Draft Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
October 19–20, 2016, Public Meeting
HSRB Website: www.epa.gov/osa/human-studies-review-board

Committee Members:	(See EPA HSRB Members List—Attachment A)	
Date and Time:	Wednesday, October 19, 2016, 1:00–5:00 p.m. EDT	
	Thursday, October 20, 2016, 1:00–5:00 p.m. EDT	
	(See *Federal Register* Notice—Attachment B)	
Location:	Via Teleconference and Webinar	
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.
	Vice Chair:	Edward Gbur, Jr., Ph.D.
	Board Members:	Jennifer Cavallari, Sc.D., CIH Alesia Ferguson, Ph.D. Kyle L. Galbraith, Ph.D. Jewell H. Halanych, M.D., M.Sc. Walter T. Klimecki, D.V.M., Ph.D. Randy Maddalena, Ph.D. Suzanne M. Rivera, Ph.D., M.S.W. Jun Zhu, Ph.D.
	Consultant to the Board: Kendra L. Lawrence, Ph.D., BCE, PMP	
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the Meeting Agenda unless noted otherwise.	

Wednesday, October 19, 2016

Convene Public Meeting

Mr. Jim Downing (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor [OSA], EPA [or the Agency]) convened the meeting at 1:02 p.m. and welcomed Board members, EPA colleagues and members of the public. He expressed appreciation to the Board members for their service and thanked EPA's Office of Pesticide Programs (OPP) for preparing for this meeting. As DFO, Mr. Downing, under the Federal Advisory Committee Act (FACA), serves as liaison between the HSRB and EPA and is responsible for ensuring that all FACA requirements are met regarding the operations of the HSRB. 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 have completed a standard government financial disclosure report, which has been reviewed to ensure that all ethics requirements are met.

Mr. Downing informed the Board that two interesting topics will be discussed during the meeting. He noted that agenda times are approximate, and the group will strive to allow adequate time for Agency

presentations, public comments and the Board's thorough deliberations. To ensure a successful virtual meeting, all participants should mute their lines when not speaking and state their names before providing remarks to ensure accurate attribution. Copies of all meeting materials will be available on the HSRB website at www2.epa.gov/osa/human-studies-review-board. 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 period is scheduled for public comment, during which each remark must be limited to 5 minutes.

In accordance with FACA requirements, 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 on the HSRB website at www.epa.gov/osa/human-studies-review-board. The HSRB also will prepare a final report in response to questions posed by the Agency, which will include the Board's review and analysis of materials presented. The final report will be also available on the HSRB website at www.epa.gov/osa/human-studies-review-board. Mr. Downing then turned the meeting over to the HSRB Chair, Dr. Liza Dawson.

Virtual Meeting Operations

Dr. Dawson reviewed the operating procedures for the virtual meeting. She informed Board members to use the feature of Adobe Connect meetings that allows them to raise their hands in the webinar to be recognized by the Chair when offering comments. When voting, the Board members will use the polling function in the webinar to agree or disagree with the proposal.

Introduction of Board Members

Dr. Dawson welcomed the Board members and asked them to introduce themselves, providing their names, affiliations and areas of expertise. Dr. Downing introduced three new members to the Board: Dr. Jennifer Cavallari, Assistant Professor, Division of Occupational and Environmental Medicine, University of Connecticut; Dr. Alisa Ferguson, Associate Professor, Department of Environmental Health, University of Arkansas; and Dr. Walter T. Klimecki, Associate Professor, Department of Pharmacology and Toxicology, University of Arizona. He also pointed out that regarding the special study on permethrin-treated clothing for the U.S. military, Dr. Kendra L. Lawrence, Health Sciences Product Manager, U.S. Army Medical Materiel Division Activity, was appointed consultant to the Board in 2016.

Opening Remarks

Dr. Thomas Sinks, Director, OSA, expressed appreciation to the Board for its hard work and time taken to review topics related to human subjects research. He also thanked EPA's Office of Pesticide Programs (OPP) for its efforts in preparing for the meeting. He informed the Board that Dr. Toby Schonfeld, EPA's former Human Subjects Research Review Official, is now the Deputy Director at the National Center for Health and Ethics at the U.S. Department of Veterans Affairs. Dr. Sinks noted that Dr. Daniel K. Nelson, Director, Human Subjects Research Protocol Office, National Health and Environmental Effects Laboratory, EPA, is on detail to OSA until a permanent replacement is named. Dr. Sinks joined Dr. Dawson in welcoming new Board members and the public to the meeting. He introduced the topics that will be discussed at the meeting: (1) Protocol for Laboratory Evaluation of Mosquito Bite Protection from Permethrin-treated Clothing for the U.S. Army after 0, 20 and/or 50 Washings; and (2) A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial. EPA looks forward to the Board's review and advice on these topics.

Brief Update on the Research Discussed at the Last HSRB Meeting

Ms. Maureen Lydon, OPP, updated members on the actions taken since the July 2016 meeting. Two agricultural handler exposure studies were discussed at the July HSRB meeting. One study focused on wettable powders and the other on water soluble packets. The Agricultural Handler Exposure Task Force (AHETF) conducted an exposure study to develop data to determine the potential dermal and inhalation exposure for workers who mix and load water soluble packets into mixing tanks so they can be applied as liquid sprays. As a reminder, water soluble packaging (or WSP) is an engineering control designed to prevent direct contact between workers and the pesticide formulation in the packages. Preventing direct contact reduces exposures. WSPs dissolve in water and release the formulation into the water without forming a dust or liquid aerosol that could contact workers. The formulation then either dissolves in the water or becomes suspended so it can be applied as a liquid spray. During the initial stages of the field study discussed in July, the task force identified work practices that EPA agreed ran counter to the use of water soluble packets to reduce exposures. For example, the task force observed that some workers placed the water soluble packets in removable baskets hanging from the open hatch and then used streams of water from hoses or overhead recirculation systems as agitation methods to break open and dissolve the WSPs. This caused visible amounts of airborne powder and liquid aerosol that came out of the mix tanks where the mixer/loader was working. The current WSP labels are silent or unclear on the use of baskets in the hatch and methods of agitation.

The Agricultural Handler Exposure Task Force, in consultation with EPA, California's Department of Pesticide Regulation (CDPR) and the Canadian Pest Management Regulatory Agency (PMRA), drafted a set of best practices for handling and adding WSPs to spray tanks. These draft instructions are aimed at ensuring that WSPs are allowed to dissolve in water and preventing them from being ruptured by streams of water or other means. In order to achieve the intended benefits from the new procedures for the proper use of water soluble packets, OPP believes that the updated procedures should be incorporated into labels for water soluble packets, and users should be trained on the new procedures.

After obtaining the HSRB's input in July, EPA solicited comment from the State FIFRA Issues Research and Evaluation Group or SFIREG. SFIREG is a network of state officials that offers advice to EPA on pesticide regulatory and enforcement matters. OPP asked SFIREG for their comments on the updated procedures and revised label language as well as several other questions. For example, EPA asked if SFIREG thought the revised label language was enforceable, about the best ways to reach handlers using water soluble packets (WSPs) in order to inform them of recommended practices for mixing/loading instructions, the preferred timing for reaching handlers of WSPs, comments on EPA's draft educational slides, and other outreach that EPA, the states and/or trade associations could conduct to effectively reach and inform handlers of WSPs. EPA also solicited similar input from the American Association of Pesticide Safety Educators. EPA is working collaboratively with state lead agencies and other stakeholders to facilitate the development and delivery of training and outreach to those who use WSP products.

OPP received input from SFIREG and pesticide safety educators at the end of August 2016 and established a small workgroup to determine how to address the states' input. The workgroup incorporated the states' comments into the revised label language. OPP intends to share the proposed final label language, reflecting input received to date, with co-regulators and stakeholders again to ensure their support prior to implementation.

OPP also determined that approximately 200 products are sold in water soluble packaging and OPP will engage the pesticide registrants for those 200 products. The EPA hopes to reach agreement with those pesticide registrants by the end of the calendar year on the revised label language and timing for incorporating it into labels for water soluble packets.

Regarding other work, the EPA finalized its science reviews to address the HSRB's comments from July. OPP is re-programming the EPA's risk assessment tool to incorporate the data from the two studies discussed in July. The risk assessment tool for the other study on wettable powders should be ready for use at the end of October 2016. The water soluble packet risk assessment tool should be ready at the same time; however, EPA first needs close-to-final label language so OPP can incorporate boilerplate label language into the risk assessment. That was EPA's update on actions taken since the AHETF studies were presented to the HSRB in July 2016. The EPA solicited questions from the HSRB.

- In response to a member query on the risk assessment tools, Mr. Matthew Crowley, OPP, replied that EPA uses a Microsoft Excel spreadsheet tool that contains default values from various data sets such as the AHETF data reviewed by the HSRB in July as well as other inputs, such as toxicity values. Current default values in the spreadsheet tool will be replaced with the AHETF data reviewed by the Board in July.

- Dr. Dawson asked about measures EPA is taking to advise registrants of the hazards associated with using wettable powders, which were found to have exposure rates higher than those of the WSP. Mr. Crowley explained that registrants are informed of any potential safety issues of their products, such as wettable powders, through the Agency's human health risk assessments data that are conducted when registrant's propose products for registration and during registration review of existing pesticide products. Thus, during the registration or registration review process, there is consideration of formulating wettable powder products in water-soluble packaging.

Topic 1: Protocol for Laboratory Evaluation of Mosquito Bite Protection from Permethrin-treated Clothing for the U.S. Army After 0, 20 and/or 50 Washings

Dr. Dawson introduced Topic 1 and asked Mr. Timothy Ciarlo, OPP, to present EPA's science review.

EPA Science Assessment

Mr. Ciarlo detailed the EPA proposal for laboratory evaluation of mosquito bite protection from permethrin-treated clothing for the U.S. Army. Permethrin is recommended by the World Health Organization for use in public health vector control programs as a direct spray to infested areas or indirectly by treating fabrics. This research has societal value because U.S. military personnel serving domestically and abroad are at risk of contracting insect-transmitted diseases. In addition, this protocol describes a special study for which the EPA does not have published methods for guidance, which is like a prior protocol reviewed by the HSRB in April 2014 involving etofenprox-treated military clothing. It is therefore consistent with existing use patterns for permethrin; however, notable differences from skin-applied repellent studies previously reviewed by the Board include the following:

Skin-applied repellents are typically evaluated in a field setting, whereas treated clothing is evaluated in laboratory "arm-in-cage" type studies. Skin-applied repellents and treated fabrics also elicit different "repellent" effects. The effect of skin-applied repellents like DEET and picaridin occurs instantaneously and is non-toxic to affected mosquitoes. This is a true repellency. With permethrin-treated fabrics, mosquitoes must contact the impregnated material and are exposed to the active ingredient for a comparatively longer period of time. The repellent effect in this case is "excito-irritant" in nature and produces avoidance behavior and failure to blood-feed. The repellent effect occurs before bite-through, but is nonetheless not a true repellency.

Different efficacy measures and endpoints are considered when comparing skin-applied repellents with treated fabrics. Efficacy of skin-applied repellents is determined by Complete Protection Time (or

CPT). That is, the amount of time between application of the material and first confirmed mosquito landing with intent to bite on treated, exposed skin. With treated fabrics, Mean Bite Protection is the relevant efficacy measure, and is determined by the reduction in number of blood-fed mosquitoes on human subjects wearing treated fabrics compared to untreated control fabrics.

A notable difference between evaluations for skin-applied repellents and treated fabrics is that human subjects will not be subjected to mosquito bites during field evaluation of skin-applied repellents, but will be subjected to bites during arm-in-cage lab evaluation of treated fabric. The most bites are expected when test subjects are wearing untreated control fabrics which contain no active ingredient. It is expected that subsequent tests with permethrin-treated fabrics will produce far fewer mosquito bites. Given that the proposed protocol uses lab-reared, disease-free mosquitoes, bites that occur during these arm-in-cage trials are unlikely to pose any health risk.

Mr. Ciarlo stated that study sponsor, LaunchBay, LLC, and independent contract research organization, i2LResearch USA Inc., will test the hypothesis that permethrin treatment provides bite protection when mosquitoes are exposed to treated fabric compared to an untreated control with a desired efficacy threshold equal to or greater than a 90 percent mean bite protection. The study objectives are to determine the bite protection level of permethrin-treated U.S. Military Army Combat Uniforms (ACUs) and Flame-Resistant Army Combat Uniforms (FRACUs) at an application rate of 0.5 percent and assess the bite protection performance after 0, 20 and 50 washes. The ACU and FRACU have different fibers and weave densities. ACU fabric is constructed with a tighter weave than FRACU fabric, and therefore presents more of a physical barrier to mosquito bite-through. Mosquitoes can and do bite through fabric, and have an easier time doing so on more breathable fabrics with a looser weave. For this reason, it is expected that mosquito bite-through rates will be lower when test subjects are wearing untreated ACU fabric vs FRACU fabric. This changes the number of human test subjects required to achieve an adequate level of statistical power between the two fabric types.

The purpose of this research is to determine whether permethrin-treated ACUs and FRACUs meet the EPA's specification for minimum bite protection level and satisfy EPA registration requirements for efficacy. Permethrin is classified as a low irritant to the eyes and skin and is not considered to be a skin sensitizer in humans. Per EPA's 2006 Occupational and Residential Exposure Risk Assessment, mean lethal doses (LD_{50}) of more than 2,000 milligrams of permethrin per kilogram (mg/kg) of body weight and more than 2,280 mg/kg constitute acute dermal and acute oral exposures, respectively. In the 2006 Permethrin Reregistration Eligibility Decision (RED), the No Observed Adverse Effect level (NOAEL) for dermal exposure is 500 mg/kg/day. Based on a 500 mg/kg NOAEL, the margin of exposure (MOE) of permethrin for this study is estimated to be 335, which is well above the Agency's level of concern.

Mr. Ciarlo remarked on the experimental design. He noted that the arm-in-cage experimental design is based on the design from a protocol testing efficacy of textiles treated with etofenprox (HSRB April 2014). Human test subjects will have their forearms covered with sleeves made from FRACU and ACU fabric, and then insert them into cages containing approximately 200 lab-reared female mosquitoes for a period of 15 minutes. Mosquitoes will be allowed to bite through the fabric sleeves and take a blood meal during this exposure period. The sleeves will be worn such that the fabric is tight against the skin, as this facilitates optimal blood-feeding conditions and represents the most conservative wear scenario. Two gloves will be worn on each hand so that blood feeding is limited to the fabric covered forearms.

Test subjects can be used to evaluate both fabric types simultaneously in two separate cages by wearing a FRACU sleeve on one arm and an ACU sleeve on the other, although one arm can be tested at a time. They will begin the day's testing by first wearing untreated, unwashed sleeves. These will be the untreated control replicates which will likely lead to the highest number of blood-fed mosquitoes. Mosquitoes will be allowed to blood-feed for a period of 15 minutes. After 15 minutes has elapsed, the number of blood-fed mosquitoes and the total number of mosquitoes in the test cage will be recorded.

