Draft Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
April 22–23, 2015 Public Meeting
Docket Number: EPA–HQ–ORD–2015-0145
HSRB Website: http://www.epa.gov/osa/hsrb

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

Date and Time:	Tuesday, April 22, 2015, 1:00 – 4:50 p.m. Wednesday, April 23, 2015, 9:00 a.m. – 12:00 p.m. (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:	Liza Dawson, Ph.D.
	Board Members:	Gary L. Chadwick, Pharm.D., M.P.H, C.I.P. George C.J. Fernandez, Ph.D. Kyle L. Galbraith, Ph.D. Edward Gbur, Jr., Ph.D. Jewell H. Halanych, M.D., M.Sc. Elizabeth Heitman, Ph.D. John C. Kissel, Ph.D. Randy Maddalena, Ph.D. William J. Popendorf, Ph.D. Kenneth Ramos, M.D., Ph.D., Pharm.B. Suzanne M. Rivera, Ph.D., M.S.W. Jun Zhu, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the meeting Agenda (Attachment C), unless noted otherwise.	

Tuesday, April 22, 2014

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 12:57 p.m. and welcomed Board members, EPA colleagues and members of the public. He thanked the Board members for their work in preparing for meeting deliberations. He wished all attendees a happy Earth Day.

Mr. Downing noted that in his role as DFO under the Federal Advisory Committee Act (FACA), he serves as the liaison between the HSRB and EPA and is responsible for ensuring that all FACA requirements are met. Also in his role as DFO, he must work with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied. HSRB members were briefed on federal conflict-of-interest laws, and they have completed a standard government financial disclosure report. An Agency ethics official has reviewed the reports to ensure that all requirements are met.

Mr. Downing informed members that there are two interesting topics on the agenda for the meeting. He noted that agenda times are approximate, and the group will strive to have adequate time for Agency presentations, public comments and the Board's thorough deliberations. All speakers, including Board members and members of the public, should use their microphone and identify themselves before speaking, as the meeting is being recorded and broadcast on the Internet. Copies of all meeting materials will be available at http://www.regulations.gov under docket number EPA–HQ–ORD–2015–0145, and supporting documents are available on the HSRB website at http://www.epa.gov/osa/hsrb. Following the presentations, time has been scheduled for the Board to direct questions of clarification to EPA staff and the 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. No members of the public had preregistered to make a public comment for the topics under consideration.

Meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and must be certified by the meeting Chair within 90 days. The approved minutes will be available at http://www.regulations.gov and on the HSRB website. The HSRB also will prepare a final report in response to questions posed by the Agency that will include the Board's review and analysis of materials presented. The final report will be available at http://www.regulations.gov and on the HSRB website. At this point, Mr. Downing turned the meeting over to the HSRB Chair, Dr. Liza Dawson.

Introduction and Identification of Board Members

Dr. Dawson welcomed the Board members. She asked Board members to introduce themselves, and members completed their introductions:

- Dr. Liza Dawson is at the National Institutes of Health (NIH) in the National Institute of Allergy and Infectious Diseases (NIAID). Her area of expertise is research ethics.

- Dr. Edward Gbur is a faculty member at the University of Arkansas. His area of expertise is statistics.

- Dr. Gary L. Chadwick is Professor Emeritus from the University of Rochester and a bioethicist with HRP Consulting Group, Inc.

- Dr. George C. J. Fernandez, previously at the University of Nevada-Reno, is a statistician at the SAS Institute.

- Dr. Kyle L. Galbraith is the Manager of the Human Subjects Protection Program at the Carle Foundation Hospital in Urbana, Illinois. He also teaches research ethics at the University of Illinois.

- Dr. Jewell H. Halanych is at the University of Alabama at Birmingham. She is a general internist and bioethicist.

- Dr. Elizabeth Heitman is a faculty member at the Center for Biomedical Bioethics and Society at the Vanderbilt University Medical Center. Her work focuses on international research ethics.

- Dr. John C. Kissel is at the University of Washington in Seattle. He is an exposure scientist.

- Dr. Randy Maddalena is at the Lawrence Berkeley National Laboratory. His expertise is in analytical chemistry and exposure science.

- Dr. William J. Popendorf is a Professor Emeritus in industrial hygiene at Utah State University.

- Dr. Kenneth Ramos is a Professor of Medicine at the University of Arizona. His expertise is in toxicology.

- Dr. Suzanne M. Rivera is an Associate Vice President for Research and a faculty member in the Department of Bioethics at Case Western Reserve University in Cleveland, Ohio. Her area of expertise is research ethics.

- Dr. Jun Zhu is a statistician at the University of Wisconsin-Madison.

Dr. Dawson next invited Dr. Thomas Burke (Science Advisor, EPA) to offer opening remarks.

Opening Remarks

Dr. Burke welcomed all attendees and thanked them for their service, both to the Agency and to the field of study, emphasizing the importance of their work, and expressed his pleasure at the opportunity to work with the HSRB. He thanked Board members for the extra time commitment they make to the Board over and above their daily jobs, and said that this work is probably the most important that any of them will do for the future of the field. Dr. Burke shared some of his background, as he assumed the position of Science Advisor in January 2015. Previously, he was Associate Dean at The Johns Hopkins University School of Public Health, and his background is in environmental epidemiology, making him familiar with the challenges of exposure and biomonitoring and implications for the subjects in research studies. Before Johns Hopkins, he was the Deputy Commissioner of Health for the state of New Jersey, where he dealt with such issues as chemical exposures and occasionally closing beaches due to problems with sewage treatment plants or dangerous debris. This gives him a both academic and regulatory

experience, which is a core challenge of the HSRB's work: the tension between moving forward in the protection of public health and ensuring that all work is both credible and ethical.

Dr. Burke suggested that public scrutiny; the balance between environmental protection, human health and regulatory considerations; and the need to protect the most vulnerable all contribute to the challenge of doing environmental science at EPA. He also stated that he was amazed at the breadth of the range of issues affected by EPA's work. When many academics are developing courses and curricula, they look to how the Agency deals with those subjects, and what lessons can be learned from that work.

Dr. Burke also emphasized that he will be an advocate for the HSRB's work during his tenure as Science Advisor. The work is challenging, and there are always multiple sides of every story. Credibility and ethics are paramount, as are, ultimately, the public health and environmental impacts of this group's decisions.

Dr. Burke closed by discussing the way scientists have been trained in specific disciplines affects EPA's work, because today's environmental challenges are not "stovepiped." He suggested that a more integrated training would benefit science students of the future, and he emphasized that the HSRB is an excellent example of how EPA has already been working to integrate science for very challenging issues.

Mr. Downing altered one meeting procedure before the presentations started. Participants on the webcast were encountering feedback from the microphones. He requested that participants turn off their microphones when not speaking to minimize the background noise on the webcast.

Dr. Dawson introduced the first presentation, *Completed Study and Monograph Report for Backpack and Handgun Application of Liquid Spray in Utility Rights of Way, by the Agricultural Handlers Exposure Task Force.*

Session 1: Completed Study and Monograph Report for Backpack and Handgun Application of Liquid Spray in Utility Rights of Way (Agricultural Handlers Exposure Task Force)

EPA Science Review

Mr. Matthew Crowley introduced himself and his work in the Health Effects Division on non-dietary, residential, non-occupational and occupational exposure assessments and EPA review studies. He presented a PowerPoint overview of the three main submissions from the Agricultural Handlers Exposure Task Force (AHETF).

The first submission, the AHETF field and analytical reports (AHE400), covered both the backpack and handgun applicator scenarios. The other two submissions, AHE1012 and AHE1013, broke apart the data and handled them as two separate scenarios, backpack and handgun applicators, respectively. Backpacks and handguns are both methods for applying pesticides in rights of way. Mr. Crowley gave an overview of his presentation, which was divided into issues common to both scenarios and issues specific to each scenario.

Overall, the study objective was to capture the range of expected dermal and inhalation exposures for workers making pesticide applications in the areas of the studies, which generally were utility rights of way and similar areas using backpack sprayers in one scenario and handgun equipment in the other. More specific study objectives related to data analysis. The primary data analysis objective was to determine whether the key statistics (i.e., geometric mean, arithmetic mean and 95th percentile) met the accuracy benchmark of threefold set in the protocol stage, that is, that these three key statistics were within threefold of the true value at least 95 percent of the time. (The threefold accuracy benchmark is described in the governing document for the AHETF.) The secondary objective was to see whether the data have enough statistical or analytical power to distinguish a proportional from an independent relationship between dermal exposure and the amount of active ingredient handled (AaiH).

The overall study design for both scenarios is in general outlined in the AHETF's Governing Document, which set out the overall approach for all of the AHETF studies. The document proposes a clustered sampling approach where selected locations (clusters) across the United States are chosen. Within each cluster, multiple workers are selected and monitored while performing tasks specific to the study objectives.

The "Backpack and Handgun Rights of Way Applicator Scenario Plan" protocol was first reviewed by the HSRB in 2010. The proposed design was to have seven spatially distinct locations (clusters) in each of which three workers would be monitored. This design is subsequently referred to as the "7 × 3" design. Locations were to be purposively selected but workers within each location were to be randomly selected in such a manner that would reflect the composition of the population of workers from that location. Detailed protocols for performing the required tasks, for the general classes of pesticides to be used, and for monitoring the worker's pesticide exposure were included in the plan.

Both inhalation and dermal exposure were monitored. Dermal exposure monitoring included hand washing and skin wipes for the head and neck. A whole-body dosimeter was used for the body and feet where skin was not directly exposed. For inhalation exposure, OSHA Versatile Samplers (OVS) were used.

Mr. Crowley presented a table of the limits of detection and limits of quantification for 2,4-D, Fosamine, Glyphosate, and Imazapyr for different monitoring matrices (i.e., inner dosimeter, socks, hand rinse, OVS air sampler per section and face/neck wipe). The source of the table was EPA's review of AHE400. There were very few results below detection or quantification limits other than the OVS tube back section.

As would be expected for any study like this, there were amendments to the protocol as well as deviations from the protocol. Mr. Crowley presented some of the amendments, which EPA overall found to be reasonable. The amendments were needed to aid in finding potential applicators. The task force encountered problems with both monitoring and recruitment, so a number of the amendments were for expanding monitoring sites and removing or relaxing restrictions to allow slight changes as to who was eligible to conduct the monitoring. Regarding protocol deviations, they are well documented and do not undermine or compromise the results.

To ensure that the data are reliable and documented well, with everything done according to protocol, the third-party Quality Assurance Unit (QAU) was used. The QAU ensures that studies follow EPA Good Laboratory Practice (GLP) Standards, including inspections onsite, checking equipment and ensuring adherence to regulatory guidelines, as detailed in the report. Along with a qualitative quality assurance program, there were also negative and positive field and laboratory control samples. For negative field controls, samples were put into the fields or nearby to see if there was any background contamination for any of the pesticides. Negative control blanks also were used. There were only a small number of detections in the negative controls but enough to justify making adjustments based on the negative controls. The positive controls were used to adjust the actual field monitoring results. The positive control samples were spiked and in the field were exposed to the same conditions as the workers. The results for the positive controls were within the normal range and generally acceptable.

Mr. Crowley displayed all of the results of the field fortification. The field fortification samples were usually done at three or four levels per cluster and ranged from 0.5 micrograms to 5,000 or 10,000 micrograms. Some of the samples were above the coefficient of variation (CV) of 25 percent, outside the optimal range, but the majority of the samples were between 70 and 120 percent average recovery and below a threshold of 25 percent CV.

Mr. Crowley turned to scenario-specific characteristics and results, starting with the backpack scenario. He read the scenario definition: "Application of liquid spray pesticides in utilities' rights of way or areas of similar terrain and foliage density/height/etc. using backpack equipment." The backpack workers loaded their backpack from a centralized tank, but importantly, they did not participate in mixing the chemical with water or mixing the solution. The scenario therefore does not represent exposure that occurs during the mixing process. The workers walk through the target area, an important difference from the handgun scenario where workers often ride tractors. Backpack workers often engage in "hack-and-squirt" applications (i.e., a direct, localized spray following a slice/cut to the base of a tree or bush). Three of the 19 applicators engaged in that scenario. Spraying occurs overhead and below the waist. The spraying sites are mostly utility rights of way, beneath transmission lines or around transmission pipelines where vegetation is being controlled to avoid equipment damage. Other similar spraying sites with dense vegetation include wildlife refuge areas, parks and drainage ditches.

Spraying and monitoring occurred in nine states across the United States over 3 years, and Mr. Crowley showed a map with the monitoring dates and locations, including types of sites. The original proposal was for seven locations, each with three applicators. The goal was efficiency in convening the research team at the field sites, but after encountering recruiting difficulties, the protocol was amended. For example, the West Virginia monitoring location was expanded to different states with "on-demand" style monitoring. In Indiana, only two of the planned three applicators were monitored, and the monitoring of these workers took place 1 year apart, which was not the original plan. The results for nine states over 3 years resulted in seven clusters, with an expanded definition of "cluster" to include multiple states and one or two applicators per cluster. The workers who were monitored were 19 males, with a wide range in age, work experience and body weight; all of them were commercial applicator employees, with no utility company employees. The original plan of "7 × 3" would have involved 21 workers. The AHETF spent 3 years on the research, with only one or two workers per cluster in some cases, but with the additional number of clusters it was anticipated that the data structure with

only 19 workers would meet the study objectives if the expanded definition of a "cluster" was used. It was determined that additional time spent to collect data for two more applicators to meet the original plan of 21 study participants would not be warranted.

Nine different models of backpack were used for the spraying. Although two workers might use the same model, they never shared the same backpack. The backpacks were 3 to 5 gallon tanks, hand-pressurized at less than 50 pounds per square inch, with the ability to spray up to 15 to 20 feet. Mr. Crowley showed the minimum, maximum and average application data, including how many times workers had to reload their tanks, the spray volume, the area that they walked (not the area sprayed), the time spent, and the amount of active ingredient handled.

