr. Manautou asked if there would be any problems with conducting a study such as this on people with normal skin. The Agency didn't answer this question; however, as Dr. Philpott cautioned it was outside the scope of the charge before the Board.

Dr. Parkin asked for the source of the size and purity of nanosilver in SILCRYST. Dr. Ryman explained that she had found limited information in the patent information for SILCRYST. Dr. Parkin confirmed that there was nothing in SILCRYST that would affect the absorption of silver. Dr. Ryman agreed that she was unable to find information that SILCRYST could affect absorption differently than other kinds of nanosilver. The reason absorption of silver from nanosilver is specified is that the detection method does not allow distinction between silver ion and nanosilver.

Dr. Philpott thanked Dr. Ryman for her presentation and patience in answering questions.

EPA Ethics Assessment

Ms. Sherman noted that the study was performed in the UK between 2006 and 2007, after promulgation of the Human Studies Rule in 2006. No one submitted this study to EPA; it was located by researchers at EPA working on nanosilver. She based her review on the published article and on some communications with one of the authors who works for Smith & Nephew, the company that produces Acticoat®.

The study provides value in two ways: in EPA's regulatory work, and in examination of the safety of the products for those with serious burns. The subjects were selected from patients that were admitted to the hospital with burns exceeding 20 percent of their total body surface area. They or their next of kin were spoken to by the investigators about participation. Six met the criteria for inclusion. There were five men and one woman, aged 22 to 56, so there were no individuals under the age of 18. Pregnancy and lactation were exclusion criteria. The one female was not tested for pregnancy, because that would not be performed in a burn unit without request from the patient. The investigator explained that this dressing was the standard of care, and would be used whether or not she was participating in the study. Ms. Sherman did not find that to be a problem, and found the other inclusion and exclusion criteria appropriate. This is a vulnerable population, and Ms. Sherman believed that the information in the protocol and that the ethics committee considered showed that they had thoroughly considered this issue. The study information was provided to patients or their next of kin, and they had 24 hours to review it before consent was solicited; withdrawal was permitted at any time for any reason. The two patients whose consent originally was provided by their representatives later were asked for their consent and they granted it.

Ms. Sherman commented that the risks of participation in the study were low. The treatment was almost identical to the medical treatment they would have received were they not in the study. The researcher could not say that the treatment was identical because the study site was asked to minimize the use of other silver products on the patients during the study. It therefore was considered an intentional exposure study. The study-related risks were from additional blood sampling, and most collections took more blood rather than adding additional collections. Additionally, there were exclusion criteria to exclude patients who might be sensitive to silver or other compounds or have other complications, including dementia or a history of poor compliance with medical treatment, which may have led to the exclusion of 20 of 26 of the patients originally considered for the study.

There were no benefits to subjects from participating in this research, although there was a societal benefit of increased knowledge about the safety of these products. Because the risks were minimal, there was a positive risk/benefit balance. The research was reviewed and approved by the Sandwell and West Birmingham Ethics Committee associated with the hospital. Ms. Sherman found the ethics review to be thorough and in line with what would be examined for studies conducted in the United States. Three subjects initially signed the consent form, one subject provided verbal consent, and then two subjects provided consent once they were able to provide consent on their own. EPA's rules allow for consent to be provided by a representative when someone is not able to give his/her own consent.

In terms of respect for subjects, it was clear in the consent form and protocol that subjects had complete freedom to withdraw at any time and for any reason. They were not paid for participation, and there were adequate protections for their privacy. They used subject information numbers, and their names were never provided to the sponsors.

The standards for documentation, §26.1303, did not apply because EPA located this study in the literature; it was not submitted to the Agency. The standard §12(a)(2)(P) did not apply because this study did not involve use of a pesticide. Also, 40 CFR part 26, subparts A and L do not apply

because the research was not conducted or supported by EPA, nor was it conducted or supported with the intention to submit the results to EPA. The Declaration of Helsinki would apply as an international standard, as perhaps would other standards in the UK. Ms. Sherman was confident that the protocol met the standards of the Declaration of Helsinki. The research was consensual and was not intended to harm the participants. In terms of EPA's decision regarding whether or not to rely on the study, the two applicable standards are 40 CFR §26.1703, which states that EPA may not rely on data involving intentional exposure of pregnant or nursing women or of children and prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A and L. All subjects were above the age of 18, and the female subject was not nursing or pregnant. EPA had adequate information, in terms of 40 CFR §26.1705, to conclude that the research was conducted under procedures at least as protective as those in subparts A through L. All of the subjects were provided informed consent, the risks were low, and there was appropriate risk mitigation. There was an independent ethics review and approval, and there was proper respect for subjects. Ms. Sherman concluded that the study was acceptable.