Test subjects will be allowed to remove their arms, wash them with unscented soap and water, and take a short break.

This process will be repeated sequentially with FRACU and ACU fabric sleeves washed 50 times, 20 times, and 0 times. Each test subject will therefore serve as his or her own control. Permethrin does tend to gradually wash out of treated clothing after a number of washings, so it is expected that the 50 times-washed sleeves will comparatively contain the lowest amount of permethrin, the 0 times-washed sleeves will have the highest, and the 20 times-washed sleeves will fall somewhere in between. The order in which the fabric treatment levels are tested is important because it reduces the potential for confounding effects of "carryover" permethrin contamination, although this is not expected. The sleeves washed 0 times, which are likely to have the highest concentration of permethrin, are to be tested last.

This study design will evaluate mean bite protection against two mosquito species – *Aedes aegypti* and *Anopheles quadrimaculatus*, and the same testing paradigm will be used for both species. *Aedes aegypti* is found in tropical and subtropical regions of the world, including the southeast United States and parts of the southwest United States. It is a vector of numerous diseases of concern to US military personnel, including dengue, chikungunya, and zika. *Aedes aegypti* is a highly anthropophilic species, preferring to live near and feed on humans, especially in highly populated urban areas. *Anopheles quadrimaculatus* is native to the eastern United States and is a competent malaria vector, although local malaria transmission in the United States no longer occurs.

Test subjects will be exposed to only one mosquito species per day of testing. Test subjects may be selected for participation in an additional day of testing against one or the other species, but this is not required. Test subjects will test each fabric treatment level once per species for a total of 10 or 15 replicates per fabric treatment level per species, which results in 20 or 30 replicates per fabric treatment level. ACU fabric is constructed with a tighter weave, which is likely to reduce the control bite-through rate. This means that 15 test subjects are needed to achieve an adequate level of statistical power with ACUs, compared to 10 for the FRACUs.

The test cages are approximately 59,000 cubic centimeters in volume and each will contain 175 to 225 female mosquitoes that have never taken a blood meal, at a density of ~1 mosquito/300 cm^3. Lab-reared, disease-free, 5 to 9 day old female mosquitoes will be used in all trials. Female mosquitoes will be preselected from stock cages. A technician will place an ungloved hand near the screened stock cage to attract mosquitoes and will then use a motorized aspirator to transfer them to test cages. Each day's mosquitoes will be selected from the same cohort.

The unit of measure for determination of efficacy for treated uniforms is percent bite protection and not Complete Protection Time as is the case for skin-applied repellents. The presence of *any* amount of blood in a mosquito's abdomen will confirm a mosquito bite. The number of mosquitoes with distended abdomens that have obviously taken a blood meal will be recorded. All other mosquitoes will be crushed on a white background to determine if a partial blood meal has occurred. If so, these mosquitoes will be recorded as blood-fed. For each trial, the treatment percent bite values will be corrected to account for the bite through values in the untreated control using Abbott's Formula. This is appropriate because each test subject serves as his or her own untreated control. Data will be pooled for the 10 or 15 subjects for each fabric treatment level. After each 15-minute exposure period, mosquitoes will be removed from each test cage with an aspirator and placed in a freezer to immobilize them. The total number of blood-fed mosquitoes will be recorded. This includes partial as well as complete blood meals. For each treatment level, the percent of bloodfed mosquitoes will be compared with the percent of bloodfed mosquitoes in the untreated controls. Once those data have been recorded, the mean bite protection at each treatment level can be calculated using Abbott's formula. This calculation will be performed for both ACU and FRACU fabric at 0, 20, and 50 washes. The percent bite protection will be calculated using the following formula:

Percent bite protection = [1 - (treatment rate)/(control rate)] × 100%.

EPA derived the sample number (i.e., subjects) for the permethrin-treated study by simulation after making the following modifications to the original statistical analysis system (SAS) code that was used for an etofenprox-treated uniform protocol reviewed in 2014: using a generalized linear mixed model, PROC GLIMMIX (subject as a random effect), rather than the generalized linear model, PROC GENMOD (subject as a fixed effect); adjusting the expected bite-through rate for untreated material to account for the differences in weave designs between the ACU and FRACU; and using additional sensitivity analyses. Due to the difference in weave tightness between the two fabric types, the bite-through rate in the ACU controls is expected to be about 10%, while in the FRACU controls it is expected to be about 75%. Two bite protection objectives were considered. The military percent bite protection specifications are 85 percent, 80 percent and 70 percent for 0, 20 and 50 washes, respectively. EPA's percent bite protection specification is 90 percent for 0, 20 and 50 washes, in other words, percent bite protection will need to be greater than or equal to 90% after 0, 20, and 50 washes.

For ACU fabrics, because of the tighter weave, the bite-through rate in the untreated control replicates is expected to be about 10%. Ten percent bite-through in the controls will be the minimum allowed. Subjects who receive less than 10% bites in the ACU controls will be excluded from further participation and replaced. Of the 200 mosquitoes in the control reps, it is expected that roughly 20 of them will take blood meals. Simulations were run in SAS assuming a true bite protection of 80 and 90%. Therefore, in trials where test subjects wear treated ACU sleeves, it is expected that roughly 1 to 4 mosquitoes will take blood meals in these treated ACU replicates. The half-width of the 95% confidence interval, at 80% power when using 15 subjects, is 6.1% if 80% true bite protection is assumed. If 95% true bite protection is assumed, the half-width of the 95% confidence interval, at 80% power when using 15 subjects, is 3.1%. The Agency's conclusion based on these power analyses is that the use of 15 test subjects can be reasonably assured of meeting both military specifications and EPA bite protection standards for permethrin treated ACUs. Various other sample sizes could have been chosen. Precision increases with the addition of more test subjects, but only marginally so with each additional subject beyond 15, and at a decreasing rate. As the number of potential test subjects decreases below 15, the precision decreases at an increasing rate to an unacceptably wide half-width of the 95% confidence interval.

Based on the etofenprox-treated uniform study which the HSRB reviewed in 2015, it is expected that a bite-through rate in the untreated FRACU controls will be about 75% (vs 10% with the ACUs). Of the 200 mosquitoes in the FRACU control reps, it is expected that roughly 150 of them will take blood meals. As with the ACUs, simulations were run in SAS assuming a true bite protection of 80 and 90%. Therefore, in trials where test subjects wear treated FRACU sleeves, it is expected that roughly 15 to 30 mosquitoes will take blood meals in these treated FRACU replicates. The half-width of the 95% confidence interval, at 80% power when using 10 subjects, is 3.0% if 80% true bite protection is assumed. If 95% true bite protection is assumed, the half-width of the 95% confidence interval, at 80% power when using 10 subjects, is 1.8%. The Agency's conclusion based on these power analyses is that the use of 10 test subjects can be reasonably assured of meeting both military specifications and EPA bite protection standards for permethrin treated FRACUs. Various other sample sizes could have been chosen. As for the ACU fabric above, precision increases with the addition of more test subjects, but decreasing the number of subjects below 10 results in an unacceptably wide half-width of the 95% confidence interval.

Several measures will be used to improve the reliability of the study results. These measures include the use of standard operating procedures (SOPs) that will already be in place and have previously met the requirements of good laboratory practices (GLPs). Also, each study subject's attractiveness to mosquitoes will be determined prior to testing (a minimum of 10% bite through with untreated control fabrics). If not enough bloodfed mosquitoes are counted following the untreated control exposure period, that subject will be removed from the study and replaced with an alternate. Technicians will assist subjects

throughout the study. They will be responsible for placing the test sleeves on subjects' arms, excluding all skin from mosquito exposure, and inserting or removing subjects' arms in or from test cages; the counting of bloodfed mosquitoes and their total number in each test cage will be determined. The study protocol will be compliant with GLP standards.

Several of EPA's scientific comments on the protocol were highlighted during the HSRB meeting. The science review, beginning on page 23, documents the entirety of the agency's science comments. The following revisions were agreed to by i2LResearch. The description of permethrin was corrected and changed from "repellent" to "insecticide" because it is a toxicant. The words "test substances" were replaced as "permethrin-treated and untreated uniform fabrics," and the actual fabric descriptions were provided in more detail (e.g., composition openness versus tightness of the weave). To avoid potential confounding results, subjects should refrain from applying fragrance products (e.g., cologne, perfume) 24 hours before the study. Subjects who have a noticeable smell of fragrance will not be allowed to participate in the study. Subjects who withdraw from the study would require replacement due to insufficient numbers. The sample size number was increased from eight (the originally proposed number) to 10 or 15 because the current protocol will evaluate mean bite protection, not the completion protection time, as originally proposed by i2LResearch. For accurate data collection and statistical analysis, the total number of mosquitoes in each cage will be recorded. Also, the raw numbers of mosquitoes with visible blood in the abdomen (bloodfed) should be recorded separately from those mosquitoes requiring crushing to verify blood feeding. For statistical analysis, the investigators mentioned that use of the Kaplan-Meier method is not necessary because the current study is designed to measure bite protection not "time to event," as required of the Kaplan-Meier statistical approach.

Board Questions of Clarification—Science

Dr. Dawson invited Board members to ask questions for clarification. HSRB members noted that there will be approximately 200 mosquitoes in the cage and EPA is assuming that mosquitoes are biting with the same probability and independently. The HSRB asked if that was a reasonable approximation as to what's going on in the cage. EPA responded affirmatively. EPA noted that the design/model was previously reviewed by the Board in 2014, and with modifications to the SAS code, the assumption that the data have a binomial distribution is reasonable. A consultant to the HSRB added that there is little to no evidence of an aggregated response due to a release of aggregation pheromones as might be seen in social insects. Individual mosquitoes are all assumed to have similar biting probabilities; it is not expected that one mosquito's behavior will affect the host-seeking behavior of others. Aggregation responses more often are observed in plant-feeding insects.

The HSRB also asked if there was a registration for permethrin for direct contact with the skin. EPA responded that permethrin-containing products that are in direct contact with the skin, such as shampoos and creams, already are in the marketplace and do not raise newfound concerns for EPA.

The HSRB asked about the calculation of the MOE. The HSRB noted that if permethrin is applied to a full uniform and an individual is wearing it, that will increase the MOE and asked if EPA had concerns about this. EPA noted that the calculation is a conservative estimate. In the calculation, EPA assumed 15% transfer to the skin, although 6% would be a better assumption and would more than double the MOE. EPA noted that soldiers would wear undergarments when wearing the treated uniforms so only the legs and forearms would be directly exposed. EPA is confident that the estimated MOE calculated for this experimental design will be representative of the broader exposure levels that actual military populations outfitted in permethrin-treated uniforms will receive. EPA also noted that several other permethrin-treated uniforms are registered with the EPA, and the MOE estimation in this type of experimental design was not deemed an issue to prevent the research from going forward. In response to an HSRB question, EPA confirmed that the estimated MOE was calculated based on a six sleeve

exposure. An HSRB member asked if the arm of a control subject is bitten numerous times and is irritated as a result, will this interfere with future bites from mosquitoes? Another HSRB member explained that it is not anticipated that control conditions (e.g., untreated bite protection tests) of this experimental design will deter subsequent mosquito bites in the same subject and bias the results. Testing from lowest to highest permethrin concentrations will reduce the chances of residual effects in the test cage.

The HSRB asked if the initial outcome of the control exposures indicates that the assumption regarding the bite-through rate is wrong, would the study stop or continue to its conclusion? EPA responded that, in the unlikely event that this occurred, the FRACU part of the study could move forward. EPA only expects that controls might be an issue in the ACU trials because of the tight fabric weave with the ACU. However, based on prior studies and a preliminary sensitivity analysis, EPA anticipates that the bite-through assumptions for this study will be reflective of the true bite-through values and not be criteria to stop the study. The ACU and FRACU clearly show differences that have been accounted for in the experimental design.

An HSRB member asked if washing a subject's arm would affect the subject's attractiveness to the mosquitoes and if it would be a good idea to wash the subject's arm before the attractiveness screen and before the untreated control trials. EPA agreed with the HSRB that this was a reasonable idea.

In response to an HSRB question, EPA clarified that the labels shown during the HSRB presentation indicating different wash conditions for ACUs and FRACUs were not the actual fabrics being tested in this study. In response to an HSRB follow-up question, EPA and HSRB members noted that the washing and drying protocols for these fabrics, which represent industry standards, will be the same and closely mimic field procedures (e.g., hot wash and dry cycles); the specific temperatures are listed in the protocol itself.

An HSRB member noted that the negative control fabric is tested and used in the Abbott's equation for all of the treatments. The HSRB inquired if it would be more appropriate to use a negative control that's treated like the fabrics but without the permethrin. In other words, it might be the case that washing a fabric 50 times would change even an untreated fabric, especially a tight weave, to allow more bite-through compared to the untreated fabric when it's new. The HSRB asked how EPA factored that into the experimental design. EPA responded that the untreated and unwashed fabrics represent the most conservative scenario because as the fabric is washed, the fiber density can loosen up making it more penetrable for mosquitoes. EPA said it would be a mistake to use an untreated control uniform washed fifty times but not zero times. The HSRB agreed and wondered if EPA would want to find the distribution of the bite-through rate as a function of washing. The HSRB agreed that if EPA wants a conservative approach, then the untreated brand new fabric is the most protective of the untreated fabric and provides the most conservative estimate.

An HSRB member asked, given that the Invexus process is new and hasn't been used for this purpose, does EPA have any data that the dermal transfer rate will be higher or lower than other methods of treatment? EPA responded that the Agency currently does not have data to demonstrate how LaunchBay's Invexus™ process used in this study affects the dermal transfer rate from treated clothing to the skin. However, the 15 percent dermal transfer rate that EPA has set for this study is more than twice what is addressed by SOPs and is significantly higher than the 0.6 percent observed in prior studies. Also, the concentration of permethrin (0.5%) used in the study is the same as other permethrin-containing products that are currently registered with EPA. In addition, LaunchBay has completed toxicity studies and dermal transfer data that will be included in the application to EPA. In response to a related HSRB question, a representative from LaunchBay clarified that the Invexus™ process has been used in other EPA-registered products, such as Egret Bednet; and the permethrin is primarily located near the surface of the fabric, not on the skin side, in fabrics treated by the Invexus™ process. An HSRB member noted that it would be helpful if background data that support these claims could be included in the study protocol.

An HSRB member noted that the material safety data sheet for the FRACU fabric tested in this study also lists formaldehyde as one of its components. The HSRB member inquired if the addition of formaldehyde plays a role in the study. EPA noted that there is a control untreated so any effect should be shown through the control. The HSRB followed up with a question about the purpose of the formaldehyde component. An HSRB member clarified that the FRACU has a treatment to retain the flame retardant properties. The study sponsor confirmed this and said the company would clarify this point in the revised protocol.

Dr. Dawson, noting no further questions of clarification, asked Ms. Lydon to present EPA's ethics review.