Mr. Crowley described how the AHETF arrived at their exposure monitoring results. The hands were washed every time the worker took a break and at the end of the work day. All of the washes throughout the day are summed; some workers had one wash, while others had three or four, depending on the breaks workers took. For the head, the face and neck were wiped; multiple samples were combined for a single analysis to calculate exposure, with extrapolation to areas covered by eyewear and residue on the scalp. For the body, the whole body dosimeter was broken into six parts and sock dosimeters were added. The three exposure components were added together for a total dermal exposure. For inhalation, the OVS tube's front and back sections were analyzed separately and summed; the microgram value was then adjusted by the pump rate and the assumed breathing rate of 16.7 liters per minute for the workers in the study. An adjustment upward by a factor of two was made for the hands, face and neck wipes, referred to as a method efficiency adjustment (MEA), which was made to account for uncertainty in the efficiency of the exposure residue collection. The total micrograms of exposure are calculated and that figure is divided by the amount of active ingredient handled.

At a 2007 HSRB meeting, EPA proposed methods to address some inefficiencies in the hands, face and neck wipes results. The contributions of hands, face and neck exposures on average is greater than 20 percent; so EPA made a policy decision to double the values because it is a fairly significant contributor to exposure that should not be underestimated. Since then, the AHETF has submitted a report, which EPA is still reviewing, that calls for removal of the MEA factor. The dermal results used by EPA for the scenarios reviewed in this meeting used the MEA factor.

Mr. Crowley presented a graph of the backpack dermal exposure monitoring results normalized to the amount of active ingredient handled. The 19 dots represented each separate worker, with descriptive statistics (i.e., minimum, maximum, mean and 95th percentile) showing the broad range of dermal exposure. He presented the results with and without the MEA. In some cases, there was very little change because the contribution to the workers' total exposure was slight, but in other cases there was a sizeable impact from the adjustment. Overall, there was an average of 27 percent; the trigger for applying the MEA is greater than 20 percent. A similar graph of the backpack inhalation exposure results, normalized to the amount of active ingredient handled, included only 17 samples because two were invalidated. One sample had a pump malfunction, and the other lacked a sample because a non-validated method was used. The sample statistics show a fairly sizeable range.

In analyzing the raw data, three methods can be used. One is empirical using sample statistics for estimates; another is to assume a regression model under the assumption of simple random sampling; and the third is to fit a mixed model that explicitly incorporates the cluster design. There are different measures for accuracy, depending on how the data are fit. The first step is to determine if the data were fit by a log-normal distribution. Mr. Crowley presented normal and log-normal probability plots for dermal and inhalation exposures, noting that an analyst generally compares how well the data fit a straight line to determine the type of fit that is appropriate. Once a log-normal fit to the data is acceptable, the data structure is examined. There is a measure called the intracluster correlation (ICC), which measures whether there is any consistency when people are monitored at the same place or time, as occurred in both the dermal and inhalation monitoring. The AHETF considered this ICC. Mr. Crowley presented parametric statistics; considering the data structure and fit, the log-normal mixed model incorporating ICC was most appropriate. The arithmetic mean and 95th percentile were calculated, with confidence intervals (generated through bootstrapping through 10,000 simulations).

Discussing the primary objective for the backpack scenario, Mr. Crowley stated that the threefold accuracy benchmark was not met because the dermal "fold relative accuracy," or "k-factor," was greater than three. Had the original "7 × 3" approach been used, there would have had even less accuracy. The AHETF recognized that the primary objective was not met and with additional simulations showed that to bring the dermal k-factor below three, they would need additional monitoring of 10 to 16 applicators, which would likely take approximately another 5 years. EPA agreed with the task force to halt monitoring at 19 given the long time period that it would take to monitor 10 to 16 more applicators. Mr. Crowley showed results when the MEA factor was plotted for the dermal data. The MEA decreased the variability, resulting in the counter-intuitive result that there was a slightly smaller estimate of the arithmetic mean, with greater accuracy than without the MEA. Despite that result, EPA decided as a policy matter to continue using the MEA dermal data.

Regarding the secondary objective, the design study was to achieve 80 percent statistical power to distinguish independence from proportionality between the dermal exposure and the amount of active ingredient the applicators handled. The goal was not to determine whether proportionality is supported but whether the data allow proportionality to be examined. The AHETF used a mixed model regression to incorporate the structure of the data for a regression of the log of the exposure versus the log of the AaiH. Generally, analysts look for a slope of 1, and whether the power objective has been met is determined based on the width of the confidence interval of 1.4 or less. A graph plotting the dermal and exposure data showed a good proportionality fit, with at least 80 percent power. EPA's analysis incorporated additional analyses, examining potential effects from aspects of the data besides AaiH, such as differences between applicators who used the "hack-and-squirt" application and those who did not. EPA examined the results visually to determine if they pointed in any particular direction. There were no visible differences sufficient to pursue them from a regulatory perspective.

Mr. Crowley turned to the handgun scenario, presenting the information using a similar structure to that of the backpack presentation. The scenario definition was the same as for the backpacks, except that applicators used handgun equipment. The applicators did not mix the solution; they rode vehicles, or sometimes walked through the areas while spraying upward and downward; "hack-and-squirt" was permitted but not used by any of the workers. Sites were

generally the same as for backpacks, except that airport fence line and roadside sites were included. Monitoring was conducted across 10 states over 3 years, with closer adherence to the original protocol involving spraying at the same time and in the same spots and less "on-demand" style monitoring. In some cases, there were three applicators per cluster, and there were 13 clusters with one, two or three applicators per cluster. The 21 workers were similar to the backpack applicators; all were male, similar in the age range, work experience and weight range, but there was one commercial applicator owner and five utility company employees. Their equipment involved a handgun attached to a mechanical pump through a hose and reel mounted to trucks, all-terrain vehicles (ATVs) or tractors. There is no manual pressurization.

Sample statistics were calculated for spray pressure, spray volume, area range, time and AaiH. Both dermal and inhalation exposure estimates were done in the same way as for backpack workers. The MEA upward adjustment was used for the hand washes and face and neck wipes. The scatter plot with jittering and sample statistics showed that the exposure overall was lower for handgun workers. The twofold MEA adjustment produced a more even distribution throughout these workers; even though some had a low contribution, it was not the same result seen with backpack workers. The average contribution of head and face exposure was 30 percent, which triggers the adjustment. For inhalation exposure, Mr. Crowley showed a scatter plot with jittering of 21 points for normalized exposure and simple statistics. EPA conducted the same analysis of the data in terms of the fit, evaluating the ICC and primary objective, with log-normal probability plots of the data that showed a reasonable fit. The AHETF properly incorporated the ICC in their mixed model, also fitting log-normal distributions.

For the primary objective, the accuracy benchmark was met. The MEA adjustment for the handgun scenario did not have the same effect as for the backpack scenario because there was not much change to the variability when the adjustment was made. There was a more even distribution of the MEA factor so, as expected, the parametric statistics were all greater and no change in accuracy resulted, unlike with the backpack scenario. For the secondary objective, the objective was to show statistical power for proportionality analysis, as in the backpack scenario and data were analyzed with a mixed-model regression. The slope of the mixed-model regression line and the confidence intervals met the secondary objective to show statistical power for determining proportionality of exposure with AaiH. As with the backpack data, EPA examined additional characteristics of the data, such as workers who only rode their vehicles and sprayed versus those who also walked and sprayed. Results showed no notable differences in these subgroups. The details were available in additional slides that Mr. Crowley made available through his presentation but did not discuss.

In conclusion, Mr. Crowley stated that overall, the AHETF study design was acceptable to EPA and adequately captured the diversity of conditions to be expected under the scenarios. The methods used for monitoring were consistent with EPA guidelines and the prevailing research. EPA recognizes that the sampling approach that the investigators used requires the assumption that the 21 handgun workers and 19 backpack applicators are representative of all U.S. applicators in the application areas. Regarding the objectives, the AHETF did not meet the primary objective for the backpack applicator scenario, but did meet it for the handgun applicator scenario. Although EPA agrees with the AHETF that additional monitoring to meet the primary objective is probably not warranted because it would take a long time and not likely alter the conclusions drawn from the smaller data set, the Agency likely will incorporate that lack of

targeted accuracy as it moves forward with its exposure assessments. EPA will recommend that Agency exposure assessors use the data but incorporate the uncertainty. The Agency recommended use of the data for regulatory assessments with AaiH normalization as a default condition.

Dr. Dawson thanked Mr. Crowley for his presentation and opened the floor for the Board members' questions of clarification.

Board Questions of Clarification—Science

Dr. Popendorf asked about the basis for the assumed breathing rate of 1.67 L min^{-1}. Mr. Crowley responded that the rate was actually 16.7 L min^{-1} and the citation is a joint EPA-California Pesticide Regulation Department-Health Canada Department for Pesticide Regulation document that attempted to standardize exposure factors. For scenarios with hilly terrain where workers were on foot, backpack sprayers would be expected to have a higher breathing rate, although there were handgun applicators who rode in a vehicle throughout the work day.

Dr. Popendorf pointed out that there was a deviation from GLP that the spray mixtures were not characterized before use. Mr. Crowley replied that the initial product might not have been on hand at the site to sample for purity if diluted solutions were being sprayed. The labelled mixture had the amount of product. Dr. Popendorf countered that if the spray was mixed on previous days, the mixture might have been nonhomogeneous and it might have been difficult to get a representative sample. Mr. Crowley agreed that these were good points and indicated that because of experience in previous studies, in this study they had strived to get samples. It was rare that the concentration of product was very different than the label. All results of the purity analysis were provided when available, and an indication was made of how far off the actual concentration was from the label concentration. Dr. Dawson asked for further comment from a member of the Task Force.

Dr. Dave Barnekow, Dow Agrosciences, a member of the AHETF, added that the intention was to test the material prior to being onsite, but there were many times that there was no access to the spray material until the day of application. The concentrate would be sampled then. Dr. Popendorf asked for clarification that a sample was taken. Dr. Barnekow responded that the anticipated active ingredient can be calculated, but samples were taken to verify the amount. Dr. Popendorf asked if the tank mixes were looked at, and Dr. Barnekow responded that they were not. Dr. Gbur asked whether other herbicides were included in the tank mix other than the active ingredient being studied. Dr. Barnekow answered that many times a cocktail of herbicides was used in rights-of-way treatments. Dr. Gbur asked if there was any effect of the other ingredients on the mixture. Dr. Barnekow replied that there was not; these herbicides have been used together for a long time and all are compatible in a tank mixture. Dr. Gbur asked whether given the growing need for new products as resistance increases, future mixtures of herbicides might be an issue being part of a mixture. Dr. Barnekow answered that the most effective herbicides are used to reduce the chance of resistance arising.

Dr. Popendorf asked about the types of gloves that were used and whether they all were made of the same materials. Dr. Barnekow stated that usually nitrile gloves were used. Dr. Popendorf responded that four different chemicals were studied and not all gloves are

equally resistant to all chemicals. Dr. Barnekow referred to the possibility that hand exposure might have resulted from individual practices such as by the removal of gloves. Dr. Popendorf suggested that future protocols for multiple chemical exposures should be written to ensure that the best gloves are used. Dr. Barnekow stated that it was the applicators' choice which gloves to use. All of the herbicides had similar toxicology and formulations. The gloves were adequate for all four chemicals. In response to a question by Dr. Popendorf, Dr. Barnekow said that if an individual wanted to wear his own gloves, this was permitted as long as they were clean of the active ingredient. An individual might choose the gloves of a certain manufacturer if they preferred them.

Dr. Popendorf observed that for fortification sampling, the CVs mostly were 25 percent. Very few were observed of less than 20 percent. The atypical samples would be expected to be both above and below the 70 to 120 percent range. Mr. Crowley explained that in the analysis of fortification sampling, both mean recovery and the CV were being considered. A set of three samples might have a mean recovery of 40 percent but a very low CV, which would not necessarily be a bad result. An analytical chemist would be in a better position to say whether high recoveries or low CVs were a better result.

Dr. Popendorf asked how tall the leggings were and how often they were washed. Dr. Barnekow responded that they might reach as high as the thigh. They were designed to protect against brush. He was not sure who provided them. The applicators were asked whether the leggings were clean, and if they said yes, they were allowed to wear them. So whether or not the leggings were clean was self-reported.

Dr. Popendorf inquired how close the applicators were to the field investigators. Dr. Barnekow responded that if the applicators were out of view, it would have been because they had stepped into a hollow. Observers stayed as close as they could without interfering with the activity. The applicators were monitored fairly closely. If they were not observed, it would have been for a short time during which it was unlikely they were doing anything differently.

Dr. Gbur asked what weather variables were measured. Dr. Barnekow responded that the variables measured were primarily wind and temperature. These values were not used in any formal analysis. Temperature was used to monitor for heat stress. Temperature and relative humidity were the two variables most important for heat stress. Spraying was conducted when wind conditions were appropriate as specified on the product label.

Dr. Gbur wanted to know whether any formal lack of fit test was done to test the distribution of data, or whether any other distributions were considered. Mr. Crowley answered that to his knowledge, no formal goodness of fit test was performed. Larry Holden, a statistician from the Task Force, confirmed this. Log normality of the data was considered a reasonable approximation. The purpose of the monograph was not to do an exhaustive analysis of the data. The data themselves were the end product. The question asked in the study was how close the data were to the original design. Dr. Gbur agreed that the log-normal fit clearly was a large improvement over the linear fit, but he was concerned that there might be other better descriptions of the data. Dr. Holden agreed but noted that the data came with the caveat that the users of the data should use it for purposes that were most appropriate.