Board Questions of Clarification—Ethics

Dr. Popendorf requested clarification on whether the authors withheld treatment from the subjects. Ms. Sherman responded that researchers did ask the study site to minimize the use of other silver products on the patients so that it could be assumed that the serum silver was related to the Acticoat® products. Dr. Philpott noted that he had examined this issue and found that there were few silver-containing products that would have been used to treat these patients except for similar wound dressings. Thus, it was unlikely that treatment of these individuals was compromised; they simply received Acticoat® instead of another silver-based product that might have otherwise have been used. Ms. Sherman added that in terms of the ethics, medical needs of the patients would have taken precedence over the study.

Public Comments

Dr. Philpott offered members of the audience the opportunity to comment on the review of the *Moiemen et al.* study. No comments were offered.

Charge Questions

Ms. Sherman read the charge questions into the record:

- Is the Moiemen (2011) study scientifically sound, providing reliable data?
- If so, can the Moiemen (2011) study be used to support the Agency's conclusion that the dermal absorption factor for silver from nanosilver on human skin is less than 0.1%?
- Is there adequate information to support a determination that the study was conducted in substantial compliance procedures at least as protective as those at subparts A-L of 40 CFR part 26?

Board Science Review

Dr. Manautou stated that because this is the only study of this nature and the estimates and calculations are conservative, his answer to the first two questions was yes, but a qualified yes. Multiple deficiencies have been noted in the study, but at least it provides some benchmark estimates of absorption.

Dr. Popendorf answered yes to the first charge question, but was unsure of the second. He had strong reservations about the assumptions made to calculate the conservative absorption factor because they are not based on any realistic physicochemical model. They are inconsistent with the time frame, the back-calculation and the analysis. He suggested an alternative way to calculate absorption examining the steady-state levels. If it is assumed that absorption equals excretion, there are some excretion values using the half-life or the 1.5 percent per day, and using the calculated values as a time-weighted average during the steady state, that is the excretion and absorption dose per day. This could be calculated from the total dose, divided by days of treatment, multiplied by the dermal absorption factor. If this is conducted on Patient 1.02, it equals 0.001 percent absorption. His answer to question two, from a scientific perspective, was no. The model used to get the 0.1 percent was not scientifically justifiable.

Dr. Green concurred that the answer to question 1 was yes, and the answer to question two is yes with recommendations. Dr. Philpott added that the consensus thus far was that the Board did not find the 0.1 figure to be very accurate and that Dr. Popendorf has provided an alternate approach to get more accurate assessments based on the data at hand. The true upper bound likely is less than 0.1.

Dr. Manautou noted that he also struggled with question 2. He agreed with Dr. Popendorf that making calculations based on steady-state levels might be an alternative approach, but it would be difficult to calculate for Patient 1.01, who was treated with silver before the study began.

Dr. Lebowitz stated that this study was sound enough to contribute to the weight of evidence. The patients' systems would not correspond to a steady-state mass balance approach. He was reluctant to state that EPA's conservative estimate of 0.1 is inappropriate as part of the weight of evidence.

Dr. Johnson did not believe that this addressed the charge questions, but he thought that making inferences from these six patients about whether there is or is not a relationship was not appropriate.

Dr. Parkin commented that EPA's review did not include all of the assumptions made in EPA's calculations, and before the Board's report is finalized, it may be useful to ensure that key assumptions are captured.

Dr. Popendorf noted that the absorption of 0.001 is the same number that came from the *Gulson et al.* nanoparticle study that the Board reviewed in April 2011. He added that absorption through burned skin could be less than in intact skin.