EPA Ethics Assessment

Ms. Lydon provided an ethics assessment for the i2LResearch protocol. Regarding the value to society from this research, the proposed study would test the mosquito bite protection of up to two fabrics, Army Combat Uniforms or ACU and Flame Resistant army uniforms, or FRACU, that have been treated with permethrin via the Invexus™ process. The unwashed fabric will be tested, along with the fabric washed 20 times and 50 times. This study would determine whether permethrin-treated ACUs and/or FRACUs meet the target level of mean bite protection at greater than or equal to 90%. If target levels are met, the treated fabrics would provide a high level of bite protection for US Army soldiers wearing the treated uniforms.

Subjects will be recruited through advertising using digital and social media from the Baltimore, Maryland area, where the testing laboratory is located. Advertisements will be posted using such mediums as Facebook, Yahoo, Bing, Google and Craigslist. As one part of the broader recruitment effort, it was proposed that the recruitment firm also use a Spanish language advertisement and an on-line Spanish newspaper that advertises in the recruitment area in order to reflect the population of treated-fabric users in the Army who are Hispanic. All advertisements will contain a link to a study-specific secure website where interested respondents can learn more about the study and complete a pre-screening qualification form. i2LResearch must submit both the advertisement and pre-screening qualification form to the EPA and the overseeing Institutional Review Board (IRB) for review and approval prior to implementation. The pre-screening forms, once completed, will automatically be uploaded into a secure and encrypted portal that only i2LResearch employees can access. As discussed in the EPA ethics review, consistent with long-standing EPA guidance, the recruitment pool and completed study should be as generalizable as possible to the target population of treated-fabric users which, in this case, is US Army soldiers wearing the treated uniforms.

The recruitment firm or i2LResearch will contact the individuals from the recruitment pool to determine whether or not they meet the basic inclusion criteria. Using the telephone screening script, the respondents will be asked basic eligibility questions and told about the purpose of the study, the insecticide used to treat the fabric, the test procedures and compensation. The telephone script shared with the HSRB provides details of what the initial call will cover. i2LResearch will make follow-up phone calls to eligible respondents who are interested. The second phone call will review the basic steps involved in the study, discuss what the training will cover, review the inclusion and exclusion criteria, compensation, the subjects' freedom to withdraw, and offer to provide the consent form in advance of the training to interested subjects. Eligible individuals who want to participate will be given a date, time, and location for the training session.

The 2-hour training is detailed in the revised protocol and includes a review of the consent form. i2LResearch will ask each subject 6 questions to ensure their understanding of the consent form. Interested subjects will sign and submit the consent form during the training and receive a copy, which includes the Study Director's contact information for any follow-up questions.

Regarding the inclusion and exclusion criteria, the fifteen proposed criteria are complete and appropriate, except that i2LResearch needs to exclude subjects with sensitivity or allergies to insecticide-treated fabrics or insect repellents, and exclude individuals with open cuts or scrapes or allergies to latex or skin care products. One of the study sponsor's proposed inclusion criteria is that subjects be able to read and speak English fluently. The researchers' rationale for this criteria in the original protocol is that the current product labels are in English; the language one speaks does not affect attractiveness to mosquitoes; and the research offers no benefits to subjects. U.S. Army soldiers are the primary intended users of the treated clothing. Through the recruitment process, to the extent feasible, researchers will work to ensure that the ethnic groups represented in the demographics of Army soldiers are reflected in the recruitment pool.

Regarding the informed consent process, each potential subject who is interested in participating in the study and has met the inclusion/exclusion criteria must participate in a 2-hour training within 4 weeks prior to their test day. The 2-hour training covers a range of topics and will discuss: the purpose of the study and the subject's role, the length of the test day and breaks during the test day, the identity and function of permethrin, the risks of participating in the study, the steps being taken to mitigate risks, the inclusion/exclusion criteria and the content of the consent form. The study staff will also review and demonstrate the procedures of a fifteen-minute exposure interval and show subjects how the fabric will be applied to their arms for the study. To confirm understanding of the consent form, subjects will be asked 6 questions, outlined in section 2.2.6 of the protocol. Once the consent form incorporates EPA's comments, it will include all elements required by federal regulations on protecting human subjects

Regarding compensation, each subject will be paid $30 for taking part in each training session. For each test day, test subjects will be paid $104.00 ($13 per hour) for any length of participation up to 8 hours. In the unlikely event that a test day exceeds 8 hours, subjects will be paid $19.50 (time and a half) for each additional hour, rounded up to the nearest hour. An alternate who is not needed to replace a test subject will be able to leave and will be paid $50. The decision as to whether an alternate is needed is expected to occur within the first 2 hours of the test. Any subject who appears for testing, but must withdraw from the test for health-related or emergency reasons, will receive full payment as for an eight-hour day (even if they worked less than eight hours), plus any overtime worked. Any subject who chooses to withdraw from the study for a non-health or emergency-related reason will be paid for the hours which they participated on that test day.

Regarding EPA's comments on the protocol, the EPA provided more than 60 detailed ethics comments, as well as additional comments on the supporting materials. i2LResearch and LaunchBay agreed to address all of the comments prior to implementing the research. The detailed comments are outlined in the EPA review which the HSRB received prior to the meeting. During the HSRB meeting, the Office of Pesticide Programs highlighted a subset of EPA's ethics comments. First, i2LResearch agreed to increase the number of test subjects proposed by EPA to ensure the scientific integrity of study. EPA's proposal is ten test subjects for testing FRACU per mosquito species and fifteen subjects for testing ACU per mosquito. Subjects have the opportunity to participate in up to 2 test days. EPA recommends increasing the number of alternates to 4 per test day to ensure that subjects are available to replace those who choose to withdraw; i2LResearch is asking the alternates to stay at the test site until the control exposures are completed, which will likely occur during the first 2 hours of the test day. EPA asked i2LResearch to revise the protocol so that if a subject withdraws after testing has begun, he or she is replaced with an alternate. The original protocol said the study would continue with the remaining subjects if someone withdrew after testing had begun. EPA also asked that the protocol be revised to state that an eligible and interested subject may choose to participate in up to two test days.

To minimize discomfort, EPA suggested increasing the time between test days to at least 72 hours (instead of 48) if a subject is participating in more than one test day. EPA also requested that participating

subjects be allowed breaks of up to ten minutes between each exposure. Similarly, for interested subjects, there would be a thirty-minute lunch break that would overlap with one of the ten minute breaks. If a subject needs a longer break, that will be allowed. The study sponsor will provide beverages and snacks to interested subjects on the test day, taking into account any food allergies the subjects may have.

EPA asked that i2LResearch explain and demonstrate the procedures of a fifteen-minute exposure interval step-by-step during the training session, in addition to reviewing the other topics identified for the training session. This helps to further ensure that subjects are fully informed prior to participating on the test day.

i2LResearch drafted questions to ensure that subjects understood the consent form. EPA suggested replacing the question that currently reads: "What type of product will be applied to your arm during each exposure period of the study?" EPA suggested the following new question: "What will you be wearing on your arm during the exposure period?" As previously discussed, EPA asked i2LResearch to add language to the exclusion criteria.

EPA asked i2LResearch to try to ensure that the recruitment pool represents the demographics of the members of the Army who are the intended users of the permethrin-treated fabrics. Doing so would be consistent with EPA guidance on this topic that the study results be as generalizable as possible to the target population. I2LResearch also needs to submit the advertisement and pre-screening qualification form to EPA and overseeing IRB for review and approval prior to implementation. In addition to the proposed recruitment efforts, EPA asked i2LResearch to post a Spanish language advertisement online and use an online Spanish language newspaper that advertises within the recruitment area in order to ensure that the Hispanic population of US Army soldiers who wear treated uniforms is reflected. EPA also asked that the size of the recruitment pool be at least 2 times that required for the study which equates to at least ninety potential subjects in the recruitment pool. EPA asked i2LResearch to update the protocol on this point in all applicable sections.

EPA also asked i2LResearch to revise the telephone screening script to reflect EPA's comments. The intent is to incorporate applicable changes from the protocol into the screening process as well. All of the changes that EPA reviewed also need to be addressed in the consent form as applicable. EPA asked i2LResearch and study sponsor LaunchBay to update the consent form to: discuss permethrin and its uses; reflect the updated exclusion criteria; update the numbers of subjects and alternates; provide ten minute breaks between exposures; update the topics to be covered during training; provide snacks and beverages to subjects at the test site and update the language on the consent form regarding no participation by pregnant or nursing women.

Regarding medical monitoring, EPA asked i2LResearch to give the on-call nurse a copy of the final approved protocol and brief the nurse on study process and test substance involved. i2LResearch should contact the on-call nurse at the initiation of each test day to let the nurse know that testing has begun for that day and reiterate that i2LResearch will call the nurse as necessary.

In the hazards section of protocol, EPA asked i2LResearch to add the psychological risks related to pregnancy testing and an associated description. As part of risk mitigation, EPA asked that i2LResearch screen a subset of the colony of mosquitoes to be used in order to check for pathogens as described in the revised protocol. EPA asked i2LResearch to revise the language associated with covering medical costs so that it reads: "If a subject is injured as a result of wearing the permethrin-treated fabric or from study procedures, the study sponsor will directly pay for medical expenses necessary to treat subject's injuries that are not covered by their insurance." The original language talked about the study sponsor reimbursing the subject. During a previous HSRB meeting, a Board member noted that the reimbursement process can be quite lengthy and the HSRB suggested that the study sponsor directly pay for medical expenses not

covered by insurance. Taking into account previous HSRB comments, EPA recommended this change and the study sponsor agreed.

EPA asked i2LResearch to clarify the benefits section and provide more details. EPA requested a reference to complying with FIFRA §6(a)(2) adverse effects reporting requirements. EPA asked that i2LResearch clarify the existing statement that "adverse effects will be followed until resolution is reached." EPA provided suggested language for consideration. EPA asked i2LResearch to revise the protocol to state that, if subjects request standard, over-the-counter antiseptics and hydrocortisone cream, it will be provided immediately upon completion of the test at no cost to subjects. The application section of the protocol will be updated to state that different sized sleeves "will be" created to fit subjects' needs, instead of "may be" created.

i2LResearch and LaunchBay have agreed to address all of EPA's comments. The revised language for the protocol, consent form and telephone screening script was provided to the HSRB to facilitate their review. The protocol with EPA's comments included provides appropriate measures to minimize 5 categories of risk. During the HSRB meeting, EPA reviewed the measures to minimize each of these risks, including: 1) adverse reaction to test substances; 2) exposure to biting mosquitoes and mosquito-borne diseases; 3) physical discomfort of multiple mosquito bites; 4) unanticipated loss of confidential information; and 5) psychological risks related to pregnancy testing. Several steps are being taken to minimize an adverse reaction to the test substances. The protocol excludes candidates who are known to be sensitive to insecticide-treated fabrics or insect repellents. The protocol excludes subjects with cuts, scrapes, skin diseases or skin conditions such as psoriasis, atopic dermatitis or eczema; these conditions could increase the possibility of a reaction to test material. Subjects will be told that if anyone experiences any skin reaction, experiences an injury, or simply feels unwell, he or she should inform i2LResearch staff right away. Such subjects will immediately be given appropriate care, may be withdrawn from testing, and may be transported to a local hospital if necessary. The closest hospital to the laboratory test site and directions will be identified prior to the test date.

To eliminate the risk of contracting any mosquito-borne diseases, the study will be conducted only with laboratory-reared mosquitoes, which are not known to harbor any pathogens. In order to ensure the mosquitoes used in the study are not carrying any diseases, the proposal was that a subset of the colony be screened for pathogens as described in the protocol; this is the same approach as that used in the last protocol for lab testing of insecticide-treated fabrics reviewed by the HSRB in 2014. In addition, the supplier will document that these laboratory-reared mosquitoes are disease free, and that they have never received a blood meal.

Several steps will be taken to minimize physical discomfort of multiple mosquito bites. The protocol excludes candidates who are allergic, hypersensitive to or phobic of mosquito bites. Subjects are alerted in the consent form to the possibility of experiencing a skin reaction to mosquito bites, and are advised to inform the study director or other staff member, if they believe they are having a reaction. Over-the-counter topical anti-itch gel or cream to relieve itching, will be available for use by subjects after completion of the study. There will be at least 72 hours between test days for subjects who participate in more than one test day. Subjects can only participate in up to 2 test days. Finally, a nurse familiar with the protocol will be on-call to provide advice or assistance in case medical advice is needed during the test day.

Regarding minimizing the unanticipated loss of confidential information, all efforts will be taken to maintain the confidentiality of the pregnancy test results. The test results will not be disclosed to anyone other than the test subject, the verifying employee, and/or the Study Director. In addition, the subjects' identities and participation in the study will be protected as follows: each subject will be assigned a code number, and only subjects' code numbers will appear on data sheets. The subjects' names will not appear

anywhere on the data sheet, or in the reports. The study records will be maintained at the testing facility in locked cabinets and electronic files kept on a password-protected computer server.

Steps are also being taken to minimize the psychological risks related to pregnancy testing. The protocol provides for discreet handling of the pregnancy testing that is required of female subjects on each test day. Female subjects will self-administer the pregnancy test in a private bathroom. After completing the test, each female subject is asked if she would like to continue in the study. If her answer is no, then no further questions are asked; she will not be asked to share the result with anyone. If her answer is yes, the result of the pregnancy test will be verified by only one member of the research team who will be female. For females who proceed with the testing, the result of the pregnancy test is not recorded.

With regard to benefits, there are no direct benefit to subjects. The primary direct beneficiary is the study sponsor. If the treated materials are proven effective and meet the target level of mean bite protection of $\geq$90%, that indicates high rate of mosquito bite protection. Indirect beneficiaries would include US Army soldiers who would wear the permethrin-treated uniforms. Regarding the risk/benefit balance, EPA believes that risks have been effectively minimized. The risks are reasonable in light of the expected benefits to society from the knowledge likely to be gained. The protocol demonstrates respect for subjects. For example, the protocol includes effective methods for protecting subjects' privacy, the proposed level of compensation is appropriate, subjects are free to withdraw at any time, and the study sponsor will directly pay for medical care for research-related injuries, not covered by subjects' insurance.

Regarding an independent ethics review, Schulman IRB reviewed and approved the protocol and informed consent materials. The Schulman IRB is accredited, registered with the Office for Human Research Protections or OHRP, in HHS, and is independent of the investigators.

This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. The primary ethical standards applicable to this research are 40 CFR Part 26, Subparts K and L, and FIFRA Section 12(a)(2)(P). Attachment 1 to EPA's Review contains a point-by-point evaluation of how this protocol addresses the requirements of 40 CFR 26 Subparts K and L. The proposed research and supporting documents, as revised with EPA's comments incorporated, meet the applicable requirements of the federal rule for protecting human subjects, including requirements of §26.1111, §26.1116, and §26.1117, and requirements of §26.1125 and §26.1203. To summarize, i2LResearch and study sponsor LaunchBay have agreed to address all of EPA's comments noted in the science and ethics review. There are no deficiencies relative to 40 CFR 26, subparts K and L, or to FIFRA §12(a)(2)(P). The protocol meets the applicable requirements of 40 CFR part 26, subparts K and L.