Dr. Kissel commented that the text of AHE400 stated that new gloves were provided by the Task Force, but that Dr. Barnekow had stated that the gloves worn depended on the mixture. Dr. Barnekow clarified that the same gloves were given regardless of the mixture because the nitrile gloves were the most general.

Dr. Kissel asked whether in the study the applicators used the same handgun or backpack that they usually used. Dr. Barnekow responded that they did.

Dr. Dawson asked why recruitment had been so difficult in the study. Dr. Barnekow replied that the investigators had started by collecting the names of all possible participants. The names went to a call center. Thousands were called, but only a few were willing to do the study. The investigators were asking to interfere with the applicators' daily activities, and candidates were very resistant. The investigators had no *a priori* relationship with the candidates. The investigators tried to remain as flexible as possible and to conduct the study at times that fit best with the participants' schedules. Recruitment was very challenging, took a long time and eliminated many people.

Dr. Heitman observed that all participants were male. Dr. Barnekow responded that there were few women to begin with in the pool. The participants represented the population that was willing to volunteer. Very few women do rights-of-way work. In the particular case of this study, no women participated.

EPA Ethics Review

Ms. Kelly Sherman discussed the ethics review of the study, which included the following:

- Examination of recruiting.
- Consent process.
- Subject demographics.
- Monitoring.
- Internal review board (IRB) oversight.
- Protocol amendments and deviations.
- Responsiveness to protocol reviews.
- Completeness of documentation.
- Substantive acceptance standards.
- Findings and conclusions.

Recruitment

Ms. Sherman's review found that the AHETF followed the recruitment process outlined in the protocol and the standard operating procedures (SOPs). The accrual process was expanded slightly through protocol amendments approved by the IRB to help the AHETF more easily find workers to recruit. The expanded language allowed the AHETF to recruit participants from multiple sites run by the same employer. It also allowed AHETF to accept referrals from one employer to speak to potential participants working for a different employer and for recommendations about applicators that did not show up in the database and public source search.

Consent Process

The review found that the AHETF closely followed the SOP for the consent process. The Study Director held private consent meetings with each participant to review the materials and answered questions. Two of the workers indicated that they preferred to speak in Spanish, so those two meetings occurred in Spanish with a bilingual researcher. Another worker self-identified as having low or limited literacy, so he selected a coworker to act as a witness who also participated in the meeting. The SOP had provisions for all of those possibilities during the consent process.

Demographics

The study included 40 participants, all of whom were male. As previously stated, two participants went through the process in Spanish. All participants were older than 18 years of age. No subject withdrew from the study at their own request, nor were any subjects removed for reasons of noncompliance with the protocol.

Monitoring

Ms. Sherman's review showed that the monitoring went relatively smoothly. There were no incidents of adverse effects or anyone feeling unwell or sick during the monitoring. The most significant risk—and therefore the aspect most closely monitored—was heat stress, which was included in a detailed section of the SOP and involved temperature, wind and relative humidity. Five monitoring units were cut short because they either reached the temperature target or came close to it. The AHETF followed all of the procedures that were laid out.

IRB Oversight

The study's initial protocols were reviewed by the Independent Institutional Review Board (IIRB) through a full convened meeting, and all the documentation was approved. The documentation dated back to after EPA and the HSRB reviewed the protocols in 2010 before the AHETF proceeded with the research and incorporated the comments that EPA and the Board provided. The subsequent amendments and deviations were all reviewed and approved or acknowledged.

During the study in 2012, IIRB was acquired by Schulman Associates IRB (SAIRB), so the documentation changed in terms of the name, but the oversight was continuous.

Protocol Amendments and Deviations

Ms. Sherman's review looked at the protocol amendments, some of which Mr. Crowley had covered in the first half of the day's presentation. Ms. Sherman also already had discussed the amendment that allowed additional sources of employers for recruitment. There were also amendments to the study's clothing restrictions, as many participants wanted to wear certain types of protective materials—the original protocol prohibited this, but that caused challenges for the recruitment process, so the protocol was amended to allow for the inclusion of those materials. A terrain restriction was relaxed as well to allow for an area that was similar to the terrain of a right of way to be monitored as well.

The ethics review also examined deviations and found that none of them were significant in terms of ethics and the effects on participants' rights, health or safety. One type of deviation identified was a shortened monitoring time or smaller number of loads handled because of the heat index cutoff. One additional deviation occurred in relation to the requirement that if a subject was going to take a restroom break, have a snack or smoke, they should wash their hands first; there was one instance when that did not happen before a participant smoked a cigarette. Another worker preferred to use his own gloves. The review found that none of these deviations were problematic from an ethical standpoint.

Responsiveness to Protocol Reviews

Ms. Sherman included in her review whether the amended protocol that was finally approved and executed incorporated the comments from EPA and the HSRB in terms of ethical aspects. She found that they addressed all of those comments adequately.

Completeness of Documentation

Ms. Sherman found that the documentation was very complete, that it was extensive, and that all of the requirements surrounding the documentation were fulfilled.

Substantive Acceptance Standards

The ethics review uses several acceptance standards when evaluating whether it is ethical to use the data from a study. One is 40 Code of Federal Regulations (CFR) §26.1703, which prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children, which was not a problem because every study participant was an adult above the age of 18 and there were no women.

Findings and Conclusions

Ms. Sherman's review concluded that there were no significant deficiencies in terms of the ethical conduct of the research. She found the protocol to be closely executed and that the deviations neither compromised the safety of the subjects nor impaired their informed consent. The subjects were fully informed and their consent was voluntary, and the procedures that were in place to prevent coercion or undue influence were all followed. She found the study to be conducted in substantial compliance with the regulations.

Board Questions of Clarification—Ethics

Dr. Maddalena asked whether, in the situations involving deviations or slight changes, the data were re-analyzed or checked, particularly for the participants who ended up on either the lower or higher ends of the distribution of the data analysis. Mr. Crowley asked for clarification or an example, and Dr. Maddalena shared the example that the study analyzed whether the individuals that did the slash-and-squirt technique happened to be outliers of the distribution of exposures and asked whether they did the same thing with participants who wore chaps. Mr. Crowley said that the study did examine the use of leggings or chaps—there was a plot and some discussion of it in the review. He also included the data as one of the supplemental slides not shown in his main presentation. He noted that in one case, despite the expectation that someone wearing chaps or leggings would have lower exposure, he recalls that this person had higher exposure, as though the chaps acted as a sink for the residue. Mr. Crowley went on to explain that there would have to be a very strong difference in that data plot for the study staff to split the data apart and examine why, because there were not a large number of samples and the data were not structured to examine large numbers of variables; the only variable the experiment was structured to examine was the amount of active ingredient handled.

Dr. Heitman thanked Ms. Sherman for her summary of the very extensive data set. She had a question about the way in which the notion of the protocol deviation is interpreted when there are also stopping rules that are SOPs. She questioned the use of the term "deviation" to describe a case when the study was modified or stopped according to an SOP that was part of the protocol. Dr. Heitman stated that this may be a matter of terminology, but expressed concern that a "protocol deviation" is when a protocol is not followed, and this study had SOPs giving specific conditions to stop monitoring. Ms. Sherman replied that perhaps it was unnecessary to report them as deviations; the reason they were reported as such was because they were outside the project limits for heat exposure. The SOP allows the study staff, during times of heat risk, to stop activities, wait in a cooler area, and then maybe resume if the temperature drops. In all cases, participants were close enough to completing their work that study staff decided to halt for the day. Ms. Sherman agreed that perhaps it was unnecessary to label those instances as "deviations."

Dr. Dawson asked if the Board had more questions. When there were none, she called for a break until 3:15 p.m.

Public Comments

Mr. Downing noted that people in room were having trouble hearing the speakers. He explained that the microphones are very directional. Speakers need to be very close to the microphone when speaking. Because of background noise, speakers also should remember to turn off their microphones when they are not using them. He then turned the meeting over to Dr. Dawson.

Dr. Dawson called for any public comments. There were none.

Charge Questions

Ms. Sherman read the charge questions into the record:

Charge to the Board—Science:

1. Was the research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph reports and associated field study report for AHE400 faithful to the design and objectives of the protocol, SOPs, and governing documents?

2. Has the Agency adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply liquid pesticide sprays to utilities' rights of way or similar areas using back pack or handgun spray equipment?

Charge to the Board—Ethics:

3. Does available information support a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

Board Science Assessment

Dr. Dawson asked Dr. Popendorf to address the first two charge questions. Dr. Popendorf commented that with regard to the first charge question, the AHETF did a good job of dealing with a difficult scenario. There were a large number of GLP deviations, but they all were well documented. The extra states added diversity while retaining randomization. The sampling scheme and the constraints of recruitment permitted the randomization to occur. There were no repeat measurements with the same applicator. There were only two pairs of workers with the same employer. A significant amount of diversity was built into the recruitment protocol.

Dr. Popendorf agreed with the Agency that the data set captured the behavior of the applicators.

Dr. Popendorf stated that the handgun scenario met its primary and secondary goals. The fact that the backpack applicator scenario did not meet the first goal is not surprising. Part of the reason the goal was not met was that the variation of exposure was larger than expected. The data ranged over five geometric standard deviations when four was expected. Dr. Popendorf agreed with EPA and the Task Force that meeting the threefold goal for accuracy for the backpack scenario was not worth extending the study. It would involve a large amount of time, cost and exposure, and different results would not be expected. Overall, he was inclined to conclude that the study met the first charge question.

Dr. Dawson asked for comments from the Board on the science assessment of the first charge question, and there were none. Dr. Dawson asked Dr. Popendorf to continue with his discussion of charge question 2.

Regarding the second charge question, Dr. Popendorf commented about the breathing rate and the small weakness in the data that the number of hand washes was highly variable. The

amount of time the chemical resided on the skin should have been minimized. Neither of these two concerns detract, however, from the overall conclusions. More could be done, however, in analyzing the data with a different approach.

Dr. Popendorf noted that the Agency indicated that it was open to reassessing the assumed breathing rates. Dr. Popendorf did not have a specific recommendation but certainly for backpack applicators, it is not a light work environment, and the breathing rate could be doubled. For handgun applicators' breathing rates, the data could be segregated by the time spent on foot versus in a vehicle. Because the inhalation route generally is less than 1 percent of the total dose, changing breathing rates will not have a significant effect on the overall study.

The hand washes varied from one to five, which is a significant amount of variability. This variability represents almost a fourfold range in the residence time of the pesticide on the skin. Dr. Popendorf pointed out that the longer the chemical remains on the skin, the more absorption takes place as opposed to adsorption on the surface. This might affect the amount of recovery. Hand doses were much higher than those on the face. Hand and face doses generally were only a quarter of the total dose, so multiplying by a MEA factor of two covers uncertainty about those doses. The highest four hand doses were 16 to 21 mg as opposed to the average of all of the others of less than 1. This represents a large statistical difference. It illustrates that there is a large capacity of the hand to hold a high dose. The high capacity indicates that the hand doses of all of the applicators with low doses was probably accurate.

A closer examination of the data would allow the formation of evidence-based conclusions about exposure. This would give confidence in the integrity of the study results. Most important, it would allow evidence-based applicator training to minimize exposure. There are 100-fold differences between the highest and lowest doses. This might represent an opportunity to improve work practices. With a reduction of exposure that is so large, there would be a strong incentive to change practices. Consideration of the site of application and the prevalence of overhead spraying did not find any patterns. Wearing chaps was anticipated to decrease exposure, but it actually increased it. There could be reasons to explain this difference. Among handgun applicators, it was anticipated that high spray pressure would increase exposure but of the three applicators with highest pressure, two had high exposure and one did not.

Dr. Popendorf showed graphs of exposure to upper body, lower body, hand and head for backpack and handgun applicators. He segregated the data into all applicators and the applicators with the top three exposed individuals removed. He described the predominance of body exposure when the high-exposure applicators were removed from the graphs. He suggested that interaction of two factors might explain the differences. It was surprising that there was a significant amount of lower body exposure. No single variable appeared correlated strongly to this, which indicates a need to look at the interaction of multiple factors on exposure.
Dr. Popendorf suggested examining foliage condition and the way in which applicators move through sprayed foliage. This could explain lower and full-body exposure. If an applicator sprayed high foliage and walked through the sprayed area, it would produce a pattern compatible with what was seen with a significant amount of upper and lower body exposure. The foliage sprayed needs to be characterized, which might not have been done, as well as field notes reviewed to see whether applicators walked through sprayed foliage. This would be an approach to explain high lower body exposure.

In a general comment about reviewing protocols, Dr. Popendorf cautioned Board members to be careful in the future when reviewing protocols to ensure that what was discussed in the meeting was adequately conveyed in the final report. In the protocol review of this study at a previous HSRB meeting, there was discussion of the foliage in the meeting minutes, but there was little of this concern expressed in the written report on the protocol.

Dr. Dawson thanked Dr. Popendorf for his review and asked Dr. Fernandez for his review of the statistics used in the study. Dr. Fernandez indicated that he would discuss limitations of the current method in estimating the standard deviation and the 95 percent upper confidence limit. Assuming a log-normal distribution, there are alternative methods to estimate the arithmetic mean, 95 percent confidence interval, and 95 percent upper limit. Dr. Fernandez used as an example the results from Table 4 of the report on handgun applicator results. The data were transformed to a log scale and were fit with a log-normal distribution. In this case, the results of the fit are needed to estimate the arithmetic mean and upper limits for exposure. It is important to use the proper method for making this estimation. The geometric mean and geometric standard deviation are calculated by exponentiating the appropriate log values from the log-normal fit. When transforming the mean directly back to the original scale, one does not get the correct estimator on the arithmetic scale. To get the correct arithmetic mean, it is necessary to add an adjustment factor of half of the error variance to the geometric mean and then exponentiating. The main concern here is estimating the upper limit. Assuming a two-parameter log-normal distribution, one sometimes underestimates the upper limit.