Dr. Philpott summarized the Board recommendations for the Agency. Board consensus was that the answer to charge question 1, whether or not the study was scientifically sound, providing reliable data, was yes. The answer to charge question 2, as to whether or not the Moiemen study could be used to support the Agency's conclusion that a DAF for nanosilver on human skin is less than 0.1 percent seemed to be a very highly qualified yes. It is acceptable if it is part of the weight of evidence for a risk assessment, taking into account a large number of caveats, and with the recommendation that EPA be clear about the assumptions used in interpretation. Calculations made by Dr. Popendorf resulted in the figure 0.001, more like that seen in the Gulson study. The general conclusion was that as a very conservative upper band, using a 0.1 percent estimate in the overall weight of evidence to make risk assessments would be acceptable to the HSRB.

Dr. Fernandez expressed concern about question 1, providing reliable data with the small sample size of six, but would allow reliable data for establishing a baseline. Dr. Philpott asked if there were any objections to qualifying the yes to question 1 to say that the study provided reliable data to establish a baseline. Dr. Johnson agreed that the data may be reliable but the conclusions may not be. Dr. Young suggested that rather than saying the data were reliable to establish a baseline, the Board should state that they were reliable given the small sample size. Dr. Philpott noted that the revised consensus answer for charge question 1 was that the study was scientifically sound and provided reliable data for the small sample size.

Board Ethics Review

Dr. Sharpe again thanked Ms. Sherman for her review. She stated that yes, there was adequate information to support a determination that the study was conducted in substantial compliance with procedures at least as protective of those of subparts A through L of 40 CFR part 46. The only ethical concern, whether treatment was compromised because of the study, had been addressed.

Dr. Northington Gamble asked if the terms "next of kin" and "legal guardian" were used interchangeably, as they might not be the same. She noted that the Declaration of Helsinki was not regulatory, but there were regulations in the UK at the time of the study. For example, in 2000, the Central Office for Research Ethics Committees was formed, and in 2004, there were the Medicine for Human Use Clinical Trial Regulations, which state that it is against the law to conduct a clinical trial involving a medicine until there is a favorable opinion from an ethics committee or an authorization from a licensed Agency. Dr. Philpott agreed but said that this just added more evidence to support the finding. The fact that Ms. Sherman did not cite the UK regulations did not affect the high quality of her review. He commented, however, that there is no such thing as retrospective consent.

Dr. Philpott stated that the Board's consensus conclusion regarding whether or not there was adequate information to support a determination that the study was conducted in substantial compliance with procedures at least as protective as those at subparts A through L of 40 CFR part 26 is yes.

Dr. Young stated that the regression that was conducted was on the log-log scale, and she had been thinking that it was on the original scale. Therefore, much of what she had said was

incorrect. She wanted to put that on the record, and it would be corrected in her write-up. Dr. Philpott confirmed that she was referring to the review of the AHETF protocol. Dr. Young stated that this was correct, but she also was referring to the previous afternoon's AEATF protocol. Dr. Philpott noted for the record that, while it would not affect the Board's overall conclusions for either the AEATF or the AHETF protocol, Dr. Young had asked to correct her statements regarding objective two, namely her recommendation to reword it given her concerns about tests of proportionality.

Preview of Upcoming Meetings

Ms. Sherman stated that the Board would review two topics in January 2012, and this likely would be a 1-day meeting. One topic is an additional protocol from the AHETF on use of handgun sprayers in greenhouse and nurseries, and the second is an AEATF completed aerosol study. There may be no topics for review in April 2012.

Dr. Philpott thanked the Board members for their hard work and participation and turned the meeting over to Mr. Downing.

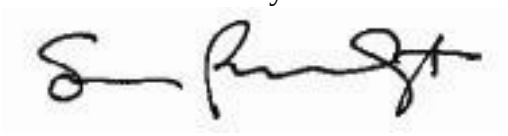
Adjournment

Mr. Downing stated that the next meeting of the HSRB would be held between the dates of January 24 through 27 of 2012, at the same location. A notice in the *Federal Register* will be published stating the exact dates and times that the HSRB will meet during that week in January. Mr. Downing adjourned the meeting at 2:51 PM.