Board Questions of Clarification—Ethics

Dr. Dawson invited Board members to ask questions for clarification. The following points of clarification were made:

A consultant to the HSRB asked whether the vector test kits would be required even if the supplier provided documents that the mosquitoes were disease free, had not been given blood meals, and were lab-reared. EPA responded that the intention of proposing the addition of a vector test kit results is to verify the certification by the supplier. An HSRB member noted that the test might not show results for new diseases such as Zika, that the test is not necessary, and that requiring the test might increase the perception of risk among study participants. The same member noted that these types of vector control tests are for field testing, rather than lab testing as proposed under this protocol. An HSRB member asked what documentation from the mosquito supplier certifying that they are disease free would look like, apart from the statement from the breeder. The same member asked what would occur if there was a positive result to a vector control test. EPA does not specify the format for documenting vector test results and the

protocol does not specify when vector testing should be performed. The associated mosquito batch will not be used in the study if vector test results are positive, based on the HSRB discussion, EPA responded that it might reconsider inclusion of vector control tests under this protocol. The chair acknowledged that the issue had been raised and proposed deferring further discussion until the ethics discussion period.

An HSRB member raised a question about the exclusion criteria (i.e., must read and understand English) and the recruitment plan to use Spanish media. EPA noted that its long-standing guidance specifies that the results of studies should be as generalizable as possible to the target population of intended users, which in this case includes Army soldiers wearing the treated uniforms. EPA provided information from the US Army website, which states that 17% of active duty Army soldiers in Fiscal Year (FY) 2015 were Hispanic. Another public source, the report titled "2014 Demographics Profile of the Military Community," published by the Office of the Deputy Assistant Secretary of Defense (Military Community and Family Policy), states that in 2014, 12% of the DOD Active Duty force was of Hispanic ethnicity. EPA noted that posting a Spanish language advertisement online and using an online Spanish language newspaper that advertises within the recruitment area was intended to reach bilingual subjects of Hispanic ethnicity. The Board member who raised the issue indicated that EPA had clarified the intent of the criterion, but she suggested further discussion of the issue during the ethics discussion period.

An HSRB member asked whether existing data show variation in mosquito attractiveness between individuals. Another HSRB member responded that men and women may have different levels of attractiveness, but the science is not settled on an individual's level of attractiveness. EPA noted that to address possible effects on the results of such male-female and inter-individual variations, the study protocol recruits a representative sample of subjects, and subjects will be instructed to wash prior to the test to remove applied skin products that might bias results. The variation in attractiveness is treated in the study as a random effect that is addressed in representative subject selection, rather than as a parameter to measure that would be considered in interpreting the results. The HSRB members suggested that the protocol should explain what representativeness the study sponsor is seeking (e.g., individual, male/female, target demographics).

An HSRB member asked when subjects would be allowed to use hydrocortisone cream – at the end of the test day? If so, would that impact the results if the subject participates in 2 test days? EPA noted that hydrocortisone cream is to be used, upon subject's request, only after the completion of a test day. The protocol states that subjects must be willing to refrain from alcohol, nicotine, and fragrance products (e.g., scented soap, perfume, cologne, hair spray, scented lotion, antiperspirant/ deodorant, etc.) 24 hours before the test. An HSRB member suggested adding hydrocortisone cream to this list of substances that cannot be used 24 hours before a subject's scheduled test day, and EPA agreed with the recommendation.

An HSRB member raised questions about how to decide what level of sensitivity is sufficient or necessary to disqualify a subject during the test control period. EPA noted that the study protocol provides general guidance on excluding subjects exhibiting excessive irritation from mosquito bites, the determination of which is subjective. Researchers have the option of preventing subjects from continuing in the study if they judge such bite reactions as dangerous to a subject's health. The decision will be made by staff who will be present at each test, adding a measure of objectivity to the researchers' decisions.

Dr. Dawson, noting no further questions of clarification, asked Mr. Downing to call for public comments.

Public Comments

Mr. Downing announced that no public comments were entered into the record. He called for any comments from the meeting attendees, and no public comments were offered.

Board Discussion—Science

Before beginning the Board's discussion, Dr. Dawson read the following science charge into the record:

> Is the protocol, "Laboratory evaluation of mosquito bite protection from permethrin-treated clothing for the U.S. Army after 0, 20 and/or 50 washings" likely to generate scientifically reliable data, useful for estimating the level of mosquito bite protection provided by different textiles treated with permethrin?

Dr. Dawson asked discussants Drs. Walter Klimecki and Edward Gbur to provide their comments. Dr. Klimecki stated that the laboratory evaluation of mosquito bite protection from permethrin-treated clothing for the U.S. Army after 0, 20 and/or 50 washings was likely to generate scientifically reliable data, useful for estimating the level of mosquito bite protection provided by different textiles treated with permethrin. This proposed research will test the use of permethrin-treated products at concentrations that are in use with the general population and do not present any new concerns. The level of exposures estimated in the study is accompanied by conservative safety margins. Dr. Klimecki noted the issues raised regarding the formaldehyde contained in the FRACU fabric and EPA's comments to address these issues.

Dr. Gbur provided a statistical review of the study. He commented that he was pleased with the statistical analysis. Having each subject serve as his or her own control, testing two species of mosquitoes, the combination of fabric types, and the number of washings are all good features of the protocol. These features allow fewer subjects to be tested and relevant comparisons to be made within the same study. Dr. Gbur commented that EPA's assumption of binomial distributions is reasonable given the use of the PROC GLIMM approach and treating the subject as a random effect. The simulation study used to determine study sample size (i.e., number of subjects) was adequate; however, it is not clear why the fixed subject calculations and the generalized estimating approach were included in the sample size calculations. The apparent reference to using GENMOD also was not clear. Overall, the statistical analysis and choice of models used in the protocol are reasonable and satisfactory.

Dr. Dawson solicited comments on the science assessment from the Board members.

An HSRB member commented that it was unlikely that formaldehyde would remain on the fabric for any length of time. It is generally a feature of SDS to include chemicals that have a potential to be present, however small the concentration.

A representative from LaunchBay pointed out that residual formaldehyde was not likely a product of the Invexus™ process or permethrin treatment, but was a carryover from the anti-wrinkle treatment. The HSRB chair asked for further clarification on the residual formaldehyde, and the sponsor confirmed that the residual chemical was a residue from previous treatments not related to the study. The HSRB chair commented that it would be helpful for information about the formaldehyde to be included in the protocol.

An HSRB member asked about the confirming evidence and steps or controls to ensure that the mosquitos were disease-free when they arrived to their destination before the start of the study. Chain-of-custody forms that accompany chemicals were used as examples of documents that provide proof of no contamination. A consultant to the HSRB explained that the confirmation from the vendor supplying the mosquitoes for the study should be the first line of proof that the insects are disease free. However, chain-of-custody documents will provide an additional level of assurance that the mosquitoes have remained free of disease *en route* to the study sponsor.

The HSRB chair pointed out that living reagents and animals for research have standard quality control and quality assurance (QA/QC) documentation and expressed concern that standards be clearly stated to the Board. A consultant to the HSRB replied that mosquito transport outside of the United States would require specific documentation that was not applicable to internal transport. Mosquitoes purchased for this study are shipped to i2LResearch in sealed containers and are kept in such containers until testing commences. The insects have not received a blood meal, and the risk associated with their spreading vector-borne diseases to human subjects is nonexistent.

The HSRB chair asked about the vendors' standard laboratory QC procedures and whether the additional testing was needed. The HSRB consultant explained that facilities that specialize in laboratory-bred mosquitoes have little to no infection rate in colonies that have been bred for many generations from the parent, unlike insects bred in the wild. The vector test kit listed in the protocol is designed for field operations where surveillance programs are being conducted to evaluate risk and should not be a requirement for this study. EPA's requirement for a secondary pathogen test could convey a perceived risk of disease where none exists. Identifying the documentation that the vendor should supply with each batch of mosquitos would be the first approach to take.

An HSRB member commented that secondary confirmation that the mosquitoes are disease free may be preferable to assure subjects that the study sponsor has taken all possible measures to ensure their safety.

An HSRB member suggested that if EPA thinks the additional confirmatory testing is needed, the Agency should provide a rational approach to address the issue. An EPA representative suggested that including Animal and Plant Health Inspection Service permits issued by the U. S. Department of Agriculture (USDA), chain of custody forms, and certifications in the protocol are ideas to consider.

The HSRB chair recommended that EPA and/or LaunchBay provide documentation that is scientifically valid, is reasonable and provides assurance to the public that the mosquitoes are disease free.

The HSRB chair suggested that a description of the SOPs from insectaries and laboratories that breed mosquitoes for research studies could be included as an appendix to the protocol.

The HSRB agreed that providing assurance that mosquitoes used in the study are disease free was not directly related to the science. They approved including a human subjects comment in the ethics review and response on this matter.

An HSRB member commented that repeated measures require treatments (or tests) to be conducted in the same order, and randomizing the order of treatment does not fit this experimental design.

The HSRB asked about the dermal uptake of permethrin and any residue remaining after washings that could confer bias to the results. Also, would additional controls be necessary to measure the difference in biting pressure at the beginning and end of the test. The HSRB consultant explained that the estimated 15 percent dermal transfer rate is conservative and that the exposure times are only 15 minutes. The permethrin is applied to the outer layer of the fabric, thereby limiting the direct contact to the skin, which is different from the current registered EPA product where permethrin permeates the entire fabric.

An HSRB member suggested including consistent wash instructions in the protocol.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Klimecki's response statement.

All the Board members present approved the response statement.

Board Discussion—Ethics

Dr. Suzanne Rivera reviewed the ethical aspects of the study and stated that EPA had more than 60 detailed ethics comments on the protocol and EPA's ethics assessment was very thorough.

Dr. Rivera read the following charge into the record:

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

She noted that the protocol adequately detailed subject recruitment, which extended to enrolling non-pregnant and non-nursing adults ages 18 to 55 and included appropriate procedures for pregnancy testing. The protocol appears to meet and address the ethical requirements to conduct third-party human research with pesticides without involving intentional exposure of pregnant and nursing adults. Steps to minimize risks to exposure, such as the use of laboratory-bred mosquitoes, are clearly identified and exercised; however, questions regarding the representation of the disease-free status of mosquitoes used in the study remain to be resolved. The Board will address these questions.

This research provides no benefits to subjects, but the benefits to society warrant the relatively low levels of risks to participating subjects. Increasing protection from mosquitoes for military troops would result in a decrease in mosquito-borne diseases. Indirectly, data generated from this study could also lead to marketable interventions beneficial to protecting society from diseases that are attributable to mosquitoes, which is disclosed to subjects on the consent forms. The protocol has procedures in place to obtain informed consent and protect patient information. EPA identified many changes that are necessary to the protocol.

Dr. Rivera directed the Board's attention to the EPA's ethics review of the protocol and highlighted two areas of concern. First, one of EPA's comments on section 2.3.1 of the protocol states that the overseeing IRB will need to "approve any revisions to the protocol in response to EPA and HSRB comments prior to implementation." While EPA's intent is to notify the study sponsor that they cannot implement changes prior to IRB approval, to avoid any misinterpretation, the statement should be revised to read that the IRB approval must be obtained prior to the implementation of any protocol revisions. Secondly, the inclusion/exclusion criteria for subjects, Section 2.3.5, limits recruitment to English speakers, whereas Section 2.3.6 calls for subjects being recruited through advertising using digital and social media, including the addition of a Spanish-language advertisement to recruit bilingual subjects. Dr. Rivera emphasized that these two sections send conflicting messages. The study will be assessing the efficacy of permethrin-treated fabrics, not a subject's ability to read English. She added that the researcher's rationale for limiting study enrollment to those fluent in English could result in an unjustified exclusion.

Dr. Dawson solicited comments on the ethics assessment from the Board members.

An HSRB member pointed out that one of EPA's ethics comments (19 in Section 2.3) states that the overseeing IRB will need to "approve any revisions to the protocol in response to EPA and HSRB comments prior to implementation." While the intent is clear for approval prior to implementation, the language should read that "the sponsor should obtain IRB approval before implementing protocol changes."

An HSRB member commented on EPA's Ethics comments 23 and 24 in Section 2.3 regarding EPA's recommendation for using a Spanish-language advertisement as part of the broader recruitment efforts presents equity of access issues when it also states that participation will be limited to English speakers. An HSRB consultant clarified that the fabric labels were not the issue regarding language. An HSRB

member suggested that requirement for English speakers be countered with interpretations of applicable study materials that subjects will need to understand. Intuitively, including Spanish-speaking subjects in the study is not entirely representative of the demographics in the recruitment location. EPA's long-standing guidance is that the resulting study should be as generalizable as possible to the target population of users, which in this case focuses on US Army soldiers wearing insecticide-treated uniforms.

The HSRB chair pointed out that representativeness for scientific reasons, such as gender and attractiveness to mosquitoes, are things that clearly could affect the science; however, no evidence suggests ethnic differences would affect the scientific research. Additionally, each subject serves as their own control; therefore, ethnicity of study subjects should not affect the study results.

The HSRB chair pointed out that in small-scale studies, such as the permethrin-treatment study, it is challenging to have recruitment that is representative of the diverse military population. One strategy would be to develop a modest set of goals such that recruitment and enrollment procedures are consistent, and whomever enrolls can understand what's being communicated.

The HSRB suggested that more evidence should be available to all interested parties to show that mosquitoes used in the study are disease free. Performing additional vector tests as indicated in the protocol may not provide the necessary reassurance.

An HSRB member commented that EPA should make the decision regarding what declaration of assurance and independent testing is necessary for laboratory-bred mosquitoes being used in human subjects research.

Dr. Dawson summarized the Board's recommendations and stated that the available information supports a determination that the research, if conducted according to the protocol, would be in substantial compliance with 40 CFR Part 26, Subparts K and L, pending the following three changes to the protocol:

- Regarding IRB approval of protocol changes resulting from EPA and HSRB review, the final wording should state that IRB approval must be obtained prior to implementation of any protocol revisions.

- Reference to using a Spanish language advertisement as part of the broader recruitment effort should be removed. There is a rationale for recruiting English speakers who will be able to understand study materials because the materials will not be translated into Spanish.

- Clarification on the source and safety of mosquitoes is needed, and appropriate documentation should be made available to reassure the study participants and public that the mosquitoes are disease free.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Rivera's ethics review statement.

The HSRB unanimously approved the statement.

Closing Remarks

Mr. Downing expressed appreciation to the Board for its participation. He stated that the Board is scheduled to reconvene at 1:00 p.m. on October 20, 2016, to address the research study for measurement of potential dermal and inhalation exposure during manual pouring of two solid formulations containing an antimicrobial. Mr. Downing adjourned the meeting for the day at 5:06 p.m.