Software exists that can fit a three-parameter log-normal distribution. The software derives the parameter values from the data and reports whether it is a correct fit, testing whether it is a correct distribution. The data are plotted with a Q-Q plot to test whether the three parameters describe a log-normal fit and to obtain a 95 percent upper value, directly estimating the upper limit from the data. Dr. Fernandez tested this approach against the reported number for the two-parameter fit. He noted that he did an online search to see if there were other methods to compute an upper limit and found none. He did find one for estimating the arithmetic mean that used an adjustment factor to obtain the arithmetic mean from the 2-parameter log-normal geometric mean. He was not able to find a similar adjustment factor for the upper limit. The upper limit is given directly, however, by the 3-parameter fit approach. Dr. Fernandez recommended that the Agency determine that estimate as well and include it in the final report. He noted the method assumes that there is not an intra-cluster correlation. That is an additional factor because the study uses a cluster design. If there is significant intra-cluster correlation, the upper limit can be calculated both ways and both resulting upper limits can be reported. The results from one or the other method or the highest value could be chosen. Using the three-parameter approach, Dr. Fernandez found a 95th percentile upper value that was somewhat different than that obtained using the two-parameter approach. Because the methodology and software are available, Dr. Fernandez suggested that EPA consider using the three-parameter method in addition to existing methods.

Dr. Dawson asked for comments from the Board.

Dr. Popendorf indicated that it is unknown whether high hand exposure might be a result of glove penetration, permeation or breakthrough. It is not likely to be a result of mishandling alone. He raised the issue that nitrile gloves might not protect from all four ingredients. It is a

standard industrial hygiene approach to select gloves based on chemical-specific permeation. It is good practice to ensure that there are a sufficient variety of gloves to match each chemical.

Dr. Maddalena observed that more information might be gained from the data, but the data were not designed to provide that information. Subjects were not selected in a way to assess other factors, and the data were not collected in a way to explore other causes of variability. It is the role of the Board, however, to identify any possible limitations of the data.

Dr. Popendorf noted that there is the ability in the data to identify patterns of exposure that are important to the charge. He used a Student's t-test to identify groups with significantly different exposures from others. He found that there were significant differences. This begs the question of whether there was information collected to explain those differences. For example, how did the high dermal exposures occur? It would be unlikely for an applicator to spray themselves directly, but walking through high foliage that was sprayed is more likely. It is not a regulatory question but a labeling concern.

Dr. Dawson asked Dr. Popendorf if he would like to state in the report that there are limited conclusions that can be drawn from this study but future studies can be designed differently.

Dr. Popendorf responded that he believes that the data are there. Currently, it is not explained and has uncertainties, but if it were better explained, a better case could be made for evidence-based conclusions.

Dr. Gbur commented that the validity of the data is a separate issue from what it can be used for. All data have limitations. As statisticians, it is preferable not to use data for purposes for which the study was not designed. It is different to state that there is additional information that should have been collected.

Dr. Popendorf replied that there are uncertainties in the data. High hand exposure and a half-dozen very high clothing exposures are not explained. These values are different from the rest of the data as indicated by the results of a Student's t-test. They deviate from the log-normal distribution. Spraying foliage and walking through the sprayed foliage would explain the body exposure. It remains unknown how some applicators got very high exposure even though they wore gloves. It fits a different pattern that is not explained.

Dr. Dawson asked Dr. Popendorf whether he was concerned that the heterogeneity in the results points to something fundamentally different occurring. This might lead to questioning of the reliance on the data. It could be argued that because it cannot be explained why some of the data are so disparate, it is uncertain whether the data can be used in a particular way.

Dr. Ramos posed the question to Dr. Popendorf of whether he believed that the study was conducted in the way it should have been. If the answer to that is no, it could be because other things that could have been done were not done. If the answer is yes, the data could be used, but in the future, more information should be obtained.

Dr. Dawson asked for clarification from Dr. Popendorf as to whether he concluded that the answer to charge question 2 was "no." Dr. Popendorf confirmed that his answer was "no."

Dr. Ramos asked whether if additional data were available, they could be used to reinterpret the results.

Dr. Gbur cautioned against overanalyzing the data. They might provide useful pointers, however, to things that might be important.

Dr. Dawson suggested the following response to charge question 2: "There may be an opportunity to look for sources of variability in the data in a qualitative way to look for differences in procedures or individuals that might account for exposure differences." She raised the issue that if no evidence exists to explain the differences, it is unclear what action the Board should recommend.

Dr. Fernandez expressed doubt that the Board wanted to recommend another study to test for explanations of the high exposure values.

Dr. Popendorf proposed that EPA statisticians reanalyze the data. If there were categories for different foliage types and spray practices, there are statistical tests that can look for significant differences. Some of the differences in exposure are striking. It is possible that there exist categories that match those differences.

Dr. Gbur referred to the census paradox. If there is a population comprised of many subgroups, the relationships between them might be very different than their relationships to the whole population. If the study's data are divided into yes/no categories, some results that appear might be artifacts. Care must be taken when comparing between categories, especially with a small data set.

Dr. Dawson asked Dr. Popendorf for a formulation of his comment that expresses his concern about the unexplained variability of the data. Dr. Popendorf responded that more but different analyses of the data should be done to provide more confidence in their representativeness. Dr. Dawson inquired whether he meant formal statistical analyses, and Dr. Popendorf replied affirmatively.

Dr. Dawson recalled Drs. Gbur's and Fernandez' comments that conducting such statistical analyses with small data sets in ways for which a study was not designed can be treacherous. She asked if there was another way to look at the data that would be informative or useful in trying to interpret or understand them.

Dr. Popendorf responded that some of the Student's t-test differences were striking. He is not proposing a fishing expedition but rather re-examining the records to look for explanations of the differences. He did not want to specify more statistical tests. The Board has not considered the issue of gloves. That is a possible explanation. If even in a small data set there are significant differences, it would be good as a regulator to investigate whether there are explanations for those differences. These explanations might provide an opportunity in the future to train workers (i.e., not walking through sprayed foliage can reduce your exposure 100-fold). Not understanding variability is a limitation of a data set.

Dr. Fernandez proposed that outliers from the log-normal distribution be detected and data collected that is associated with those outliers. That would be a formal way to look for explanations.

Dr. Dawson suggested that the Board indicate that further exploration is warranted because of the high variability of the data. Formal statistical testing is not appropriate because that would not be in accordance with the way in which the study was designed. Descriptive explorations, however, could take place.

Dr. Maddalena noted that discarding data might be seen as unethical.

Dr. Dawson stated that there were no fundamental objections among the Board members to Dr. Popendorf's point as she had stated it. The differences were over the way in which it should be worded. Dr. Popendorf agreed to provide a statement regarding the issue of variability at the next day's meeting.

Board Ethics Assessment

Charge Question

Dr. Heitman read the charge questions into the record:

Charge to the Board—Ethics:

Does available information support the determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

Dr. Heitman's response was that the available information provided on the AHETF's completed study does support a determination that the studies were conducted in substantial compliance with those subparts.

More broadly, Dr. Heitman emphasized that there already is quite a bit of detail on this study. The original protocol was approved in May of 2010. There were items that were very useful to have in that report, but there also were things unmentioned that probably could have been included or expanded upon in more detail. The protocol was originally reviewed and approved in May 2010 by IIRB, which became part of SAIRB, an Association for the Accreditation of Human Research Protection Programs (AAHRPP)-accredited IRB registered with the Office of Human Research Protection. This satisfied the IRB review component. The HSRB reviewed the protocol and the IRB documents in October 2010, and the Board concluded at the time that with a few modifications, specifically the Informed Consent Document, as well as translating the consent materials into Spanish, the protocol was likely to meet the accrual requirements. The Office of Pesticide Programs (OPP) confirmed that these modifications were made prior to the initiation of the study, and the documents that the Board has reviewed also show that the requested modifications were made.

Recruitment began in February 2011, and by May 2011, the study had enrolled 40 participants, although recruitment took longer than expected. Researchers conducted 19 backpack monitoring units and 21 handheld monitoring units across 9 or 10 states—Dr. Heitman's notes do not match Mr. Crowley's presentation, which included one more state in its count. The protocol was written to include both men and women, although no women were enrolled. Participants were adults, ages 19 to 68; no children were enrolled.

The documentation indicates that all participants received approved information on the nature of the study, as well as its risks and procedures to minimize risk, and that these disclosures were provided to the participants in their choice of either English or Spanish, both orally and in writing. All participants signed the approved informed consent documents, one participant after hearing it read aloud to him in Spanish as he was self-reported to have low literacy skills. Participants received a total compensation of $100 for their time and participation in the study, and the study was closed in September 2013.

Over the study period, there were eight approved protocol amendments, which included changes to study sites and modifications that added certain items from participants' own personal protective equipment (PPE) to the list of accepted or required PPE. Some modifications expanded the list of prescribed analytic methods and expanded the list of approved analytic laboratories and personnel, although Dr. Heitman did not feel that those modifications had any discernable effect on the study's ethical characteristics.

There also were five reported protocol deviations. Dr. Heitman already had questioned whether those should be counted as protocol deviations. She suggested that "deviations" should refer to scenarios that were unexpected, whereas these five so-called deviations were scenarios accounted for in the protocols, such as the heat risk cutoff point—planned stopping based on criteria in the protocol that provide ethically appropriate protections for the study participants. She suggested that this is more a linguistic problem.

Of the true protocol deviations, the only event that appears to have had any potential effect on the study's ethical protections was the potential increased risk of exposure to a participant who smoked a cigarette during the monitoring period without first washing his hands. Dr. Heitman stated that whether he had additional exposure, either by skin or by mouth, was unclear.

Except as noted, Dr. Heitman agreed with the conclusions and observations of EPA's ethics review and found that the study substantially met the provisions of subparts K and L of 40 CFR Part 26. She emphasized that those exceptions are not necessarily objections but are notes that the identified risks were appropriately minimized, particularly the risk of heat-related distress and illness. There were no adverse effects reported and no withdrawals from the study. Stopping rules for heat stress were invoked on five occasions in various capacities, but Dr. Heitman reiterated that following the established stopping rules should not be considered protocol deviations; they were part of the protection against risk. She expressed concern that the study could be "dinged" by referring to these as "deviations" instead of something else. She suggested the Board consider alternative wording for those scenarios before the final report. There were no other incidents reported during monitoring. The extent of potentially increased risk of harm that accompanied periods of non-monitoring, both from intentional actions of

participants who broke protocol and turned off their monitors and personal intercoms, as well as the inadvertent failure of one personal air pump, is unknown. Dr. Heitman was not certain that the study could have been modified to achieve a more acceptable risk-benefit ratio.

Dr. Heitman expressed that the $100 compensation—$20 for taking part in the recruitment interview and $80 for participating in the spring—was not such a large amount as to be coercive but was sufficient to justly compensate participants for their effort in the study.

Dr. Heitman agreed that the study was well designed for the equitable selection of study participants. The original review from HSRB was that the study was designed to recruit an appropriately diverse population of people who represent the herbicide and pesticide sprayers in each of the areas where the study was conducted and to minimize selection bias. The three-phase recruitment process was intended to identify qualifying employment sites as well as to minimize the risk that potential participants would feel coerced to participate or coerced not to participate. Mr. Crowley noted that statistical inference requires the assumption that the sample is representative of all U.S. backpack and handgun applicator scenarios in applicable areas, and although the study protocol was written to include both male and female participants and had appropriate measures in place to exclude pregnant and lactating women, ultimately the participants were exclusively male. This caused Dr. Heitman to question whether and how the sample truly was representative of exposure for female workers, and it will be ethically important to consider—especially as changing labor trends may bring more women into this kind of work—whether the risks to women are appropriately represented in this sample.

Dr. Chadwick raised the question that, since this workforce tends to be predominantly male, whether the study could have gotten female participants without actively recruiting females and oversampling. He continued that, because this study is not evaluating the *effects* of exposure, only the *amounts*, it may not be as important an aspect in this particular study. Dr. Heitman clarified that she raised the issue predominantly as a question because there has been discussion about gender representation in these cases in the past, and because the study went to great lengths to write in the protocol the exclusion criteria for pregnancy and lactation and how to recruit women without recruiting potentially pregnant women. Because there were no female study participants, Dr. Heitman questioned the applicability of this study. She emphasized the changing labor market, where there are more women working in all areas that have traditionally had only male workers, and questioned whether others on the Board felt strongly that these data would be inapplicable to anyone outside of a male population in the regions of the study.

Dr. Dawson commented that members of the Task Force explained that if 99 percent of workers doing the spraying are men, it may be practically and logistically impossible to include female participants in the study. She and Dr. Heitman then expressed concern to Dr. Chadwick that if there are differences in physical strength between women and men, or differences in the height and arm length, then there could, in fact, be differences in the exposure results between genders. Dr. Dawson concluded that perhaps this is a comment for the future rather than a criticism of this particular study.

Dr. Dawson questioned whether there were events other than the heat-related stopping rules that were spelled out in the protocol that the study described as "deviations." Dr. Heitman

mentioned the participants who turned off their personal air pumps when they were not supposed to and the man who smoked a cigarette. Unlike the heat rules, however, those instances were not part of the protocol, and Dr. Heitman agreed that they were true deviations.

Dr. Dawson asked if there were any further comments from the Board. When there were none, she asked Dr. Heitman if her response to the charge question is "yes," and Dr. Heitman agreed that the study did substantially meet the standard. Dr. Dawson turned the meeting over to Mr. Downing. Dr. Galbraith questioned whether the Board needed to officially vote on the charge before closing the meeting for the day, and Dr. Chadwick reminded the Board that there was time on the next morning's agenda that could include the vote.