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, Ph.D., M.S. 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
Statistical Training Specialist
SAS Institute, Statistical Training and Technical Services
Sparks, NV

*+Vanessa Northington Gamble, M.D., Ph.D. — Term: 10/19/2009–10/31/2012
University Professor of Medical Humanities and
Professor of History
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 T. Parkin, Ph.D., M.P.H.
Professorial Lecturer (EOH) Term: 10/1/2007–8/31/2013
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)
^ Present via telephone October 19-20, 2011
# Present on October 19, 2011 only
+ Present on October 20, 2011 only

Attachment B

Federal Register Notice Announcing Meeting

[Federal Register Volume 76, Number 187 (Tuesday, September 27, 2011)]
[Notices]
[Pages 59697-59699]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2011-24816]

ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-ORD-2011-0693; FRL-9472-4]

Human Studies Review Board (HSRB); Notification of a Public Meeting

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The U.S. Environmental Protection Agency (EPA) 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 19-20, 2011, from approximately 9 a.m. to approximately 5:30 p.m. Eastern Time. Comments may be submitted on or before Wednesday, October 12, 2011.

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2011-0693, 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 Avenue, 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 Avenue, 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-2011-0693. 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 electronic storage media you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes 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/.

SUPPLEMENTARY INFORMATION:

Location: The meeting will be held at the 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 ten business days prior to the meeting using the information under **FOR FURTHER INFORMATION CONTACT**, so that appropriate arrangements can be made.

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, ``Public Meeting,'' under subsection D. ``How May I Participate in this Meeting?'' of this notice.

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). This notice might also be of special interest to participants of studies involving human subjects, or representatives of study participants or experts on community engagement. Since many 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/.

[[Page 59698]]

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

EPA's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by the first of October 2011. 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-2011-0693 in the subject line on the first page of your request.

1. Oral comments. Requests to present oral comments will be accepted up to Wednesday, October 12, 2011. 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, under **FOR FURTHER INFORMATION CONTACT**, no later than noon, Eastern Time, Wednesday, October 12, 2011, 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, Wednesday, October 12, 2011. 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 Kleibacker listed under **FOR FURTHER INFORMATION CONTACT**. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. App.2 9. The HSRB provides advice, information, and recommendations to EPA on issues related to scientific and ethical aspects of human subjects research. The major objectives of the HSRB are to provide advice and recommendations on: (1) Research proposals and protocols; (2) reports of completed research with human subjects; and (3) how to strengthen EPA's programs for protection of human subjects of research. The HSRB reports to the EPA Administrator through EPA's Science Advisor.

1. Topics for discussion. At its meeting on October 19 and 20, 2011, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding these topics:

a. A new scenario design and associated protocol from the Antimicrobials Exposure Assessment Task Force II (AEATF-II), describing proposed research to monitor the dermal and inhalation of workers while pouring liquid antimicrobial pesticide products from both conventional and reduced-splash containers. 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 pour liquid antimicrobial pesticide products from conventional and reduced-splash containers, 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 workers who load liquid pesticides with closed system equipment. 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

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described, this research is likely to generate scientifically reliable data, useful for assessing the exposure of those who load liquid pesticides with closed system equipment, and to meet the applicable requirements of 40 CFR part 26, subparts K and L.

c. The unpublished report of the completed Carroll-Loye Biological Research, Inc. study No. Mas-003 to evaluate in the field the repellent efficacy against mosquitoes of a product containing 16% para-methane- 3,8-diol and 2% lemongrass oil. The protocol for this study was reviewed favorably by the HSRB at their meeting in October 2010. EPA seeks the advice of the HSRB on the scientific soundness of this completed study for use to estimate the duration of complete protection against mosquitoes provided by the tested repellent, 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.

d. A published report by Moiemen et al. (2010) of an intentional exposure human study measuring dermal absorption of silver from the use of nanosilver-containing wound dressings to treat major burns. EPA seeks the advice of the HSRB on the scientific soundness of this completed study for use in support of an assessment of the absorption of nanosilver particles through the skin, and on whether there is adequate information to determine that the study was conducted in substantial compliance with procedures at least as protective as those in subparts A-L of EPA's regulation at 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 regarding the Board's Final meeting report, will be found at http://www.epa.gov/osa/hsrb/ or from the person listed under **FOR FURTHER INFORMATION CONTACT**.