Thursday, October 20, 2016

Convene Public Meeting

Mr. Downing reconvened the meeting at 1:00 p.m., introduced himself, and welcomed back the Board members, EPA colleagues and members of the public.

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 on the HSRB website. The Board also will prepare a report in response to questions posed by the Agency, which will include the HSRB's review and analysis of materials presented, as well as the Board's advice and recommendations. The final report will be available on the HSRB website. Mr. Downing again thanked the Board members for their participation in this meeting and then turned the meeting over to the HSRB Chair, Dr. Dawson.

Virtual Meeting Operations

Dr. Dawson reviewed the virtual meeting procedures, including the muting of phones and use of the buttons on the Adobe Connect portal to agree/disagree in voting during the proceedings.

Introduction of Board Members

Dr. Dawson requested that the Board members introduce themselves again. The members did so, providing their names, affiliations and areas of expertise.

Opening Remarks

Dr. Dawson explained that Dr. Tom Sinks would not be attending the meeting today.

Follow-Up Discussion From the Previous Day

Dr. Dawson reminded members of the prior discussion on the Invexus™ process and the potential for permethrin transfer to the skin. The information LaunchBay presented supports the contention that the amount of permethrin attributable to the treatment process that will transferred to the skin will be minimal. She recommended including comments in the protocol that would explain why these low estimations were reasonable. The Board agreed to add this information to the protocol response.

She commented that the Board's review complements OPP's review and was a productive exchange. The aim and common goal is to demonstrate that scientifically sound and necessary studies are being conducted. Dr. Dawson expressed gratitude for the collaborative efforts of the researchers and OPP.

Topic 2: A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial.

Dr. Dawson called Session 2 to order and invited Mr. Timothy Leighton, OPP, to present his science assessment.

EPA Science Assessment

Mr. Leighton provided a science assessment of the completed Antimicrobial Exposure Assessment Task Force (AEATF) II Solid Pour Study. The study, which was performed using an HSRB-approved protocol, estimated dermal and inhalation exposure of consumers and occupational workers when pouring powder and granule antimicrobial products, using cyanuric acid (CYA) as a surrogate test material. The

study had many objectives, but its two main objectives were the following: (1) to capture the range of expected dermal and inhalation exposures for the scenarios; and (2) to have a sufficient sample size to determine the arithmetic mean and 95th percentile exposure estimates within 3-fold accuracy.

Mr. Leighton described the scope of the solid pour exposure scenarios. Solid pour represents four of AEATF's 17 exposure scenarios and comprises the following: (1) consumers pouring powders, (2) consumers pouring granules, (3) occupational workers pouring powders, and (4) occupational workers pouring granules. Mr. Leighton described the study location, participation of each subject in both powder and granule pouring events with changes in monitoring equipment between events, and factors that ensured variability in the amount of active ingredient handled (AaiH). Dermal and inhalation exposure to CYA were monitored for 18 different consumers and 18 different occupational subjects, subjects wore outer and inner dosimeters, and subjects wore personal particulate samplers.

Mr. Leighton noted that the components of the personal particulate samplers were listed in reverse order on page 21 of the science assessment, and he indicated the correction in his presentation. The science assessment memo read: "The results from the IOM cassettes are reported herein as the "total" or "inhalable" air concentration monitored from the glass fiber filter (<100um) and "respirable" from the foam plug (<4um)." In his presentation, Mr. Leighton corrected this as follows: the multidust polyurethane foam plug is used to sample **inhalable** particles <**100** um and the glass fiber filter is used to sample **respirable (<4 um)** particles that pass through the foam plug).

Mr. Leighton presented a summary of key study design parameters, including site locations; weather, which included conditions with wind speeds up to 10 miles per hour (mph); receiving containers; product containers; sampling dates; and sampling durations, which tended to be short. Varying the parameters produced variations in AaiH and particle size. Mr. Leighton then shared photographs of different study designs, including pouring from different step heights into a receiving tank; pouring from a pool deck into a swimming pool that was built specifically for this study; pouring of powders by a worker wearing chemical-resistant gloves; use of a scoop to pour powders, air monitors worn by test subjects within their breathing zone; use of a scoop for granules by a consumer, which generated less of a dust cloud than powder; pouring granules into a pool by a consumer; and pouring powder into a pool, which also created a large dust cloud.

The AEATF II was responsive to EPA and prior HSRB comments. EPA and the HSRB made many recommendations to improve clarity, study design and safety (e.g., varying pour height, moving around the pool during the scenario, using a partially closed lid, wearing respiratory protection) that resulted in clarifications and modifications by the AEATF II to the study protocol that were to EPA's satisfaction. The AEATF II made 16 protocol amendments, some of which were minor, including the following modifications of note: the inclusion of consumers who did not own pools, the inclusion of employees of AEATF II companies, and the removal of 25-pound (lb) containers. The study had 10 reported protocol and two SOP deviations, as well as a few minor deviations identified by EPA (e.g., use of a sump pump in the pool), but EPA thinks that these deviations do not undermine or compromise the exposure results.

Mr. Leighton highlighted the hand-wash removal efficiency and stated that AEATF II corrected hand and face/neck results with an 85 percent correction factor to account for sampling and method efficiency. AEATF II cited prior dermal absorption studies done in rats (Inokuchi et. al., 1978) that reported results of skin wiped at 6-, 9- and 12-hour dose intervals. EPA removed AEATF's 85 percent correction factor (because the rat skin wipe results were derived using the analyses of both the gauze used during dosing and post-application removal of material from the rat skin, and therefore, the amount of residue removed from the skin is unknown) and considered the following options to account for removal efficiency: (1) require a human hand-wash study be performed; (2) use a default correction factor; and (3) use no correction factor. EPA decided on option three, no correction of the data, and provided compelling arguments to support its decision, based on short sampling times, low dermal absorption of CYA,

(Inokuchi (1978) showed only 1 to 3% of CYA in excised rat skin 21 hours after dosing), and the fact that the solid formulation of CYA is very water soluble. EPA resolves to recalculate study data if new information is obtained with regard to hand wash removal efficiency for this active ingredient. Initial results showed that all laboratory and field blanks (controls) for hand wash and face/neck wipes had test results less than the limit of quantification (LOQ). Also, readings for six whole-body dosimeters (WBD) worn internally, two glass fiber dosimeters and 8 foam plug dosimeters were slightly greater than the LOQ. The laboratory and field recoveries were satisfactory, and these studies were performed per EPA Good Laboratory Practice Standards (40 CFR Part 160).

Two statistical methods were used to estimate unit exposures (UE): empirical estimates and log-normal simple random sample (SRS). Log-normal SRS was found to best represent the UEs determined in this study (Tables 1A and 1B of EPA's science report). Mr. Leighton noted that statistician Dr. Jonathan Cohen, ICF International, provided valuable input to EPA on this project beginning in 2006. One of the main goals in selecting a surrogate chemical (e.g., CYA) is to achieve a low LOQ, which will minimize the potential for having nondetectable (ND) results driving the risk assessment decisions. Results from this study showed that all of the hand and face/neck wipes, except one, had levels greater than the LOQ. Almost all WBD and inhalation samples were greater than the LOQ. He pointed out that the effect of NDs was reviewed (Appendix A in EPA's science review), and nearly identical results were obtained using all four substitution methods, which included substituting non detects with 0, ½ LOQ, the full LOQ, and maximum likelihood methods as discussed at prior HSRB meetings. The EPA used a substitution of one-half the LOQ for nondetected samples.

Mr. Leighton discussed some of the results from the different pouring scenarios. Regression plots for long dermal exposures (occupational granules) showed a strong linear relationship between the log of long dermal exposures and the log of AaiH. The relationship between short dermal exposures (consumer granules) and AaiH showed that exposure increased with increasing AaiH, but the linearity was not as significant. Minimal differences were noted between the experienced and inexperienced consumer subjects. A consumer subject who did not own a pool was identified by AEATF II as a potential outlier to the data. This subject, identified as powder ME17 and Granule ME9, had the highest exposures of the data set. The subject's pouring practices were described as messy. The effect of the potential outlier was not pronounced, with the exception of the dermal granular exposure values. For the dermal granular exposure estimates, the UE is 1.87 mg/lb active ingredient using all of the data, and 0.948 mg/lb active ingredient when excluding the ME9, and EPA decided to use all the data. The Agency's argument for this decision is that the use of antimicrobials is not restricted to experienced homeowners and that the subject was observed being messy, not negligent. Mr. Leighton briefly summarized some of the results. Trends showed that powder UEs were greater than granule UEs, and consumer UEs were not directly comparable to occupational UEs because of the differences in clothing configurations and the use (or not) of chemical resistant gloves. Detailed results of the various scenarios have been included in EPA's science review.

One of EPA's standard analyses in assessing these types of studies is to determine whether the sample size is adequate. The results of the threefold relative accuracy goal (slope less than or equal to 3) for the log-normal SRS model showed that the slopes were less than 3 for all scenarios, except for consumer granule dermal exposure, whose slope was 3.6. Mr. Leighton pointed out that the slope was less than 3 when ME9, the subject mentioned above whose data appeared to be an outlier, is excluded from the data set. EPA concluded that the sample size is sufficient and did not require additional monitoring for this scenario. In addition, proportionality or log-log linearity calculations indicated that exposure tended to increase with AaiH. Utilizing a threshold concept, EPA can characterize the exposure estimates when they under- or over-estimate exposure relative to the AaiH. In most situations, the estimated exposures using the normalized unit exposures (slope = 1) are greater than the estimated exposure using the linear regression (slope <1).

Mr. Leighton remarked on the study design limitations. The study was not designed to monitor exposures from the very large packaging containers (e.g., 1000-lb Super Sack® containers). During the study, use of the 25-lb container was discontinued, and therefore, these container sizes are not recommended for consumer packaging. The particle sizes of powders and granules were provided in the EPA science review; assessors need to determine the representativeness of these surrogate data in comparison to use of the data in future assessments.

EPA plans to use UE data from this solid pour study to generically estimate potential exposure to low-or-moderate-volatility pesticides packaged as solid formulations for open pouring. The Agency will assess occupational and consumer exposures using the appropriate clothing configurations tested in this study. In addition, EPA will assess the exposures using chemical-specific hazard and dermal absorption data, as appropriate, to estimate internal dose and risk.

In conclusion, EPA confirms that the study results are sufficiently sound to support estimates of dermal and inhalation UE. The hand-wash removal efficiency study is not required now. There is no justification to exclude any exposure measurements as outliers. An adequate number of samples were collected, and data limitations should be acknowledged in the assessments.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification.

In response to an HSRB question, there was a discussion that the outliers identified in the consumer granule scenario were 3.7 standard deviations from the mean based on a straight calculation. These data may not be true outliers and could be representative of the diversity built into the study design. Consumer handling practices (messy versus nonmessy) may play a role as well. The HSRB member noted that he supports the use of the full data set.

The HSRB turned the discussion to use of cyanuric acid (CYA) as a surrogate for other solid pour formulations and asked EPA to comment on the anomalies such as the clumping of the product and the various aspects of the scenario that may or may not translate to other products or scenarios. One of the HSRB members highlighted that, based on the reading material provided, there is a tendency for this material to clump when stored. The HSRB noted that if a large clump falls out of the container, it removes that mass of the active ingredient from the plume pathway. An HSRB member asked, how much concern should we have for this particular surrogate representing all other products? EPA responded that the majority of consumers using powders and granules are using them for hot tubs, spas and swimming pools. EPA noted that when you look at the photographs included in the study, you will see that when users broadcast the material with a scoop, you lose the clumping and get the powder. Because of the diversity of pour approaches brought into the study design, EPA believes it captures the representativeness of use of the product. Use of CYA as a surrogate for other solid pour formulations is not a concern for EPA, including whether it tends to clump and splash. The broadcasting scenario and diversity of pour designs (e.g., scoops) used in the study should address this issue.

An HSRB member asked for additional information about the composition of other products in the universe that this product cyanuric acid is supposed to represent. A representative of the task force and the study director responded that antimicrobial formulations containing high levels (up to 100 percent) of active ingredient are primarily restricted to occupational and industrial use where personal protective equipment is used. Products for consumers have 1 percent or less concentration of biocide.

An HSRB member noted that, on page 45 of the study, it states that when the whole body dosimeters are removed from subjects, the researchers hang them on hangers. The HSRB member asked if any of the product falls off when the dosimeters are placed on hangers. The study director responded that she did

not think that a lot of product was lost during the process of removing or hanging the dosimeters. The HSRB member noted that the introduction of a safety factor could take care of some of these imperfections. The HSRB member recommended that, in the future, consideration be given to placing the dosimeters on plastic immediately after removing the dosimeters from the subjects.

An HSRB member asked a question about how the air calibration checks were conducted. In response, EPA and the study director clarified that air calibration checks were conducted in a clean area away from the testing site and were performed before monitoring. A timer was used to record the monitoring period.

An HSRB member asked for clarification regarding the terminology "log-normal" and "log-log linear" model. In response, EPA's statistics contractor clarified that the log-normal statistical model assumes a normal distribution; the log-log linear regression model is assessing the log UE against the log AaiH.

Hearing no additional questions of clarification, Dr. Dawson asked Ms. Lydon to present EPA's ethics review.

EPA Ethics Assessment

Ms. Lydon provided the ethics assessment of completed study AEA07 and began with recruitment. Subjects were recruited through advertisements in 2 daily newspapers in Northern Ohio and a regional (English/Spanish) publication. Because of initial low response rates, newspaper advertisements were run for a second week and radio ads were also used, based on a protocol amendment approved by the overseeing Institutional Review Board (IRB). For 2014 recruitment for the consumer phase of the study, in order to increase the response rate, people who did not own a pool and/or had no previous experience with pool chemicals were allowed to participate based on another IRB-approved amendment. For 2015 recruitment for the occupational phase, in order to increase the response rate, the inclusion criteria were expanded; people who had occupational experience handling solid chemicals but were not necessarily currently employed in that position were allowed to participate in the study, based on a protocol amendment. A second protocol amendment expanded the inclusion criteria to allow employees of task force member companies to participate in the study. Another amendment increased compensation for participating in the occupational phase to $175. Using the approved telephone screening scripts and taking into account IRB-approved protocol amendments, interested callers were interviewed via telephone to determine if they met the inclusion criteria. If subjects were interested and eligible, they were scheduled for an informed consent meeting. In summary, recruitment was consistent with the amended protocol. The process was free of coercion or undue influence.

Regarding the informed consent process, initial consent meetings were held with 1 to 3 potential subjects. The Study Director provided an overview of the study and asked subjects to read the consent form. After subjects read the consent form, the Study Director read the consent form to the group and answered questions. The study purpose, inclusion and exclusion criteria, and freedom to withdraw were described in detail and subjects were encouraged to ask questions at any time. Label safety statements were explained and subjects were asked if they wanted to see the labels and/or Safety Data Sheets but they declined. Subjects were allowed to take the consent form home to discuss with family/friends but none chose to do so.