Mr. Downing agreed to hold the vote the next morning, when the Board would reconvene at 9:00 a.m. Dr. Dawson requested that the statisticians on the Board consider the wording about the deviations from Charge Question 2 prior to the meeting so the Board could discuss it before the vote. Mr. Downing requested a printout of the Board members' suggestions so he could make copies for the Board and make them part of the meeting's public record on the website. The meeting adjourned for the day at 4:41 p.m.

April 23, 2015

Commencement of Public Meeting and Review of Administrative Procedures

Mr. Downing reconvened the meeting at 9:05 a.m., introduced himself, and welcomed back the Board members, EPA colleagues and members of the public. He wished the attendees a happy day-after-Earth Day. Because there were new attendees, he reviewed the administrative procedures.

The Agency appreciates the Board members' time and efforts in preparing for this meeting. He and the Board members would like to thank their EPA colleagues for their work preparing for this meeting. Mr. Downing noted that in his role as DFO, he serves as a liaison between the HSRB and EPA and is responsible for ensuring that all FACA provisions regarding the operations of the HSRB are met. Also in his role as DFO, he must work with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied. HSRB members were briefed on federal conflict-of-interest laws, and each HSRB member has filed a standard government financial disclosure report. These reports have been reviewed to ensure that all ethics requirements were met.

Mr. Downing informed members that there is an interesting topic on the agenda for this day of the meeting on an insect repellent protocol. He noted that agenda times are approximate, and the group will strive to have adequate time for Agency presentations, public comments and the Board's deliberations. The meeting was being webcast over the Internet, so Mr. Downing reminded all of the Board members to be mindful of that when using the microphones.
Mr. Downing indicated that there was a public docket for this meeting. Copies of all meeting materials will be available at http://www.regulations.gov under the docket number listed on the agenda, and supporting documents also are available on the HSRB website. Following each of the EPA presentations, time has been scheduled for the Board to direct questions of clarification to EPA staff. This time is to be used for points of clarification rather than Board discussion. A

public comment period will be provided, and remarks must be limited to 5 minutes. Mr. Downing informed the Chair that he had no public comments to share.

Meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and must be certified by the meeting Chair within 90 days. The approved minutes will be available at http://www.regulations.gov and on the HSRB website. The HSRB also will prepare a report in response to questions posed by the Agency that will include the Board's review and analysis of materials presented, as well as the Board's advice and recommendations. The final report will be available at http://www.regulations.gov and on the HSRB website. Mr. Downing repeated his thanks to the Board members for their participation in this meeting and turned the meeting over to the HSRB Chair, Dr. Dawson.

Introduction of Board Members

Dr. Dawson wished the attendees a good morning. She requested that the members introduce themselves again. The Board members complied, providing their names, institutions and areas of expertise.

Follow-Up on Previous Day's Discussion

Dr. Dawson noted that there was an agenda item from the previous day's discussion that needed to be discussed further. The Board needed to finalize its consensus on its scientific review. She first introduced Mr. Crowley, who had requested the opportunity to provide more information about gloves.

Mr. Crowley acknowledged that the review he gave had not covered the topic of gloves as thoroughly as it could have. Yesterday, there had been discussion of the chemical resistance of the gloves that were used by the applicators. The types of gloves were documented in the submission. Most were nitrile, but others were rubber. The type provided depended on the recommendations on the product label. He presented a table of the resistance to different types of products by different types of gloves from Chapter 10 of EPA's *Label Review Manual*. All of the products used were in Category A (i.e., dry and water-based formulations). Mr. Crowley noted that there was internal correspondence within the company about ensuring that the correct gloves were used. From the table, it is evident that either nitrile or rubber were appropriate for Category A chemicals. He recognized that nitrile or rubber gloves might not apply to some chemicals, but this was not the case for those used in this study.

Dr. Popendorf stated that high hand exposure most likely resulted from penetration rather than permeation. He asked whether the gloves were open cuffed or tight fitting. Mr. Crowley replied that he did not have that information. He conceded that different types of cuffs might explain differences in exposure, but noted that permeation was not a factor.

Dr. Dawson asked Dr. Popendorf to read his recommendation on the science assessment into the record. Dr. Popendorf commented that the key sentence was the last one, but he read the entire reworded recommendation to the Board:

"The Board recommended using a higher breathing rate to estimate the inhaled dose of applicators while on foot. The Board also identified a heretofore small, unrecognized weakness

in the data resulting from the variability in the number of hand washes and the resulting average time that the deposits were allowed to reside on the skin before attempting removal; however, neither of these concerns was thought to have a major impact on the study's conclusions. In addition, the Board concluded that the inability to explain the high variability in general because of the high-end exposures in particular was a limitation of the study."

Dr. Dawson asked for comments on this response. She asked for a procedural clarification as to whether the Board normally included a similar level of detail in its response to a charge question. She proposed rewording it to include the last sentence noting that the high variability was unexplained. The details of the Board's analysis could be included in the body of the report. Dr. Popendorf responded that it was an option. The Board could simply say that there were three additional limitations. He deferred to the judgment of the Chair. Dr. Dawson elaborated that she was suggesting to the Board that its response to the charge be an overall statement that additional limitations have been identified and that they are discussed in more detail in the body of the report. Dr. Dawson asked if there was any dissent from this response. There was none.

Dr. Dawson indicated that no consensus had yet been reached on the Board's ethics assessment.

Charge Question

Dr. Heitman read the charge question into the record again:

Charge to the Board—Ethics:

Does available information support a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

Dr. Heitman read the proposed response, which she did not think needed further discussion:

"The available information provided on the Agricultural Handlers Exposure Task Forces' completed study of backpack and handgun application of liquid sprays in utility rights of way, AHE400, supports a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26."

Seeing no comments on the proposed ethics recommendation, Dr. Dawson closed the discussion of the agenda item, stating that a lack of dissent indicated that a consensus had been reached.

Session 1: Protocol for Field Testing of Skin Applied Mosquito Repellent Products (SC Johnson)

EPA Science Review

Mr. Kevin Sweeney summarized that SC Johnson submitted an insect repellent field testing protocol to determine the complete protection time (CPT) of the company's 18 skin-

applied repellent products to support the use of the EPA Repellency Awareness Graphic. Testing will be conducted in Florida and Wisconsin with 20 human subjects per product (10 at each site). The difference between this protocol and past protocols brought to the Board is that testing will be at a fixed dose, and there will not be a dosimetry phase.

Mr. Sweeney summarized that EPA's Repellency Awareness Program is designed to raise public understanding of the fact that skin-applied mosquito and tick repellants can provide health protection by raising consumer awareness, increasing EPA and consumer confidence in label claims, and improving protection against vector-borne diseases. Mr. Sweeney highlighted the protective features (i.e., species and time repelled) conveyed in the EPA Repellency Awareness Graphic. The graphic clearly informs consumers about the duration of repellent protection so that they can make informed choices about the repellent products that they purchase and use.

Mr. Sweeney reiterated the study objectives, which were to determine, using volunteer human subjects, the CPT of up 18 SC Johnson skin-applied products in the field against wild mosquitoes, ultimately to support use of the EPA Repellency Awareness Graphic on these product labels. The data from this research can be used by EPA to revise the Repellency Awareness Graphic and provide better protection of consumers from nuisance bites as well as preventing those bites that lead to arthropod-borne diseases. All test materials are EPA-registered SC Johnson skin-applied insect products that are minimally irritating to the skin and eyes. SC Johnson submitted data regarding the estimate of the margin of exposure (MoE) via the dermal route for each of the 18 products tested. The proposed exposures to the subjects in these tests are not of concern for the three active ingredients to be tested. Mr. Sweeney displayed the data tables submitted by SC Johnson, commenting that the data conform to any concern EPA may have and that the exposure of the subjects is absolutely minimal for DEET, picaridin and p-menthane-3,8-diol (PMD) products.

Rather than the typical dosimetry phase, SC Johnson has proposed that a standardized dose of 1.67 mg of product/cm^2, which is equivalent to 1 g/600 cm^2, will be applied to each subject. A set dose can be related to known consumer behavior based on past tests reviewed by the HSRB in which dosimetry was employed for skin-applied insect repellent products, so EPA developed a table based on available dosimetry data from lotion, aerosols and pump sprays. Based on the analysis of these studies and dosimetry data, 0.9 g/600 cm^2 (pump spray) and 0.8 g/ 600 cm^2 (aerosol) are recommended by EPA. The dose has been used in past publications. Formulation types to be tested include pump sprays, aerosols, lotions and towelettes; data may be bridged between the towelettes and pump spray because of the similar formulations.

Studies will be conducted in two U.S. locations: temperate forests in Wisconsin and swamp and marshlands in Florida. When unable to complete testing at U.S. sites, depending on the season, SC Johnson proposes to conduct testing at established sites in Cairns, Australia. Although the Australian protocol did not address all needed parameters (e.g., mosquito species, disease vectors, environmental conditions), additional information has been and subsequently will be submitted. Mr. Sweeney described the experimental design proposed by SC Johnson, which will include equal numbers of males and females and negative controls. The data collected from the negative controls will not be used in the calculation of the median CPT. For each product treatment there will be a total of 20 randomized, treated subjects and four negative

control subjects. The randomly selected subjects will be blinded, and a second product treatment group may be added to some of the field tests. Bodily location of the test (i.e., arms or legs) will be based on mosquito behavior on the day of the test. Mr. Sweeney summarized the experimental concentrations of the DEET, picaridin and PMD products. The concentrations between the towelettes and the pump spray will need to be compared.

The SC Johnson protocol clearly defines the endpoints and measure, and the unit of measure for determination of the repellent effects (i.e., CPT) is consistent with past studies. CPT will be calculated as time from application of each test substance to a subject and the first confirmed landing on that subject, defined as two landings of mosquitoes on treated skin within a 5-minute exposure period or in two consecutive exposure periods. Kaplan-Meier survival analysis will be used to calculate the median CPT; this is consistent with past studies, has been accepted by EPA and the HSRB, and is recommended by the World Health Organization. The proposed sample size of 10 subjects per field site represents a reasonable compromise between decreasing confidence interval width and limiting costs based on past analyses by EPA. SC Johnson also has put forth a variety of measures to ensure reliability as described in the submitted protocol and adequately addresses compliance with scientific standards. Refinement and clarification are required for experimental design and data analysis, particularly for the inclusion of Australian field-testing sites.

Mr. Sweeney highlighted EPA comments and recommendations on the SC Johnson protocol and the company's responses to improve the protocol. Regarding inclusion of field testing sites in Australia, EPA noted that the protocol does not specify possible sites or identify the endemic mosquito species at those sites. SC Johnson provided more details on established sites in Cairns, Australia, but EPA specified that the company should provide complete scientific details. EPA stated that the field site qualification should describe in more detail how the study director will know that the selected site was free from mosquito-borne disease transmission for 1 month prior to the start of the test, and SC Johnson responded that it would consult the U.S. Geological Survey, Centers for Disease Control and Prevention (CDC), and state health department websites for updates. In response to an EPA recommendation, SC Johnson will change "mosquito biting pressure" to "mosquito landing rate" in the protocol to reflect that landing rates rather than subject bites are counted and recorded in the study. EPA asked for further elaboration and explanation of the sample size, to which SC Johnson responded that the sample size is adequate and unlikely to overestimate CPT. EPA asked SC Johnson to describe how the data will be analyzed if the number of test subjects at the end of the test is less than 10 (i.e., if subjects withdraw) or alternates are used to replace subjects that withdraw. SC Johnson responded that Kaplan-Meier survival analysis accounts for missing observations, and subjects will not be replaced if they withdraw before their CPT is determined. EPA recommended that treatment allocation be described when testing is conducted on consecutive days with different products and when more than one test substance is tested per day. SC Johnson responded that subjects will be treated with only one test substance and different subjects will be recruited if a second substance is tested on the same day. A 1-day interval between each day of participation in testing will be followed. EPA asked whether treatment exposures will occur during periods of insufficient landing pressure and if treatment data are collected during these periods, how will they be used in CPT calculation. If they are not used, EPA asked how the lack of data will be considered in the Kaplan-Meier survival analysis and calculation of median CPT. SC Johnson responded that a limit on exposure periods with insufficient pressure is set to 10 percent and gaps

will be reported. EPA countered that this response does not mention how first confirmed landings will be addressed if there is a missing exposure period between landings. EPA recommended that the conditions for delaying the start of the test for test substances with expected longer CPTs should be fully described. SC Johnson replied that for DEET and picaridin with active ingredient amounts of 12.0 to 15.99 percent, the first exposure to the test system will be delayed 2 hours; for DEET and picaridin formulas with active ingredient amounts of 16.0 percent and above, the first exposure to the test system will be delayed for 3 hours after treatment. EPA asked SC Johnson to justify the lack of a positive control substance. SC Johnson responded that there was a lack of information on how the positive control data would be used to normalize the data. Based on dosimetry results, EPA considered the following to be appropriate doses for studies conducted under this protocol: lotion, 0.9 g/600 cm^2; pump spray, 0.4 g/600 cm^2; and aerosol 0.8 g/600 cm^2. SC Johnson responded that one dose regardless of formulation would reduce variability in the study. SC Johnson provided revised protocol sections to fully describe product application to the limb for pump sprays and lotions. SC Johnson also agreed to make protocol revisions to stipulate that all raw data accompany all study submissions, identify which limb was treated in the Appendix III data sheet, and provide more detail on data compilation and processing.

Ultimately, if amended to address the concerns described above, the SC Johnson protocol entitled, "Field Testing of SC Johnson Personal Mosquito Repellent Products to Support the Use of the EPA Repellency Awareness Graphic," likely will yield scientifically reliable information, satisfying the scientific criteria from the HSRB-recommended framework.