Dated: September 21, 2011.

Paul T. Anastas

EPA Science Advisor

[FR Doc. 2011-24816 Filed 9-26-11; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
OCTOBER 2011 PUBLIC MEETING AGENDA

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

Wednesday, October 19, 2011

10:30 AM* **Convene Public Meeting and Review Administrative Procedures –** Jim Downing (Designated Federal Officer, EPA Human Studies Review Board [HSRB], Office of the Science Advisor, EPA)
Introduction and Identification of Board Members – Sean Philpott, Ph.D. (HSRB Chair)
Welcome – Mary Greene, Ph.D. (Deputy Director, Office of the Science Advisor, EPA)
Opening Remarks – Steven Bradbury, Ph.D. (Director, Office of Pesticide Programs [OPP], Office of Chemical Safety and Pollution Prevention, EPA)
OPP Follow-up on Previous HSRB Recommendations – Mr. William Jordan (OPP, EPA)

Session 1: A completed Carroll-Loye Biological Research, Inc. (CLBR) study (No Mas 003) to evaluate the field repellent efficacy against mosquitoes of a product containing 16% para-methane-3,8-diol and 2% lemongrass oil

10:50 AM **EPA Science and Ethics Reviews –** Clara Fuentes, Ph.D. (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
11:20 AM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor
11:40 AM **Public Comments**
11:50 AM **Board Discussion**

Charge to the Board:

- Is the CLBR completed study No Mas 003 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?

- Does available information support a determination that the study No Mas 003 was conducted in substantial compliance with 40 CFR part 26, subparts K and L?

12:45 PM **Lunch**

Session 2: A new scenario design and associated protocol from the Antimicrobial Exposure Assessment Task Force II (AEATF-II), describing proposed research to monitor the dermal and inhalation exposure of workers while pouring liquid antimicrobial pesticide products from both conventional and reduced-splash containers

1:30 PM **EPA Science and Ethics Reviews** – Mr. Tim Leighton (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
2:30 PM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor
3:00 PM **Public Comments**
3:15 PM **Break**
3:30 PM **Board Discussion**

Charge to the Board:

If the AEATF liquid pour study proposal 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 exposure of individuals who manually pour liquid antimicrobial products?

- 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 2011 PUBLIC MEETING

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

Thursday, October 20, 2011

9:00 AM* **Convene Public Meeting and Review Administrative Procedures –** Jim Downing (Designated Federal Officer, EPA Human Studies Review Board, Office of the Science Advisor, EPA)
Introduction and Identification of Board Members – Sean Philpott, Ph.D. (HSRB Chair)
Follow-up from Previous Day – Mr. William Jordan (OPP, EPA)

Session 1: **A new scenario design and associated protocols from the Agricultural Handler Exposure Task Force (AHETF) describing proposed research to measure dermal and inhalation exposure to workers who use closed system equipment to load liquid pesticide products from returnable and non-returnable containers**

9:15 AM **EPA Science and Ethics Reviews** – Mr. Jeff Evans (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
10:00 AM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor
10:30 AM **Public Comments**
10:45 AM **Break**
11:00 AM **Board Discussion**

Charge to the Board:

If the AHETF closed system liquid loading study proposal 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 exposure of workers using closed systems to load liquid pesticide products from returnable or non-returnable containers?

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

12:30 PM **Lunch**

Session 2: A published report by *Moiemen et al* (2011) of an intentional exposure human study measuring dermal absorption of silver from the use of nanosilver-containing wound dressings to treat major burns

1:30 PM **EPA Science and Ethics Reviews –** Jessica Ryman, Ph.D. (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
2:15 PM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA
2:40 PM **Public Comments**
2:50 PM **Break**
3:05 PM **Board Discussion**

Charge to the Board:

- Is the Moiemen (2011) study scientifically sound, providing reliable data?
- If so, can the Moiemen (2011) study be used to support the Agency's conclusion that the dermal absorption factor for silver from nanosilver on human skin is less than 0.1%?
- Is there adequate information to support a determination that the study was conducted in substantial compliance procedures at least as protective as those at subparts A-L of 40 CFR part 26?

4:30 PM **Adjournment**