If a potential subject met the inclusion/exclusion criteria and was still interested in enrolling, he/she met one-on-one with the study director. Their identification was checked to verify identity and age. During individual meetings the potential subjects were asked again if they had further questions. After answering questions, the Study Director gave a short standardized oral comprehension test to ensure each subject understood what was being asked of them. Subjects signed and dated the consent form, and

completed and signed the Worker Qualification Worksheet. Each volunteer was given a copy of the consent form to take home and $20 for attending the consent meeting.

The fact that the Study Director asked subjects, during the consent process, if they wanted to see the labels and/or safety data sheets was consistent with the safety precautions section of the protocol. However, a different section of the protocol (on page 752 of the completed study) states that potential volunteers will be given copies of the safety data sheets and product labels in addition to the consent form and subject qualification worksheet. As a result, the protocol for study AEA07 provides inconsistent guidance on providing safety data sheets and labels to subjects. In the future, when reviewing protocols, the study sponsor and EPA should ensure that different sections of protocol are consistent when discussing the same topic.

In summary**,** the subjects were offered but declined the opportunity to see the Safety Data Sheets and product labels; however, the label safety statements were explained during the consenting process and reviewed with the subjects again on the day of monitoring.

Turning to subject demographics, for the consumer monitoring phase, twenty subjects volunteered to participate. Eighteen subjects (eleven males and seven females) were monitored and all met the inclusion criteria. Two other subjects withdrew prior to their scheduled monitoring. For the occupational monitoring phase, twenty subjects volunteered to participate. Seventeen males and 1 female were monitored.

EPA reviewed the implementation of monitoring events compared to the guidance in the amended protocol. Implementation of monitoring events is discussed in at least thirteen different sections of the study including: study design, study conduct, description of the test site, pouring parameters, environmental monitoring, exposure monitoring, the role of researchers, procedures of monitoring events, consumer monitoring, occupational monitoring, conduct of monitoring events, environmental conditions, and observations of subjects. EPA compared the information in these sections of the study to the amended protocol. The monitoring events were conducted in substantial compliance with the amended protocol, with the exception of the reported and unreported deviations discussed later.

Regarding safety precautions, the Study Director confirmed that the precautions described in the study were implemented. As described in protocol amendment 3, a nurse was not available so the on-site medical professional was a first responder, whom the Study Director confirmed was certified. The first responder implemented all activities assigned to the nurse, including examining hands and faces before the study for cuts, abrasions, skin conditions and checking for signs of dermal irritation after monitoring events.

As a study precaution and consistent with the protocol, subjects were given safety glasses and dust masks to wear during pouring. Subjects in the occupational monitoring phase were also given new chemical-resistant nitrile gloves. Subjects also wore inner body dosimeters in the form of long underwear and outer dosimeters (meaning a long sleeved shirt and pants). The study adhered to other risk mitigation measures referenced in protocol (in the "risks to subjects" section) including: adhering to the range of duration for subjects to handle containers, telling subjects to take breaks at their discretion, although none chose to do so, and closely observing subjects during monitoring events.

The observation notes highlight a protocol deviation when discussing consumer monitoring for the powder formulation and monitoring event 14. Subject 3 commented, before monitoring, that he doesn't use powders and the handling technique should be different due to smaller particles. The Study Director recommended to subject 3 that he not toss the powder across the pool. This recommendation deviates from the protocol which states subjects will be allowed to handle the containers as they normally do. This

deviation did not negatively impact the health and safety of the subject and likely reduced the subject's exposures.

Turning to compensation, the eighteen test subjects who participated in the consumer monitoring phase in August 2014 were compensated $100 each. Two subjects withdrew before their scheduled monitoring day. All twenty test subjects who participated in the occupational monitoring phase, conducted during the spring of 2015, were compensated $175 each. Amendment 10 increased compensation for the occupational phase based on new information learned by the Study Director, as described in EPA ethics review. Each subject who attended a consent meeting was compensated $20.

Turning to protocol amendments, AEATF II submitted sixteen amendments to the overseeing IRB, Schulman IRB, which approved all of them. Ten of the sixteen amendments are discussed in OPP's ethics review because they are of ethical interest. (Due to time limitations, EPA did not repeat the applicable 7 pages of EPA's ethics review during the HSRB meeting presentation.) Of the 10 amendments, OPP found one component of amendment 3 to be problematic from an ethics standpoint**.** AEATF II has already agreed to a follow-up action to address it for the future.

Part of amendment 3 submitted to the IRB states that: "Changes to the protocol currently require review and approval by the IRB prior to implementation. This is changed to: 'All other amendments must be reviewed and approved by the IRB.'" The stated reason for the change submitted to the IRB was: "Protocol amendments are normally signed by the Study Director before they are sent to the IRB and thus already implemented." Schulman IRB approved amendment 3, which includes six different components, on September 23, 2014. From an ethics standpoint, EPA has a problem with the last change proposed by amendment 3. It revised the language in section 7 (oversight of ethical conduct) of the EPA and HSRB-reviewed protocol as follows: "All protocol changes (amendments and deviations) shall be reported to the IRB in writing by letter, fax or email. Proposed changes (amendments) deemed necessary to eliminate apparent immediate hazards to the human subjects may be implemented without prior IRB approval. All other amendments must be reviewed and approved by the IRB ~~prior to implementation, or as specifically instructed by IRB policy in this regard~~." The revision proposed by the study director eliminated the need for Schulman IRB to approve future amendments (which did not involve imminent hazard) <u>prior to</u> implementation. As described in 40 CFR §26.1108, each Institutional Review Board (IRB) must follow written procedures for ensuring "prompt reporting to the IRB of proposed changes in research activity" and "ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects."

The approved research is based on the content of the approved AEA07 research protocol. The overseeing IRB for study AEA07 is Schulman IRB, whose website includes their policy on amendments that reads as follows: "Under normal conditions, you must submit to the Board all amendments, including administrative letters, or changes to the protocol for review and approval prior to the implementation. When submitting a revised protocol, provide a summary of changes between the revision and the previously reviewed version. Occasionally, safety concerns may require you to implement an amendment prior to Board approval. When changes to the protocol are implemented in order to eliminate an apparent immediate hazard to a research subject without prior Board approval, you must report changes to Schulman within 10 business days. Administrative changes to a protocol generally require Board approval. However, when you submit changes that are limited to typographical corrections or changes in contact information, Schulman will acknowledge receipt. Board approval is not required for these."

With regard to submittal of amendments, study sponsors need to follow the overseeing IRB's policy, which in turn must be consistent with 40 CFR §26.1108. Section 22, part A, of the protocol that was reviewed by EPA and the HSRB states that, "Proposed changes (amendments) deemed necessary to eliminate apparent immediate hazards to the human subjects may be implemented without prior IRB

approval. All other amendments must be reviewed and approved by the IRB prior to implementation or according to IRB standard procedures." OPP approved the protocol based on this language and reasonably assumed that it would be retained given the importance of an independent ethics review prior to implementing protocol changes.

When study sponsors submit completed human research studies to OPP, information pertaining to the ethical conduct of the research must be provided to EPA as described in 40 CFR §26.1303, which further references 40 CFR §26.1125 (a) through (f) and correspondence between the IRB and the investigators or sponsors. The ethical conduct of the completed research must be consistent with 40 CFR Part 26 and EPA can only rely on completed research which is scientifically sound and conducted in an ethical manner with one exception as noted in 40 CFR §26.1706. Compliance with the federal rule with regard to submittal of protocol amendments is considered when OPP reviews the ethical conduct of the study.

In summary, in order for AEATF II and its study directors to implement current and future human research studies in conformance with 40 CFR Part 26, all amendments to the approved research protocol must be submitted to the IRB for review and approval prior to implementation, except for changes necessary to eliminate immediate hazards to human subjects, and as documented in the overseeing IRB's amendment policy. The Office of Pesticide Programs (OPP) believes that the traditional language in the protocol on the amendment process as reviewed by OPP and the HSRB should have been retained.

After reading the completed study, OPP explained its position to AEATF II. With one exception, AEATF II has already agreed to seek IRB approval of all protocol amendments prior to their implementation in current and future human research studies to be submitted to the Office of Pesticide Programs consistent with the published policy of the overseeing IRB. The published policy must comply with 40 CFR §26.1108; the only exception would be situations involving imminent hazard to human subjects.

Because amendment 3 was approved by Schulman IRB on September 23, 2014, but its 6 components were implemented in August, 2014, the actions taken by the study sponsor under amendment 3 were, in effect, deviations from the protocol at the time they were implemented. They became formal amendments to the protocol only after the IRB approved them in September, 2014. When OPP posed questions to AEATF II regarding the timing of implementing their protocol amendments, the Task Force provided a chronology of their amendments. This was provided to the HSRB in Attachment 5 of EPA's ethics review and lists the IRB approval date of each amendment and the researcher's implementation date. Attachment 6 to the ethics review provides AEATF II's accompanying documentation certifying that 6 of their amendments were implemented after IRB approval (either on the same day as the IRB approval or a subsequent day). AEATF II certified that the following 6 amendments were implemented <u>after</u> IRB approval: Amendments 1, 2, 6, 9, 10 and 11. Each of these amendments, plus amendment 5, is described in EPA's ethics review. Amendment 12 was never implemented.

Eight amendments were implemented before the IRB had approved them but <u>after</u> the IRB had approved the component of amendment 3 which stated "All other amendments must be reviewed and approved by the IRB" without stating when they must be reviewed. These eight amendments (3, 4, 7, 8, 13-16) were all reviewed and approved by Schulman IRB on the dates included in Attachment 5 to EPA's ethics review.

Amendment 4 removed the use of 25 pound buckets of powder from consumer monitoring and specified other smaller containers to be used by the three affected subjects and monitoring events (MEs). The rationale submitted to the IRB was that, "Using the smaller containers is more representative of actual products that might be used by the average consumer. Switching to smaller containers was discussed with EPA in August, 2014, prior to implementation." However, when justifying the timing of amendment 4 to EPA in 2016, AEATF II stated that amendment 4 was implemented in August, 2014,

about a month prior to IRB approval, in order to eliminate a potential and immediate hazard. EPA does not agree that this situation falls within the category of eliminating an apparent "immediate" hazard. At the time of implementation, there were other options available, such as waiting for IRB approval of amendment 4 before continuing to monitor subjects in the consumer pouring phrase. The EPA agrees that switching to smaller containers reduced exposure to dusts and powder generated when handling the 25-pound pail during the consumer pouring phase. Amendment 4 was submitted to the IRB 38 calendar days after implementation so the IRB reporting timeframe of 10 days was not met. In the future, if AEATF implements changes to the protocol to eliminate an apparent immediate hazard without prior Board approval, AEATF II has agreed to report changes to the IRB in conformance with the IRB policy.

Due to recruitment challenges, amendment 11 expanded the inclusion criteria for the occupational phase to allow employees, or spouses of employees, of companies represented in the Task Force to participate in the study with specific enrollment safeguards as required by SAIRB. AEATF II discussed this with EPA's former Human Research Ethics Reviewer in March 2015 to ensure OPP's support prior to submitting the amendment to SAIRB. Two employees of AEATF member companies (subjects W33 and W40) participated in the occupational monitoring phase. The facilities located in the monitoring area were regional manufacturing and/or research and development facilities, so the subjects did not even know the parent companies participated in AEATF II. As recommended by EPA and required by Schulman IRB, the following safeguards were implemented: 1) language was added to the consent form; 2) recruiting did not take place in the workplace; 3) no managers were present during recruiting, the consent process or testing; 4) employers/managers were not notified of employees who responded to the advertisements or participated in the study; 5) employees in the study were treated the same as other study participants; 6) no study participants including employees were identified by name or any other way in the study report; and 7) employment affiliation and company name were not recorded in the raw data." This amendment did not negatively impact the rights or health and safety of participating subjects.

Amendment 15 clarified that the extraction time for sample analysis was 4 hours, and updated the contact information for the Study Director. The substance did not raise ethical issues. However, in April 2016, Schulman IRB requested that the Study Director submit a non-compliance acknowledgement because the IRB "noted that these changes took place in 2014 and should have been submitted to the IRB for review and approval prior to implementing the changes." Turning to reported deviations, those are included on pages 94-95 of the study. They did not negatively impact the health and safety and/or rights of subjects

EPA identified four unreported deviations. During the conduct of the study, air temperature, relative humidity, wind speed and direction were recorded at 15 minute intervals, although the protocol states that air temperature and humidity will be documented at five minute intervals. The discrepancy between two different sections of the protocol with regard to providing copies of the Safety Data Sheet and labels to subjects was previously noted. The study observer assigned to subject three recommended that he not toss the powder across the pool; given that study staff are not supposed to influence how subjects use the product, this is a deviation. Finally, the implementation of certain protocol amendments prior to IRB approval could be considered deviations at the time they were implemented. The unreported deviations did not result in a negative impact on the health and safety of subjects.

EPA next discussed the two reports of dermal irritation. During occupational monitoring, as described in the study, "Two of the 18 test subjects (W30 and W35) reported some dermal irritation on their faces at the end of their powder monitoring events (ME 11 and ME 16). Both subjects stated that they felt fine after their faces were washed. Slight skin irritation is a known adverse effect listed on the Safety Data Sheet for cyanuric acid and washing the affected area with soap and water is recommended." The "stop criteria and medical management" section of the protocol states that: "If a subject reports an eye irritation (or other adverse effect) during the work period, they will be asked to immediately stop working.

Research staff will then move the subject to a clean area and assist the subject in gently washing the eye with clean water. The nurse will determine whether medical treatment is necessary." Under protocol amendment 3, the on-site medical professional was a certified first responder. The Study Director confirmed: "Since slight skin irritation is a known potential adverse effect (listed on the MSDS), the first aid instructions on the label were followed. For skin irritation, the instructions are to wash the contaminated area with soap and water. The emergency responder instructed the subjects to first have their faces wiped by the researcher and then wash with soap and water. Once this was completed, she checked with the individuals to see if the skin was still irritated. In both cases, washing with soap and water alleviated the irritation; thus she determined that no medical treatment was necessary." In summary, the amended protocol was followed.

Regarding subject W24, pages 65-66 of the study state in part that: "One test subject (W24, granule ME 6 and powder ME 18 on March 30, 2015) contacted the Study Director the morning after occupational monitoring complaining of stomach pain, vomiting, and sweating. Although these symptoms were not indicative of cyanuric acid exposure, the Study Director accompanied him to the emergency room. No diagnosis was made and the subject was later released from the ER. Follow-up phone calls to the subject were made on April 1 and 2 to monitor his status. On April 2 the subject was feeling better and had returned to work; no further follow-up was done." Appendix H to the study provides the details.