Board Questions of Clarification—Science

Dr. Maddalena asked whether the CPT is defined by EPA or if it has been introduced in different forms in the past. Mr. Sweeney responded that it has come in different forms in the past from the Board because of the nature of the data. The recommendation discussed with the Board was that survival analysis was the best method to analyze the data. Mr. Bayazid Sarkar, EPA OPP statistician, added that the Board has reviewed the analyses, presented to the Science Advisory Board, and estimated the median CPT using time-to-event analysis. The Board has approved the survival analysis approach, which is a non-parametric method.

Dr. Maddalena noted that the ultimate goal is to label a product using consistent data. He asked how the change from "bite" to "landing" to "first confirmed landing" has been made consistent. Mr. Sweeney responded that "first confirmed landing" has been used since 2006, when the studies first were brought forward; therefore, determination of CPT has been consistent.

Dr. Fernandez asked how the time period displayed on the product label was determined. Mr. Sweeney responded that the labeling reflected the median time. Mr. Sarkar added that each time on the label for a given pest is calculated with separate data and gives a point estimate of the median time to first confirmed landing. Dr. Fernandez did not think that the label was clear and asked whether it was explained in the fine print. Mr. Sweeney and Mr. Sarkar stated that the lower bound of the confidence interval was not reported. Dr. Fernandez asked whether it was standard practice to report only the median value. Mr. Sweeney indicated that this is common practice.

Dr. Gbur asked whether many dropouts or censored observations were expected in the studies. Mr. Sweeney replied that for the higher active ingredient concentrations, some subjects will stay during the entire test period. Generally, there have not been a lot of dropouts, so they are not expected. Dr. Gbur noted that it did not sound like the researchers expected a great deal of censoring, and Mr. Sweeney agreed.

Dr. Zhu asked whether the researchers had considered constructing confidence intervals. Mr. Sarkar replied that the confidence interval is calculated for each time when the data are analyzed. Dr. Zhu asked whether the researchers had a sense of the width of the confidence interval. Mr. Sweeney responded that it is not that wide for the median values, which were tighter than the mean values. Dr. Zhu inquired about the method used to construct the confidence interval. Mr. Sarkar replied that the confidence interval of the median was constructed by using the *proc lifetest* procedure in SAS® statistical software, which calculates a survival estimate with an associated confidence interval.

Dr. Zhu asked whether the median time disclosed on the label is described anywhere. Mr. Sweeney said that it is not described on the label because it is believed that there is no value in doing so. Dr. Halanych commented that medical products are often labeled without details about statistical calculations. Dr. Dawson thought that a general discussion about the label could occur separately from the protocol discussion, and if there was time, the label issue could be discussed with EPA colleagues.

Dr. Galbraith asked why two landings within a certain period of time are required. Mr. Sweeney explained that the second landing confirms the first. Dr. Galbraith requested clarification that only the first landing is measured. Mr. Sweeney replied that every landing is reported in the data tables.

Dr. Ramos asked Mr. Sweeney to elaborate on the reason for not using a negative control. Mr. Sweeney responded that there was concern about the number of bites that test subjects might receive if there were many negative controls. Dr. Ramos asked for clarification that it was not because of an inability to make these measurements. Mr. Sweeney explained that it could be done, but the decision was made to protect the subjects, particularly with the presence of the West Nile, Chikungunya and dengue viruses in the United States. Dr. Ramos noted that there are latencies to effect and loss of effect of the product, so the potential for bites remains.

Mr. Sweeney clarified that as soon as five landings occur, the measurements are stopped, which could occur in as little as 30 seconds, and the subjects no longer are exposed. Negative controls would need to be exposed for the full 5 minutes, and it would be more difficult to protect from bites, particularly with the large mosquito population at the Florida site.

Dr. Popendorf asked how the investigators choose which of the subjects' limbs to expose and whether this introduced any bias. Mr. Sweeney said that right or left limbs are chosen randomly and whether the leg or the arm is chosen will be based on how the mosquitoes at the site are landing the day of the test. Some species attack low and some attack high and low.

Dr. Popendorf asked whether the investigators' goal is high or low pressure. Mr. Sweeney responded that the intent is to reflect the landing pressure and biology of the

species at the site to ensure that the repellant is challenged adequately. Dr. Popendorf asked for clarification that the highest pressure is chosen, and Mr. Sweeney replied that he assumed that was the case.

Ms. Julie Palm, SC Johnson, added that the goal of choosing between the arm and the leg is to take the more conservative approach, choosing the limb on which more landings are occurring. The test sites are evaluated before the study to determine the most appropriate limb for the study.

Dr. Popendorf asked why the pump spray could not be used directly without the pipette. Ms. Palm responded that the product is removed from the packaging and applied with a pipette in the case of the pump spray and a spatula in the case of the lotion. Only the aerosol is applied directly from the packaging. The pipette traditionally has been used to ensure that the exact, calculated dose of product is applied. Dr. Popendorf asked about overspray in the case of the aerosol, which cannot be pipetted. Ms. Palm explained that through practice, aerosol can be applied in amounts close to the target dose.

Dr. Popendorf asked whether dosage information is contained on the label. Ms. Palm responded that this information is not on the label.

Dr. Maddalena asked about the criteria or definition for an established site. Mr. Sweeney said this is not stated specifically in the protocol. An established site is one that has been used before at which mosquito pressure is known. Ms. Palm confirmed that an established site is one at which SC Johnson has tested previously. Dr. Maddalena commented that it is beneficial that the company has previous experiences at the test sites to understand any hazards.

Dr. Maddalena asked whether the previous studies also follow the 5-minute increments used in this study. Mr. Sweeney explained that two different study routines have been used, and in each case the exposure period has been 5 minutes, either at 30- or 15-minute intervals. The 15-minute intervals are used to avoid gaps and obtain more data points. In response to a question by Dr. Maddalena, Ms. Palm explained that the time of landing can be recorded, and all landings within a 5-minute period are recorded. Dr. Maddalena was concerned about whether the number of staff members in the field is adequate to record all activity. Ms. Palm confirmed that enough staff members are present to record the landings.

Dr. Maddalena asked whether all landings are counted or if there are cases in which a mosquito lands, immediately leaves before taking a biting posture and is not counted. Ms. Palm responded that a landing is counted when a mosquito lands and is stationary.

Dr. Gbur asked whether established sites were free from mosquito spraying by government entities. Ms. Palm responded that the sites traditionally are not locations that are sprayed, and each site is tested prior to the study to ensure that there is adequate landing pressure. Dr. Gbur was concerned about a resistant mosquito population in areas that have been sprayed. Ms. Palm explained that resistance is not a concern for the active ingredients. Mr. Sweeney added that the mode of action for the active ingredients is repellency rather than toxicity.

Dr. Popendorf asked whether there are criteria for how precise the median needs to be. Mr. Tom Rosholt, Vice President at Morpace, Inc., and former statistician consultant for SC Johnson, replied that the statistical power of 10 subjects had not been calculated. In examining past studies, there was not a wide difference in the upper and lower bounds of the point estimate. Withdrawal from the study also was not seen. Dr. Popendorf asked for clarification that there were not criteria for the bounds. Mr. Rosholt agreed that the subject number of 10 was not based on specific criteria. He examined the analysis of past data, and the point estimate and lower bounds were not more than three times. Dr. Zhu asked what was meant by "three times." Mr. Rosholt responded that the upper and lower bounds are not more than three times the point estimate for the median. He described the upper and lower bounds for some of the studies. Dr. Zhu noted that a sample size calculation could be done to control the confidence interval. Mr. Rosholt said that the confidence interval is adequate.

Dr. Zhu asked for further details about the randomization of the protocol. Mr. Sweeney said that the randomization is described in the protocol, and SC Johnson could provide clarification. Ms. Palm explained that subjects' right or left limb are randomly selected based on their test subject number, which is randomly assigned.

Dr. Fernandez pointed out that that there is an option in the statistical analysis software, SAS, to calculate the sample size, and he wondered whether this analysis should be included in future studies. Dr. Dawson reminded the Board members to limit their questions to clarifications on the proposed study.

Dr. Chadwick noted that there are 10 subjects, two controls and four alternates at each site for each product. Ms. Palm explained that the alternates only are present in the morning in case test subjects do not show up or someone withdraws before the test is started. Dr. Chadwick asked whether there is a statistical reason that the two alternates are not treated in case a test subject left before the test is complete. Ms. Palm responded that the investigators are attempting to limit the exposure risk to as few people as possible. In terms of the statistical aspect of the question, Mr. Rosholt explained that using 12 versus 10 subjects would have a marginal effect on the confidence limit and would increase the number of people being exposed. With respect to the concern regarding use of the median rather than the lower confidence limit, the proxy to deal with uncertainty is to use the lower CPT of the two sites.

Dr. Kissel noted that, at EPA's recommendation, SC Johnson included in the MoE calculations an adjustment for differential adsorption efficiency observed. Did EPA examine whether the numbers were statistically different in making the recommendation to apply a correction factor? Mr. Sweeney replied that he was unable to comment, and staff from the Health Effects Division would need to provide this answer. He assumed that the recent registration review for DEET was considered.

In response to a question from Dr. Kissel, Mr. Sweeney explained that grams per centimeter squared (g/cm^2) referred to grams of product and not grams of active ingredient.

Dr. Dawson asked how often the websites with information about mosquito disease are updated. Mr. Sweeney replied that they are updated weekly by the CDC. The CDC's data feeds into the U.S. Geological Survey website, which is maintained regularly. Bird population by

county also is included in the website. Ms. Palm added that in the event that the website has not been updated recently, the investigators contact the state and mosquito abatement district to confirm any activity. The website is the first but not the only source for these data.

EPA Ethics Review

Ms. Sherman explained that the goal of this testing is to upgrade the efficacy data already on file and allow SC Johnson to be able to obtain the new EPA Repellency Awareness Graphic, which is similar to a sunscreen's SPF number and provides consumers with knowledge about how much protection the products provide. This provides societal value because it more clearly articulates the amount of protection, which is useful to consumers. Subjects will be recruited from a professional company that maintains a database of interested volunteers. Potential volunteers are contacted twice and given all of the necessary information about the study. The primary locations of the study will be Wisconsin and Florida, with the goal of completing the studies this summer so that the graphic can be applied to the label for next summer. If testing cannot be completed prior to the end of the U.S. summer, a site in Australia, following all Australian human testing laws, may be used.

The four main categories of risks to study participants are: (1) possible adverse reaction to test material; (2) exposure to biting mosquitoes or mosquito-vectored disease; (3) general risks of being in the field; and (4) loss of privacy or confidentiality. There are no direct benefits to the subjects; the primary direct beneficiary is the sponsor. Indirect beneficiaries will include repellent users who may be able to determine the duration of efficacy more easily via the graphic. Risks have been effectively minimized, particularly through training and exclusions of subjects sensitive to products or mosquitoes, and the risk-benefit balance is reasonable.

SAIRB reviewed and conditionally approved the protocol and informed-consent materials, and final approval is conditioned on the sponsor obtaining EPA and HSRB review and addressing EPA comments on the protocol. The consent form is complete and addresses all of the necessary elements required by regulations. Effective methods for protecting subjects' privacy have been implemented, and the proposed level of compensation ($60 for the training session, and $15/hour on the day of the study up to 8 hours and $18/hour after 8 hours) is appropriate. Subjects will be free to withdraw at any time, and medical care for research-related injuries will be provided at no cost to subjects.

This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under pesticide laws. The primary ethical standards applicable to the conduct of this research are found in 40 CFR 26, subparts K and L and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 12(a)(2)(P). Attachment 1 to the EPA Ethics Review contains a point-by-point evaluation of how this protocol addresses the requirements of 40 CFR 26, subparts K and L. SC Johnson has agreed to revise the protocol in response to each of EPA's comments. The EPA Ethics Review finds that the study protocol meets the applicable requirements of 40 CFR 26, subparts K and L.

Board Questions of Clarification—Ethics

Dr. Heitman stated that no rationale was given in the protocol for exclusion of non-English speakers. The goal of the pool of subjects was to be representative of the U.S. population. Ms. Palm responded that it was a goal of the study to get a good representation of all of the people who would use repellents. It was judged that given the amount of interaction needed between the subjects and the investigators, however, it was important to ensure that the subjects understood their instructions. Dr. Heitman noted that particularly for Florida, it was not representative to systematically exclude non-English speakers. There is no scientific reason to exclude them. Dr. Dawson suggested that this would be a good topic for the Board Discussion later. This period was intended for questions of clarification.

Dr. Heitman asked Ms. Palm whether SC Johnson employed interpreters. Ms. Palm replied affirmatively.

Dr. Halanych inquired whether there would be any effort to contact participants after the exposure to see if they had any symptoms of disease. Ms. Palm answered that participants will be given a 24-hour contact number.

Dr. Galbraith had a question about the reason for the age limit imposed on participants. Ms. Palm responded that the age limit was set at 55 because there was a risk from diseases such as West Nile virus in older adults.

Dr. Maddalena asked for an explanation of the statement that the company would contact participants if significant new findings occur and asked for an example of what a significant new finding might be. Ms. Palm explained that this was standard language in protocols particularly for medical studies. Any evidence that exposure to one of the active ingredients had put participants at greater risk than what was already explained to them would be such a finding.

Dr. Rivera pointed out that the protocol stated that the researchers would address claims of research-related injury of participants as covered under workers' compensation laws. This is not typical. It treats participants as if they were employees rather than volunteers. Ms. Palm answered that the protocol had been reviewed by SC Johnson's legal department. Dr. Rivera countered that normally subjects were not treated as employees. Ms. Sherman concurred. She had hoped that the reference to covering participants under workers' compensation laws was in an earlier version of the protocol. There were several versions that were amended by the IRB.

Public Comments

Dr. Dawson opened the floor for public comments.

Dr. Robin Todd, *i2L*Research USA, Inc., indicated that he had done a number of repellent studies. He voiced his support for using a single, standardized dose of 1 g/600 cm^2. He asserted that repellent studies need direct comparability and that they should not be subject to individual choice on how to apply products. He has run studies with this dose previously.