A section of EPA's ethics review highlights the guidance relevant to this incident which includes: the "stop criteria and medical management" section of the protocol); section 2.9 of AEATF SOP 11C, as well as SOP 11F; the approved consent form, specifically the sections on risk and medical treatment for study-related illness or injuries; and a primary point of reference for safety information in the protocol is the Safety Data Sheet (SDS) in Appendix B, and the product labels referenced and included in the protocol. OPP reviewed this guidance and compared the researchers' follow-up actions to the guidance.

First, it's important to review the role of subject W24. Over a 2-minute period, subject W24 poured a 25- pound bucket of the granular formulation into a tank, and over a 3-minute period, he poured three 25-pound buckets of the powder formulation into a tank, both while standing on the top step of a 13-inch stand. During the occupational exposure monitoring phase of the study, as a study precaution and consistent with the protocol, all subjects wore two layers of clothing (long underwear under a long sleeved work shirt and long work pants), and a dust mask, chemical-resistant gloves, and safety glasses. Appendix H states that, subject W24 "is a 22-year old male. He works at a chemical production plant and worked on Monday before coming to Ricera after work. As a materials handler, he did indicate that he worked with a number of chemicals during the day."

After subject W24 spoke with the Study Director the morning after his participation in the study and told the Study Director that he was ill, the Study Director offered to take the subject to the Emergency Room (ER) and the subject accepted this offer. The Study Director (SD) and 2 members of the SD's research team drove the subject to the ER, stayed with the subject until he was released, and drove him home. The Study Director shared the product's Safety Data Sheet with the physicians in the ER and explained the subject's involvement in the study. The Safety Data Sheet, updated in 2014 and discussed in the approved protocol, was the Study Director's point of reference for symptoms.

Appendix H states that: "The only health hazard listed on the SDS for 'cyanuric acid, dry' is slight eye and skin irritation. There is no GHS[1] signal word as CYA is classified by OSHA as nonhazardous (29 CRF 1910.1200). First Aid Measures (section 4) of in the SDS indicates that inhaling powder or particles

[1] GHS refers to the Globally Harmonized System of Classification and Labeling of Chemicals.

may cause respiratory tract irritation or cough; exposure of skin may result in slight skin redness or irritation; eye exposure may cause mild irritation of the eye lids and conjunctiva; and there are no known effects from ingestion." Under 'note to physician', the Safety Data Sheet states: "This material causes mild irritation to the skin and eyes. Removing the material via irrigation is usually sufficient. There is no antidote. Cyanuric acid is readily removed from the body via the renal system and is not bio-accumulated. Treatment is supportive care."

The Study Director wrote, "The subject's symptoms of nausea/vomiting, diarrhea, abdominal cramps/pain, muscle aches, and sweating were not consistent with the information known about exposure to cyanuric acid." The Study Director told EPA: "It is AEATF policy to pay for research-related injuries or illnesses not covered by a subject's or his employer's insurance. However, in this case, the symptoms that appeared the following day were not reflective of exposure to cyanuric acid. For this reason, the task force did not offer to pay for the medical expenses, and the subject did not request that we pay the bill."

Based on available information, the Study Director concluded that the incident was not the result of the subject's participation in the study. As a result, the study sponsor was not required to pay for the medical costs associated with the subject's visit to the ER that were not covered by his insurance or his employer's insurance.

As documented in Appendix H, the Study Director called the subject back after their initial conversation and offered to take the subject to the ER to be examined; OPP believes this was an appropriate action on the part of the Study Director in light of the language in SOP 11C that the "Study Director will instruct him/her to call 911 or seek medical treatment…". On this point, the study team went beyond the requirements of the protocol and standard operating procedure (SOP) by taking the subject to the hospital emergency room (ER), waiting there until the subject was released, and taking the subject home.

As a result of the Study Director offering to take the subject to the ER, he might have assumed, given his state of distress and illness, that the study sponsor would pay for the costs of his visit that were not covered by his or his employer's insurance. The consent form states that "If you experience a skin reaction, respiratory irritation, eye reaction, or other physical injury that you believe is related to your participation in the study, you should seek medical treatment and call the Study Director immediately." The subject calling the Study Director implies that the subject believed his reaction could have been related to his study participation. According to Appendix H, the Study Director questioned the nurse and doctor who examined the subject at the emergency room about the results of their tests and diagnosis, "but they said they couldn't tell me anything due to the HIPAA laws." The Study Director documented that, "To my knowledge they also did not provide W24 with any information about the tests that they had run or a diagnosis. They suggested that he see a local doctor the next day if the symptoms persisted and provided a prescription for anti-nausea." Given the facts as presented in Appendix H, the language in the signed consent form, protocol and SOP 11C (which is explicitly referenced in the protocol), AEATF was not required to pay for the subject's medical and treatment costs that the subject's own insurance or his employer's insurance did not cover. While acknowledging this, EPA's Office of Pesticide Programs believes it would have been preferable for the study sponsor to do so out of an abundance of caution. The doctor and nurse were prohibited under HIPAA laws from sharing a diagnosis and, as a result, the Study Director's consultation with them did not yield any information that she could factor into her decision as to whether or not the illness was due to participation in the study.

The factors which were taken into account in deciding that the incident did not result from the subject's participation in the study were reflected on page 704 of the study: "Based on the SDS and discussion with the manufacturer of cyanuric acid combined with the very short duration of exposure (5 minutes) and the fact that the subject was wearing protective equipment, the Study Director does not believe that this event was associated with participation in the exposure monitoring study." Section 2.9 of

SOP 11C states, in part, that: "2.9 If a test subject contacts the Study Director within 24 hours of participating in a study with complaints about a skin or eye reaction of other adverse effects that he/she believes are related to his/her participation in the study, the Study Director will instruct him/her to call 911 or seek medical treatment and to call the toll-free number on the product label. The Study Director will not make any medical recommendations. A follow-up phone call to the individual will be made by the Study Director or designee (who had the required ethics training) within 24 hours of a volunteer subject's phone call. The purpose of the call will be to inquire about the health of the individual and to close the case."

The study team went beyond the requirements of the protocol and SOP when they drove the subject to the hospital emergency room (ER), waited there until the subject was released, and took the subject home. Two follow-up phone calls were also made to the subject to inquire as to his health status. As noted on pages 65-66 of the study, "Follow-up phone calls to the subject were made on April 1 and 2 to monitor his status. On April 2 the subject was feeling better and had returned to work; no further follow-up was done." The only applicable portion of section 2.9 of SOP 11C that was not carried out was instructing the subject to call the toll-free number on the product label. As such, this is a protocol deviation. As the Study Director explained to EPA: "The subject was in considerable distress when he contacted the Study Director. Based on the subject's condition, the Study Director decided not to ask him to call the toll-free number; instead the study team took him to the ER and waited there until he was released and took him home. This went beyond the requirements of the SOP. The Study Director did contact and inform the chemical supplier company of this incident from the ER. The company did not provide any additional direction or information for her or the ER staff to follow."

At the EPA's request, the Study Director asked the chemical supplier company what the company does with the information it receives from such calls. The Study Director clarified that, "According to the chemical company, the information would be reviewed internally to determine whether there were any reporting requirements under TSCA." [The Toxic Substances Control Act (TSCA) Section 8(e) states that U.S. chemical manufacturers (including importers), processors, and distributors must notify the EPA within 30 days of obtaining information that reasonably supports the conclusion that their chemical products present a *substantial risk of injury to the health or environment*.]

It is reasonable that the Study Director did not ask the subject to call the toll-free number on the label at the time that he was ill and had to be driven to the emergency room. However, in hindsight, near the conclusion of the Study Director's second follow-up call with the subject, it would have been preferable for the Study Director to provide the subject with the toll-free number and suggest that he call it to report his illness; during the second phone call, the subject said that he was feeling better and had returned to work so it would have been an appropriate time to recommend this to the subject. Consistent with SOP 11C, which is referenced in the protocol, EPA believes the Study Director should have provided the toll-free number to the subject and instructed the subject to call the chemical company to report what had occurred. As it relates to this incident, the Study Director complied with the requirements of the protocol and relevant SOPs with the exception of instructing the subject to call the toll-free number on the product label, as discussed above. The fact that AEATF did not instruct the subject to call the toll-free number on the product label is a protocol deviation.

As discussed in the ethics review, after consulting with Schulman IRB, the Study Director determined that the Subject W24 incident did not fit any of the IRB's reporting categories and, as a result, did not require formal reporting to the IRB.

As a result of considering the incident involving subject W24 and reviewing applicable language in the protocol, SOPs and the consent form, the Office of Pesticide Programs identified the following lessons learned and follow-up actions:

1. In future screening of potential subjects for human research studies as appropriate, study sponsors could ask a standard question, "What specific chemicals, if any, do you currently work with as part of your job?" If the study sponsor and/or EPA recognize that the specific chemicals with which the subject works could potentially present a problem in terms of the subject's involvement in the study, the subject could be excluded from participation. The related exclusion criterion could be, "Works with chemicals which are potentially problematic in terms of subject's participation in study." EPA should consider this option, only as appropriate, when reviewing future protocols.
2. In the future, when a consent form includes language similar to "*The Study Director in consultation with the on-site medical professional will decide if you have an illness or injury that is due to your participation in the study*," EPA should request that a provision be included in the protocol that the on-site medical professional cannot be a member of the study team as was the case here. In such circumstances, it's preferable to have a medical professional who is not employed as a member of the research team consulting with the Study Director when determining if an illness or injury resulted from the subject's participation. This avoids even the appearance of impropriety.
3. In future studies, if an incident occurs, AEATF needs to follow all applicable aspects of AEATF II SOP 11C if this SOP is referenced in the protocol, including the Study Director instructing the subject to call the toll-free number on the product label and ensuring the subject has the product label, consistent with the protocol.

Regarding subject 9, pages 83-84 of the study states, in part: "The subject (AEA07-09) who performed ME 9 had no pool maintenance experience and no experience pouring solid pool products; his extremely messy work practice…reflected his inexperience. Based on his inexperience and the fact that he was selected to do the more complex task of pre-dissolving product in a bucket, it was decided that ME 9 was not representative of the population being monitored for that particular task and should be removed from the dataset." Page 87 of the study adds that: "The highest unit exposure… during the pouring of granules was seen with ME 9. This ME was removed from the granular pouring dermal dataset due to the complexity of the task and the unfamiliarity of the subject with the procedure of pre-dissolving pool chemicals and was also removed from the inhalation dataset." From an ethics standpoint, there is no reason to exclude the data associated with ME 9 and the EPA does not intend to do so.

Protocol amendment 2 modified the inclusion criteria for consumer monitoring to allow participation by people who did not own a swimming pool and did not have experience with adding granules or powder products to a pool to be more representative of first-time pool owners. Given that the protocol was specifically amended to allow participation by subjects who did not have experience adding granules or powder products to a pool, it would be unreasonable for the EPA to exclude data from such a subject solely because of inexperience. EPA does not intend to exclude the ME 9 data.

Attachment 1 to EPA's ethics review provides AEATF II responses to EPA and HSRB comments on the protocol. AEATF was responsive to ten of the twelve applicable comments from EPA and the HSRB on the protocol. Regarding one comment which was not addressed, EPA asked that the research-related injuries section of the consent form be revised to add skin reactions and respiratory reactions to the list of reactions for which subjects should seek medical attention and call the Study Director if they thought the symptoms were due to the study. This comment was addressed. The HSRB thought that the subjects should call the Study Director if they were experiencing symptoms regardless of whether or not the subject thought they were related to the study. AEATF did not think it was appropriate to advise subjects to seek medical treatment for symptoms unrelated to the study

Secondly, the protocol states that if two or more subjects develop an adverse skin reaction after leaving the test site, all subjects will be contacted by the Study Director to determine whether further medical management is appropriate. EPA asked that this sentence be expanded to include eye or respiratory irritation. The Task Force had agreed to address this comment but AEATF II stated they

inadvertently missed this change when making the other requested changes. The other 10 changes requested by the HSRB and EPA were incorporated into the revised materials.

Schulman IRB submitted additional documentation at EPA's request. With that additional information, the IRB correspondence records are complete. The requirements of §26.1303 are satisfied.

The substantive acceptance standards include: 40 CFR §26.1703, which prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children; 40 CFR §26.1705 which prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 CFR 26; FIFRA §12(a)(2)(P) which makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent.

In summary, in EPA's ethics review, the Office of Pesticide Programs recommends that AEATF II take the following actions: 1) With one exception, AEATF II has already agreed to seek IRB approval of all protocol amendments prior to their implementation in current and future human research studies to be submitted to EPA's Office of Pesticide Programs (OPP) consistent with the published policy of the overseeing IRB, which must comply with 40 CFR §26.1108; the only exception would be situations involving imminent hazard to human subjects; 2) In the future, if AEATF II implements changes to the protocol to eliminate an apparent immediate hazard to a research subject without prior IRB approval, AEATF agrees to report changes to the overseeing IRB within the reporting timeframe dictated by IRB policy; 3) In future studies, if an incident occurs, AEATF II needs to follow all applicable aspects of AEATF SOP 11C if this SOP is referenced in the protocol, including the Study Director instructing the subject to call the toll-free number on the product label and ensuring the subject has the product label, consistent with the protocol; and 4) When implementing future AEATF II studies, it's important to follow the protocol with regard to the recording intervals for air temperature, relative humidity, wind speed and direction.

The agency's ethics review also recommends the following actions for the EPA and study sponsors in general: 1) When reviewing protocols in the future, the study sponsor and the EPA should ensure that all sections of the protocol are consistent when discussing the same topic; 2) In future screening of potential subjects for human research studies, study sponsors could ask a standard question, "What specific chemicals, if any, do you currently work with as part of your job?" If the study sponsor and/or the EPA recognize that the specific chemicals with which the subject works could potentially present a problem in terms of the subject's involvement in the study, the subject could be excluded from participation. The related exclusion criterion could be, "Works with chemicals which are potentially problematic in terms of subject's participation in study." The EPA should consider this option, only as appropriate, when reviewing future protocols; and 3) As discussed previously, in the future, when a consent form includes language similar to "*The Study Director in consultation with the on-site medical professional will decide if you have an illness or injury that is due to your participation in the study,*" the EPA should request that a provision be included in the protocol that the on-site medical professional cannot also be a member of the study team. In such circumstances, it's preferable to have a medical professional who is not employed as a member of the research team consulting with the Study Director when determining if an illness or injury resulted from the subject's participation in the study. This avoids even the appearance of impropriety.

With regard to findings, all subjects were at least 18, pregnant or nursing women were excluded, and all female subjects were tested for pregnancy. Subjects were free to withdraw, as demonstrated by the two subjects who withdrew prior to their monitoring day. The protocol was amended when needed and implemented according to the amended protocol, with the exception of the reported and unreported deviations; these deviations as implemented did not compromise the safety or consent of subjects. EPA recommended follow-up actions. Subjects were informed and their consent was voluntary, without coercion or undue influence.