Dr. Ulrich Bernier, a research chemist from Gainesville, Florida, who has done repellent studies for the U.S. Department of Agriculture's Agricultural Research Service, also supported

SC Johnson's proposal of using 1 g/600 cm^2 because it is a standardized dosage that has been used historically.

Board Science Assessment

Dr. Dawson asked Dr. Maddalena to address the first charge question.

Charge Question

Dr. Maddalena read the first charge question into the record:

Charge to the Board—Science:

Is the protocol likely to generate scientifically reliable data useful for estimating the complete protection time of various EPA-registered, SC Johnson skin-applied mosquito repellents in the field against wild adult mosquito populations?

Dr. Maddalena proposed breaking the discussion into two parts: one on the protocol, which can be discussed fairly quickly; and the other on the metric/label itself, which may engender a longer discussion. For the benefit of those new to the Board, there may be some benefit from explaining more about the label. For example, Dr. Popendorf had commented that time to the first unconfirmed landing in addition to the first confirmed landing might add information. Issues of dose-response had been raised as well. Dr. Dawson agreed with the approach of discussing the protocol issues first, followed by more general issues.

The first key point is that there is somewhat of a disagreement between the Agency's approach of using a single dose and the Task Force's idea. Public comments had helped clarify the issue. Dr. Maddalena supported linking the metric to previous data as much as possible. There is a long history of measurements being made with a single dosage. He was comfortable with erring on the side of consistency and repeatability with the cost of being less representative, having already given up a considerable amount of representativeness with respect to the population and the use of the product. He noted that "application" might be a more apt term than "dose." The dose will differ depending on the concentration of the active ingredient in the product.

Another point relates to the randomization of selection of right or left limbs for the subjects. Dr. Maddalena understood that having the investigator select the limb was the most conservative approach, but he wanted to know what was gained by randomization at the expense of considering the subjects' handedness when they are being asked to protect themselves by using an aspirator. The protocol described in the detail the aspirating technique, the definition of a mosquito landing, and what constitutes a mosquito's biting posture. The mosquitos will be captured for further analysis. Clarification is needed about what is gained from randomization to right and left limbs given the tradeoff of some subjects using their non-dominant hand.

The delay period is expected to result in fairly long periods in the field. Delaying the start of exposure to mosquitos is reasonable, but Dr. Maddalena would like the delay period to be described more formally. The Agency had similar comments. SC Johnson had responded to EPA by specifying the waiting period for different products. He proposed instead that the company

specify that for a product that is expected to last 6 hours, they would wait "6 minus 'X' hours, with X being enough time to allow at least two full cycles." He would like the protocol to include the decision points that would allow consistency in the data with regard to waiting time. This is predicated on not changing the survival function. It assumes that efficacy will be a flat line until it approaches product failure or breakdown. If that is the case, he would like more details on how the waiting period is determined.

Regarding landing pressure, Dr. Maddalena speculated that landing pressure would correlate to some degree with product performance. He wanted clarification on whether there was some correlation or whether it was simply a case of having or not having enough landing pressure to do the test and if the landing pressure was sufficient to perform the test, the results would be independent of landing pressure. If there was a day with a high landing pressure or a day with low landing pressure and there was some correlation with efficacy, it would provide a lot more variability in the data.

An additional point is that subjects have the opportunity to repeat participation as long as there is at least 1 day between treatments. Dr. Maddalena asked whether there was any limitation on the number of times subjects were allowed to come back. At the extreme, it would not be desirable to have all the testing be performed on one individual. As written, there is no information in the protocol on limiting repetition.

Dr. Dawson asked Dr. Zhu for her statistical review. Dr. Zhu indicated that some of her initial comments were addressed. The discussion of randomization was very helpful. She agreed with Dr. Maddalena on the need for justification of the randomization protocol.

Alternative experimental designs could be used to make the comparison more comparable across products. This is a larger, more long-term question. There are principles of designing experiments that could be used. Randomization is good in experimental design. Blocking is another concept that is a way to control known sources of variation. Data can be collected from the same subject on multiple products.

Dr. Zhu also commented on the sample size. She continued to advocate for consideration of the way in which the sample size influences the confidence interval.

Dr. Dawson asked Dr. Zhu for clarification regarding whether she was calling for justification of randomization by limb or randomization by product. Dr. Zhu answered that whenever randomization was specified in the protocol, a rationale should be given.

Dr. Dawson asked if Dr. Zhu had a recommendation about blocking. Dr. Zhu replied that this topic could be deferred to the general discussion.

Dr. Dawson asked for comments from the Board members on Drs. Maddalena's and Zhu's reports. Dr. Popendorf asked for justification of the 1-day interval between repeat tests for subjects. He was concerned that is was not adequate and that there might be carryover.

Dr. Popendorf also commented that the landing pressure protocol likely would produce a large confidence interval for the median because of random events. The combination of the

landing pressure protocol and the dependency of product efficacy on concentration will introduce variability. The applicant should be aware of this potential problem.

Regarding application methods, Dr. Popendorf asserted that if acceptable amounts of product could be applied by aerosol, the same should be true with the pump applicator. There also should be a contingency plan if there is an overdose using the aerosol.

Dr. Popendorf also recommended that if five bites qualified as sufficient pressure, it might be valuable information to record the time of the fifth bite.

Dr. Gbur suggested that blocking might be used if subjects had repeated sessions. This would require further consideration.

Dr. Kissel expressed strong concern that the acute dermal toxicity estimates for the repellents were "fantasy numbers" with no basis in reality. They are based on dermal acute toxicity studies with rats in which the active ingredient is painted on. Such large amounts are applied that the dose never reaches the rat's skin. The Agency should discontinue use of this traditional protocol. Dr. Dawson added that this was a general comment that could be discussed later.

Dr. Ramos observed that the design of the experiment was based on there being a dose-response associated with the use of repellent. If the dose-response is too steep or too flat, it cannot be determined whether the active ingredient or something else such as the scent of the repellent is repelling the mosquitos. There is a need to know the shape of the dose-response curve. If it is observed that a low concentration is much less effective than the highest concentration, it will give confidence that the data reflect an active-ingredient effect response. Otherwise, confidence in the study will be compromised. Dr. Dawson asked whether Dr. Ramos was referring to the variation in dose among products. Dr. Ramos clarified that different DEET-containing products had concentrations ranging from 5 to 98 percent. Without a pharmacological effect of concentration, it will be difficult to determine what might be contributing to the efficacy of a given active ingredient-containing product.

At Dr. Dawson's request, Dr. Maddalena read his recommendation on the charge question into the record:

"The Board concludes that the protocol titled 'Field-Based Testing of SC Johnson's Personal Mosquito Repellent Products' supports the use of the EPA repellency awareness graphic, if modified according to Agency and HSRB recommendations, and is likely to generate scientifically reliable data useful for estimating the complete protection time, as defined in the protocol, of the various EPA-registered SC Johnson skin-applied mosquito repellents in the field against adult mosquitos."

Dr. Maddalena pointed out that this statement focused just on the protocol.

Dr. Dawson asked if there was any dissent or disagreement with Dr. Maddalena's recommendation.

Dr. Popendorf was not sure if the statement needed to be changed, but he expressed concern that the protocol might not produce reliable data for some of the products. Dr. Maddalena pointed out that the recommendation contained a caveat. Dr. Popendorf anticipated that some of the products would produce good data, but other products, such as those with low ingredient concentrations, depending on the bite pressure could have data with very wide confidence intervals. Dr. Dawson doubted that there would be changes to the protocol that might address this concern. Dr. Maddalena agreed with Dr. Popendorf's concerns. He pointed out that the data were being used to support the graphic. As such, median protection means median protection. Dr. Ramos agreed with Dr. Maddalena. It cannot be known until the data are collected what the dose-response will be. If the protocol is written in such a way as to yield these data, then the answer to the charge question should be "yes." Dr. Popendorf concurred.

There were no further comments. Dr. Dawson concluded the discussion of the first charge question. After the ethics discussion, the Board could continue with its discussion of more general scientific concerns.

Board Ethics Assessment

Charge Question

Dr. Chadwick read the charge question into the record:

Charge to the Board—Ethics

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

Dr. Chadwick indicated that the research proposal describes the risks to subjects and procedures to minimize those risks (e.g., the training session, temperature limits, first aid and 911 access, the 24-hour call number). The proposal has been reviewed and provisionally approved by SAIRB, which will provide oversight throughout the conduct of the study. It is a protocol for third-party research with the intention of submitting the resulting data to EPA. The applicable standards are 40 CFR Part 26, subparts K and L, in addition to the FIFRA provision that testing require fully informed and voluntary consent. The protocol has a consent process, and a form has been conditionally approved by the IRB. The protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Before the research is initiated, the protocol should be revised to reflect the comments of EPA and the HSRB.

Dr. Chadwick indicated that some specific discussion points have been identified. One concern is the representativeness of the sample in the pool. Selection of volunteers might not result in a representative sample. This is a generalizability issue. There was concern regarding the exclusion of non-English speakers, especially in Florida. Another point is whether there should be a limitation on the number of repeat tests per person. It is a risk minimization issue. There was concern about research being done outside of the United States where there might be different mosquito species and different vector-borne diseases. This is a generalizability issue. In the event that new information is discovered (e.g., a mosquito is determined to carry a vector-borne disease in the population where the subjects were tested, a product was found to be

contaminated), a process is needed so that subjects can be contacted. There was concern about whether the model for care and compensation for injury would be the filing of a worker's compensation claim, insurance or separate funding by the company. The consent form states that the study is being classified as confidential. It was uncertain what this referred to: data confidentiality or a restriction regarding disclosure to subjects.

Dr. Dawson asked Dr. Chadwick whether he had a recommendation that the protocol be changed to include non-English speakers. Dr. Chadwick responded that exclusions based on anything other than a scientific basis should be justified. The onus should be placed on the company to provide a rationale for excluding non-English speakers or to change the protocol. Dr. Rivera noted that the protocol ethics assessment indicates that volunteer selection is equitable. There is no indication whether the equitableness of exclusion of non-English speakers was considered. She agreed with the need to require a rationale from the company that all exclusions are equitable or to require that the company change its approach. Dr. Chadwick added that the company should provide a demographic breakdown of its pool of volunteers to the IRB. There is a presumption that there will be adequate representation of different subgroups of the U.S. population. If the company states that its volunteers are a representative sample, it should provide data to document this assertion. Dr. Dawson added that there are scientific and ethical reasons for requiring representativeness. The ethical reasons for requiring representativeness include the need for equitable access to the research benefits for all subgroups of the U.S. population. She recognized that there is no direct benefit to the participants. She noted that this protocol is not developing new interventions that might exclude certain groups from their use; the products tested are already on the market. If there is a concern that different products might work differently with different people, there is a scientific need to test them on a representative population. Dr. Rivera recognized differences between this protocol and that of a clinical trial, but she hypothesized that there might be variability in the uptake of the chemicals by subgroup. There could be benefit in having scientific knowledge regarding different populations because many agricultural workers are Spanish-speaking. Dr. Ramos commented that the presenter had stated the intention to have a sample that is representative of the population. The exclusion of Spanish speakers, therefore, conflicts with one of the stated goals of the protocol.

Dr. Halanych indicated that there is a need to weigh the benefits of dexterity from handedness against the benefits from randomization of body side left or right. It is a safety concern.

Dr. Halanych also noted that the symptoms of some diseases transmitted by mosquitos do not present until between 3 or 14 days after infection. It is important that the 24-hour hotline number is provided, but it also should be emphasized to participants that they should feel free to call the number after the study has ended if they have any concerns.

Dr. Popendorf noted that representativeness of the Florida population and that of the entire United States might be different. Dr. Dawson responded that at a minimum, a description of the two study sites demographics should be provided. There should be discussion of the representativeness of the volunteer population at both sites and how that relates to representativeness of the U.S. population.

Dr. Dawson asked Dr. Chadwick for his final recommendation. Dr. Chadwick indicated that he would not reiterate the discussion of the ethical issues that need to be changed in the protocol. He stated that his response to the charge question was the following: "The study will be conducted in substantial compliance with the requirements of 40 CFR 26 subparts K and L. The amended protocol when approved should meet all the appropriate ethical standards for the protection of human subjects in research and all requirements for documentation of ethical conduct of the research. This study is determined to be scientifically valid and relevant. There is no regulatory barrier for EPA's reliance on it under FIFRA."

Dr. Fernandez asked for clarification of whether the products tested will be marketed outside of the United States. He wanted to know whether there might be consequences from this research for other countries' populations such as in India. Mr. Sweeney responded that the data are used for EPA to satisfy requirements for labeling in the United States. Ms. Sherman added that some of these studies might be used in other countries for product registration, but EPA is concerned with U.S. product labels.

Dr. Dawson asked whether the Board members agreed with the recommendation. Dr. Kissel expressed his dissent. He stated that EPA's calculations of risk are indeterminate in the absence of further information. He therefore declined to approve the study. Dr. Dawson asked for clarification of whether Dr. Kissel believed a risk level can be determined based on the problems of determining dermal toxicity. Dr. Kissel replied that the risk level could be determined with more information. EPA would have to take a more rational approach, and he expressed doubt that this would occur. To meet the provisions of doing human subjects research, EPA has protocols that include doing MoE calculations, but the way in which they are done is not adequate. Dr. Dawson noted that this objection is not specific to this protocol but pertains to a larger problem. Dr. Kissel concurred that it was a generic problem that applies to this protocol. Dr. Dawson noted Dr. Kissel's dissent in regard to risk determination and asked for comments from the Board members. She indicated that Dr. Kissel's comment would be included in the final report. Dr. Chadwick asked whether this concern was something that the IRB would consider in its final risk profile. Dr. Kissel expressed doubt that the IRB would consider this issue or take into account his statements about the issue that he made in this meeting. EPA did conventional toxicology, which in Dr. Kissel's opinion was inadequate. If the IRB is comprised of conventional toxicologists, they would come to the wrong conclusion. Dr. Dawson stated that Dr. Kissel would like the state of the science to move forward. Dr. Dawson observed that IRBs would not be expected to represent the views of all scientists and might defer to the accepted wisdom in a particular area. Dr. Heitman asked whether the Board could give specific instructions on what should be examined. Dr. Dawson asked for Dr. Kissel's recommendation. Dr. Kissel responded that he would need to examine the dermal toxicity studies that were performed to make specific comments and determine if they have been interpreted incorrectly. Dr. Ramos pointed out that this protocol is not a toxicity study but rather is for products that are already on the market and have been approved for use. The Board is being asked to judge whether the protocol has been designed to enable the Agency to evaluate efficacy of repellency. He stated that Dr. Kissel's point was well taken and should be reflected in the report but goes beyond the charge question that the Board is being asked. Dr. Kissel clarified that he did not believe that the subjects were at great risk, but that belief was not based on EPA's calculations but rather on experience with the products as they have been used on the market. He stated that the criteria for the study being ethical are for EPA to have followed particular protocols

correctly, but he questioned the correctness of EPA's MoE calculations. Dr. Dawson proposed to the Board that there are issues about statistics and there are general issues about the protocol, but with the exception of Dr. Kissel's abstention, the Board agrees that the study is ethical to meet the goals as defined in the protocol with the suggested modifications. All of the Board members with the exception of Dr. Kissel, who abstained with the understanding that the issue would be included in the report, agreed that the protocol was ethical if the Board's concerns were addressed.

Board General Study Design Questions

Dr. Dawson noted that there were general study design questions that were raised in the discussion of SC Johnson's protocol that went beyond the particular study. The Board had agreed to discuss the general design questions—the statistical and reproducibility issues, rather than the dermal toxicity issues—separately from those on the protocol. She proposed to include the general design questions as an agenda item for the next HSRB meeting. Mr. Downing responded to Dr. Dawson's question that this suggestion would not represent a change to the current meeting's agenda. There were no alternative proposals from the Board. Mr. Downing indicated that he would discuss this proposal with his colleagues, but assumed that the proposal would be acceptable. Dr. Dawson turned the meeting over to Mr. Downing.

Adjournment

Mr. Downing stated that the Board had met its objectives in this meeting and it had been a productive meeting. He noted that the next meeting was scheduled for July 15–16, 2015. A notice of the times of the meeting would be issued in the *Federal Register* and posted on the HSRB website. Ms. Sherman pointed out that there were no topics as of yet for the meeting, and therefore, there likely would not be a July meeting. Mr. Downing stated that if the meeting did take place, it would be virtual rather than face-to-face. Mr. Downing adjourned the meeting at 12:22 p.m.

Respectfully submitted:

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

Certified to be true by:

Liza Dawson, Ph.D.
Chair
Human Studies Review Board
United States Environmental Protection Agency

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

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Liza Dawson, Ph.D.
Research Ethics Team Leader
Division of AIDS National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Bethesda, MD

Vice Chair

Edward Gbur, Jr., Ph.D.
Professor
Agricultural Statistics Laboratory
University of Arkansas
Fayetteville, AR

Members

Gary L. Chadwick, Pharm.D., M.P.H, C.I.P.
Senior Consultant
HRP Consulting Group, Inc.
Training & Consulting in Human Research Protections
Fairport, NY

George C. J. Fernandez, Ph.D.
Statistical Training Specialist
SAS Institute, Statistical Training and Technical Services
Sparks, NV

Kyle L. Galbraith, Ph.D.
Carle Foundation Hospital
Human Subjects Protection
Urbana, IL

Jewell H. Halanych, M.D., M.Sc.
Assistant Professor
Internal Medicine Residency Program
Montgomery Regional Campus
University of Alabama at Birmingham
Birmingham, AL

Elizabeth Heitman, Ph.D.
Associate Professor of Medical Ethics
Center for Biomedical Bioethics and Society
Vanderbilt University Medical Center
Nashville, TN

John C. Kissel, Ph.D.
Department of Environmental and Occupational Health Sciences
School of Public Health
University of Washington
Seattle, WA

Randy Maddalena, Ph.D.
Physical Research Scientist
Indoor Environment
Lawrence Berkeley National Laboratory
Berkeley, CA

William J. Popendorf, Ph.D. M.P.H.
Professor Emeritus
Department of Biology
Utah State University
Logan, UT

Kenneth Ramos, M.D., Ph.D., Pharm.B.
Associate Vice President
Precision Health Sciences
Professor of Medicine
Arizona Health Sciences Center
Tucson, AZ

Suzanne M. Rivera, Ph.D., M.S.W.
Associate Vice President for Research
Case Western Reserve University
Cleveland, OH

Jun Zhu, Ph.D.
Professor of Statistics and Entomology
Department of Statistics
University of Wisconsin-Madison
Madison, WI

Attachment B

FEDERAL REGISTER NOTICE ANNOUNCING MEETING

[*Federal Register* Volume 80, Number 43 (Thursday, March 5, 2015)]
[Notices]
[Pages 11986–11988]
From the *Federal Register* Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2015-05068]

==========

ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-ORD-2015-0145-0001; FRL 9923–83–ORD]

Human Studies Review Board (HSRB); Notification of a Public Webinar/Teleconference

AGENCY: U.S. Environmental Protection Agency (EPA).

ACTION: Notice.

Summary

The Environmental Protection Agency (EPA) Office of the Science Advisor announces a public meeting of the Human Studies Review Board to advise the Agency on the EPA ethical and scientific reviews of research with human subjects.

Dates

This public meeting will be held on April 22-23, 2015, from approximately 1:30 p.m. on Wednesday, April 22 to approximately 4:45 p.m. eastern standard time and on Thursday, April 23, 2015 from 8:30 a.m. to approximately 11:30 a.m. Comments may be submitted on or before noon (eastern standard time) on Wednesday, April 15, 2015.

Addresses

The meeting will be held at the Environmental Protection Agency, Conference Center, Lobby Level, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA 22202.

Comments: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2015-0145, by one of the following methods:

Internet: http://www.regulations.gov: Follow the online instructions for submitting comments.

Email: ORD.Docket@epa.gov.

Mail: The EPA Docket Center EPA/DC, ORD Docket, Mail code: 28221T, 1200 Pennsylvania Avenue, N.W., Washington, DC 20460.

Hand Delivery: The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue, N.W., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. eastern standard 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*.

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2015-0145. The Agency'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 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 email. 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 email comment directly to the EPA without going through *http://www.regulations.gov*, your email 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, the 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 the EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, the 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; email address: *downing.jim@epa.gov*; mailing address Environmental Protection Agency, Office of the Science Advisor, Mail code 8105R, 1200 Pennsylvania Avenue, N.W., Washington, DC 20460. General information concerning the EPA HSRB can be found on the EPA Web site at *http://www.epa.gov/hsrb*.

Supplementary Information

Meeting access: Ample seating is available at the meeting 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.

Webcast: This meeting may be webcast. Please refer to the HSRB Web site, *http://www.epa.gov/hsrb/* for information on how to access the webcast. Please note that the webcast is a supplementary public process provided only for convenience. If difficulties arise resulting in webcasting outages, the meeting will continue as planned.

Public Meeting

A. Does this action apply to me?

This action is directed to the public in general. This notice may, however, be of particular interest to persons who conduct or assess human studies, especially studies on substances regulated by the EPA, or to persons who are, or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act or the Federal Insecticide, Fungicide, and Rodenticide Act. 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 listed under FOR FURTHER INFORMATION CONTACT.

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

In addition to using regulations.gov, you may access this Federal Register document electronically through the EPA Internet under the "Federal Register" listings at *http://www.epa.gov/fedrgstr/*.

Docket: All documents in the docket are listed in the *http://www.regulations.gov* index. Although listed in the index, some information is not publicly available, *e.g.*, CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in *http://www.regulations.gov* or in hard copy at the ORD Docket, EPA/DC, Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue, N.W., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. eastern standard 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*). The Agency's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by the

last week of March 2015. 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, at *http://www.regulations.gov* and the EPA HSRB Web site at *http://www.epa.gov/hsrb/*. For questions on document availability, or if you do not have access to the Internet, consult Jim Downing listed under FOR FURTHER INFORMATION.

C. What should I consider as I prepare my comments for the 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 the 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 the EPA, it is imperative that you identify Docket ID number EPA-HQ-ORD-2015-0145 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, April 15, 2015. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via email) to Jim Downing, under FOR FURTHER INFORMATION CONTACT no later than noon, eastern standard time, Wednesday, April 15, 2015, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Official 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 Board 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 HSRB 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 standard time, Wednesday, April 15, 2015. You should submit your comments using the instructions in section I., under subsection C., "What Should I Consider as I Prepare My Comments for the 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 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 5 U.S.C. App. 2, sec. 9. The HSRB provides advice, information, and recommendations to the 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 the Agency's Science Advisor.

1. *Topics for discussion.* At its meeting on April 22-23, 2015, EPA's Human Studies Review Board (HSRB) will consider ethical and scientific issues surrounding the following topics:

a. A Completed Study and Monograph Report for Backpack and Handgun Application of Liquid Spray in Utility Rights of Way (Agricultural Handlers Exposure Task Force)

b. A New Protocol for Field Testing of Skin Applied Mosquito Repellent Products (SC Johnson)

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: February 20, 2015.
Thomas A. Burke,
Science Advisor.
[FR Doc. 2015-05068 Filed 3-4-15; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
APRIL 2015 PUBLIC MEETING AGENDA

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

Wednesday, April 22, 2015

HSRB WEBSITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA–HQ–ORD–2015–0145
Webcast of the HSRB Meeting
The Webcast of the meeting is at the following website:
https://epa.connectsolutions.com/hsrb

1:00 p.m.* **Convene Public Meeting –** Jim Downing, Designated Federal Officer, EPA Human Studies Review Board, Office of the Science Advisor
Introduction of Board Members – Liza Dawson, Ph.D., HSRB Chair
Welcome – Thomas A. Burke, Ph.D., M.P.H., Science Advisor, EPA

Session 1: **Completed Study and Monograph Report for Backpack and Handgun Application of Liquid Spray in Utility Rights of Way (Agricultural Handlers Exposure Task Force)**

1:20 p.m. **EPA Science Review –** Mr. Mathew Crowley (Health Effects Division, OPP, EPA)
2:05p.m. **Board Questions of Clarification** – Liza Dawson, Ph.D. (HSRB Chair), EPA, and Principal Investigator/Sponsor
2:30 p.m. **EPA Ethics Review -** Ms. Kelly Sherman (OPP, EPA)
2:45 p.m. **Board Questions of Clarification** – Liza Dawson, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor
3:00 p.m. **Break**
3:15 p.m. **Public Comments**
3:25 p.m. **Board Discussion**

Charge to the Board – Science:

1. Was the research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph reports and associated field study report for AHE400 faithful to the design and objectives of the protocol, SOPs, and governing documents?

*Agenda times are approximate and subject to change depending upon the discussion.

2. Has the Agency adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply liquid pesticide sprays to utilities' rights of way using backpack or handgun spray equipment?

Discussant: William Popendorf, Ph.D. (George Fernandez, Ph.D., statistics)

Charge to the Board – Ethics:

3. Does available information support a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

Discussant: Elizabeth Heitman, Ph.D.

4:50 p.m. Adjourn

*Agenda times are approximate and subject to change depending upon the discussion.

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
APRIL 2015 PUBLIC MEETING AGENDA

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

Thursday, April 23, 2015

HSRB WEBSITE
http://www.epa.gov/osa/hsrb/ Docket
Telephone: (202) 566 1752
Docket Number: EPA–HQ–ORD–2015–0145
Webcast of the HSRB Meeting
The Webcast of the meeting is at the following website:
https://epa.connectsolutions.com/hsrb

9:00 a.m.* **Convene Public Meeting –** Jim Downing, Designated Federal Officer, EPA Human Studies Review Board, Office of the Science Advisor
Introduction of Board Members – Liza Dawson, Ph.D., HSRB Chair
Follow-up on Previous Day's Discussion – Ms. Kelly Sherman, OPP, Office of Chemical Safety and Pollution Prevention, EPA

Session 1: **Protocol for Field Testing of skin applied mosquito repellent products (SC Johnson)**

9:10 a.m. **EPA Science Review –** Mr. Kevin Sweeney, (Registration Division, OPP, EPA)
9:30 a.m. **Board Questions of Clarification** – Liza Dawson, Ph.D. (HSRB Chair), EPA, and Principal Investigator/Sponsor
10:00 a.m. **EPA Ethics Review –** Ms. Kelly Sherman (OPP, EPA)
10:20 a.m. **Board Questions of Clarification** – Liza Dawson, Ph.D. (HSRB Chair), EPA, and Principal Investigator/Sponsor
10:45 a.m. **Public Comments**
10:55 a.m. **Break**
11:05 a.m. **Board Discussion**

If the SCJ study proposal is revised as suggested in EPA's science and ethics reviews and if the research is performed as described:

Charge to the Board – Science:

- Is this research is likely to generate scientifically reliable data, useful for assessing the efficacy of these insect repellent pesticide products?

Discussant: Randy Maddalena, Ph.D. (Jun Zhu, Ph.D., statistics)

*Agenda times are approximate and subject to change depending upon the discussion.

Charge to the Board - Ethics:

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

Discussant: Gary Chadwick, Pharm.D., M.P.H, C.I.P.

12:05 p.m. Adjourn

*Agenda times are approximate and subject to change depending upon the discussion.