In conclusion, AEATF II agreed to implement the follow-up actions recommended by EPA. Available information indicates that the AEATF II Solid Pour Study AEA07 was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification.

An HSRB member asked if the first responder who replaced the nurse during the study was certified. The study director confirmed that the first responder was certified and that the certification card for the onsite medical professional was photocopied and included in the raw data.

An HSRB member noted that the protocol called for a female member of the study team to verify pregnancy testing results and asked for confirmation that the individual checking the testing results was female. The study director confirmed that, as a female study team member, she certified the results of the pregnancy tests conducted on female subjects in accordance with the SOP.

In response to an HSRB question, EPA confirmed that no information indicates that it is typical for the IRB to approve an amendment removing the requirement for them to approve protocol changes before implementation except in instances of imminent hazard. Ms. Lydon noted that EPA had sent a letter to the overseeing IRB's liaison to AEATF II for study AEA07 explaining the perspective of EPA's Office of Pesticide Programs; the letter explained that in order for study sponsors and study directors to implement current and future studies in conformance with 40 CFR Part 26, all amendments to the approved research protocol must be submitted to the IRB for review and approval prior to implementation, except for changes necessary to eliminate immediate hazards to human subjects, as described in 40 CFR §26.1108(a)(4), and as documented in the overseeing IRB's amendment policy. When reviewing protocols and completed studies, OPP emphasizes this point to all study sponsors and study directors who submit materials to OPP for review. EPA's letter did not specify that study AEA07 was the impetus for the letter to the IRB.

In response to an HSRB question, the study director confirmed that the AEATF II SOP does not include a provision for retrieving medical records in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations. A physician member of the HSRB pointed out that HIPAA regulations often are misunderstood and, in many cases, medical records are provided if permission from the patient is granted, which could be included in an adjusted SOP.

Hearing no additional questions of clarification, Dr. Dawson asked Mr. Downing to call for public comments.

Public Comments

Mr. Downing called for public comments. No public comments were offered.

Board Discussion—Science

Dr. Dawson asked Drs. Randy Maddalena and Jun Zhu to provide their science and statistics reviews.

Dr. Maddalena read the science charge into the record:

> Is the research in study AEA07 likely to generate scientifically reliable data, useful for assessing the exposure of occupational workers and consumers who manually pour or scoop solid formulation antimicrobials products?

Dr. Maddalena noted his agreement with EPA's science review and stated that AEATF II had faithfully addressed the issues previously identified by the Board. The protocol design and execution were of the highest quality and produced a valuable data set on this exposure pathway for consumer and commercial users of these products. The wide range of products handled in the final tests was impressive. The data quality objectives were met and showed trends of increasing exposure with increased handling of product.

EPA identified protocol deviations that needed to be addressed, but they do not appear to affect the science. For example, ME17 in the consumer powder scenario was observed not following the proper procedures for pouring. The suggested corrective actions may reduce the exposure for this particular participant, but did not appear to affect study overall. Also, the order of activities (e.g., granules pour before the powder pour) was changed from random selection to one that was systematic, conferring a bias to more experienced users. Given the range of experience in the subject population, Dr. Maddalena did not see this as cause for concern. However, the amount of carryover from granules to powders was noticeable. Neither EPA nor the AEATF II has addressed this issue in terms of how it might have affected assessing exposure. EPA and AEATF II highlighted several outliers. These incidences of identifiable outliers might be better described as purposeful diversity of the experimental design. Statisticians may offer a different opinion.

Dr. Maddalena remarked on the data limitations that EPA identified and explained that these limitations will be noted in the record. One limitation identified was representativeness; subjects were selected from one region in the United States. Activities conducted in this study will not likely be different in one region of the United States compared to another. Environmental conditions, such as seasonal changes and temperature, are in fact more concrete limitations to consider. The particle adherence to the skin will be different under humid conditions compared to milder temperatures, which could bias the results. He pointed that this test surrogate substance, which contains 100 percent active ingredient (ai), relative to all granule and powder formulations might lead to limitations in generalizability. Since, products have different amounts of ai, measurement of the amount of product used versus the amount of product that adheres to the skin (exposure) may not be the same value. Evidence would be needed to show that the level of ai is evenly distributed across the product. Dr. Maddalena reiterated that the science, the protocol, execution of the protocol and data collected were very impressive; however, including a conceptual model of exposure would be one major improvement to make.

Dr. Zhu provided the statistics review. She stated that the statistical analysis was thorough and well conducted. Two models were used to estimate the UE, and the simpler approach was selected to answer the study question. She pointed out the challenges statisticians have in identifying study outliers versus variations in sample distribution and reiterated Dr. Maddalena's comments for designing conceptual models of exposure to better address this issue.

Dr. Dawson asked for comments from the Board members. In discussion, the following point was reiterated: After the researchers removed the whole body dosimeters (WBD) from the subjects during the study, the researchers hung the WBDs on hangers. An HSRB member recommended that, in the future, consideration be given to placing the dosimeters on plastic immediately after removing the dosimeters from the subjects. Given the potential for loss of the granules and powders, laying the removed dosimeters on plastic throughout the testing process would capture falloff from the WBD and allow a more uniform calculation of UE.

Dr. Dawson summarized the Board's main points: consider closer examination of unexpected exposure pathways such as the potential clumping of powders when pouring from bucket; developing conceptual models in the future for exposure routes and pathways would be helpful; evaluate the use of

cotton as surrogate for solid formulations to represent moistened skin; evaluate the loss of product from WBDs when hanging on hangers; and although the hand wash removal efficiency is addressed adequately in this particular study, the removal efficiency still needs to be addressed in future studies.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Maddalena's scientific review statement:

> The Board concludes that research in study AEA07 is likely to generate scientifically reliable data, useful for assessing the exposure of occupational workers and consumers who manually pour or scoop solid formulation antimicrobial products.

The HSRB unanimously approved the statement.

Board Discussion—Ethics

Dr. Jewel Halanych reviewed the ethical aspects of the research. Dr. Halanych read the following charge into the record:

> Does available information support a determination that the study was conducted in substantial compliance with Subparts K and L of 40 CFR Part 26?

Dr. Halanych supported EPA's ethics assessment of the study. She highlighted four main ethical concerns. The number of protocol changes that were implemented prior to IRB approval is alarming. Two of the changes: (1) prior IRB approval is not needed for protocol changes; and (2) changing the requirement from a study nurse to a certified first responder, could have affected safety. The IRB should have had the opportunity to review this amendment prior to implementation and discuss whether or not a certified first responder was sufficient. In addition, medical personnel reviewing an adverse reaction and determining if it is study-related should be independent of study personnel. Regarding the medical emergency with subject W24, the study director should have instructed the subject to call the product toll-free number on the label.

Dr. Dawson asked for comments from the Board members. In discussion, the following points were made:

One HSRB member raised the question of whether or not the study should have paid for subject W24's visit to the emergency room (ER). Based on the known negative effects of cyanuric acid, HSRB members did not think the subject's visit to the ER had anything to do with his study participation. It seemed to be an unrelated coincidence.

Another HSRB member raised a question about the intended nurse who was to be on site and the nurse's qualifications compared to a certified first responder. The protocol amendment stated that a first responder, not a nurse, would be present during the study. It did not specify the required credentials (e.g. whether or not the first responder would be certified). The qualifications of a certified first responder might be comparable to a nurse. One HSRB member highlighted that if this protocol amendment had been properly reviewed by an IRB, the IRB members would have likely inquired about the qualifications of the first responder to determine adequacy. HSRB members noted during the discussion that details should be provided in the protocol about the qualifications for medical personnel, both those on call and evaluators for adverse events (AE) who determine if the event is related to the study.

In response to a question from the HSRB, EPA explained that, in the Agency's experience, the medical professional cited in the protocol is generally not a member of the study team. An HSRB

member stated that she recommended that a requirement for medical professionals to be independent of the study team be stipulated in future protocols.

An HSRB member also raised the point that the onsite medical professional is not always independent of the study, in practice. Another HSRB member had a different opinion as to whether or not the on-site medical professional needed to be separate from the study team but did not feel strongly about it.

An HSRB member suggested that a statement be included in future consent forms that informs subjects that, if they wish, they can authorize the medical provider to discuss the diagnosis associated with a potential study-related adverse event with the Study Director. Another HSRB member suggested that consent forms also include details on the coverage of medical costs incurred when receiving treatment for a study-related illness and an illness where there is a disagreement as to whether it resulted from the subject's participation in the study

An HSRB member noted that using a subject's current work with specific chemicals as a potential exclusionary criterion should be approached with caution and reviewed from all sides. Attempts to evaluate potential chemical to chemical interaction could be very challenging due to insufficient sources of data. During the discussion, one HSRB member noted that a potential alternative is a required washout period between a subject's chemical exposures at work and participation in a study.

The Board agreed that feedback to the IRB in the final HSRB report regarding protocol amendments and the need to approve them prior to implementation would be appropriate.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Halanych's statement, which she read into the record:

> The Board concludes that the available information supports a determination that the research was conducted in substantial compliance with 40 CFR Part 26, Subparts K and L.
>
> The Board recommends:
>
> - EPA instruct the overseeing IRB to adhere to the federal regulatory requirement for IRB review and approval of protocol amendments prior to implementation, except in instances of imminent hazards to subjects. Specifically, EPA should communicate to the overseeing IRB that they should not have approved the AEA07 protocol amendment which allowed future amendments to the protocol to be implemented prior to IRB review and approval.
>
> - The creation of SOPs that help to determine if adverse events are study related, including a timeline for making this decision. The SOPs should ensure that on-site medical professionals and individuals making the decision on whether adverse effects are study related are independent from the study sponsor and study team. The SOPs should also include instructions on how to negotiate provisions of HIPAA and ensure that subjects know they can authorize release of medical information if they wish.
>
> - Study sponsors should not be required to cover medical costs for adverse events that are not study related.

The HSRB supported the comment from EPA that subject W24 should have been reminded to use the toll-free number of the company on the product label in order to report his illness.

The HSRB unanimously approved the statement.

Adjournment

Dr. Dawson thanked the Board members for their efforts and turned the meeting over to Mr. Downing.

Mr. Downing announced that the next HSRB meeting is scheduled for December 13, 2016, from 2:00 p.m. to 3:30 p.m. for the HSRB to finalize its report from the October 19–20, 2016 meeting. He also informed the Board that, after 32 years with EPA, Ms. Lydon will be retiring on November 30, 2016 and thanked her for conducting ethics reviews of human subjects research and presenting those reviews to the HSRB.

Mr. Downing thanked the HSRB members for their participation and adjourned the meeting at 5:03 p.m.

Respectfully submitted:

Jim Downing
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 Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Vice Chair

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

Members

Jennifer Cavallari, Sc.D., CIH
Assistant Professor
Division of Occupational and Environmental Medicine
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Gary L. Chadwick, Pharm.D., M.P.H., CIP
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George C. J. Fernandez, Ph.D.
Statistical Training Specialist
SAS Institute
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Kyle L. Galbraith, Ph.D.
Human Subjects Protection
Carle Foundation Hospital
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Members (continued)

Jewell H. Halanych, M.D., M.Sc.
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Internal Medicine Residency Program
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The University of Alabama at Birmingham
Birmingham, AL

Walter T. Klimecki, D.V.M., Ph.D.
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Tucson, AZ

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

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 of Entomology
Department of Statistics
University of Wisconsin–Madison
Madison, WI

Consultant to the Board

Kendra L. Lawrence, Ph.D., BCE, PMP
Health Sciences Product Manager
U.S. Army Medical Materiel Development Activity
Fort Detrick, MD

Attachment B

***FEDERAL REGISTER* NOTICE ANNOUNCING MEETING**

ENVIRONMENTAL PROTECTION AGENCY

[FRL-9953-70-ORD]

Human Studies Review Board; Notification of Public Meetings

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA) Office of the Science Advisor announces two separate public meetings of the Human Studies Review Board (HSRB) to advise the Agency on the ethical and scientific review of research involving human subjects.

DATES: A public virtual meeting will be held on October 19-20, 2016, from 1:00 p.m. to approximately 5:00 p.m. Eastern Time each day. A separate, subsequent teleconference meeting is planned for Tuesday, December 13, 2016, from 2:00 p.m. to approximately 3:30 p.m. for the HSRB to finalize its Final Report of the October 19-20, 2016 meeting.

ADDRESSES: Both of these meetings will be conducted entirely by telephone and on the Internet using Adobe Connect. For detailed access information visit the HSRB Website: http://www2.epa.gov/osa/human-studies-review-board

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact the HSRB Designated Federal Official, Jim Downing on telephone number (202) 564-2468; fax number: (202) 564-2070; email address:

downing.jim@epa.gov; or mailing address: Environmental Protection Agency, Office of the Science Advisor, Mail code 8105R, 1200 Pennsylvania Avenue NW, Washington, DC 20460.

SUPPLEMENTARY INFORMATION:

Meeting access: These meetings are open to the public. Meeting materials are available at the HSRB Website: http://www2.epa.gov/osa/human-studies-review-board for questions on document availability, or if you do not have access to the Internet, consult with Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.**

Special accommodations. For information on access or services for individuals with disabilities, or to request accommodation of a disability, please contact Jim Downing listed under FOR FURTHER INFORMATION CONTACT at least 10 days prior to the meeting to give EPA as much time as possible to process your request.

How May I Participate in this Meeting?

The HSRB encourages the public's input. You may participate in these meetings by following the instructions in this section.

1. Oral comments. Requests to present oral comments during either conference call will be accepted up to Noon Eastern Time on Wednesday, October 12, 2016, for the October 19-20, 2016 meeting and up to Noon Eastern Time on Thursday, December 8, 2016 for the December 13, 2016 conference call. To the extent that time permits, interested persons who have not pre-registered may be permitted by the HSRB Chair to present oral comments during either call at the designated time on the agenda. Oral comments before the HSRB are generally limited to five minutes per individual or organization. If additional time is available, further public comments may be possible.

2. Written comments. Submit your written comments prior to the meetings. For the Board to have the best opportunity to review and consider your comments as it deliberates, you should submit your comments by Noon Eastern Time on Wednesday, October 12, 2016, for the October 19-20, 2016 conference call, and by noon Eastern Time on Thursday, December 8, 2016 for the December 13, 2016 teleconference. If you submit comments after these dates, those comments will be provided to the HSRB members, but you should recognize that the HSRB members may not have adequate time to consider your comments prior to their discussion. You should submit your 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.

Background

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act 5 U.S.C. App.2 § 9. The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subjects research that are submitted to the Office of Pesticide Programs to be used for regulatory purposes. 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.

Topics for discussion. On Wednesday, October 19, 2016, EPA's Human Studies Review Board will consider a Protocol for Laboratory Evaluation of Mosquito Bite Protection from Permethrin-treated Clothing for the U.S. Army after 0, 20 and/or 50 washings. On Thursday, October 20, 2016 the HSRB will consider: A Study for Measurement of Potential Dermal and

Inhalation Exposure during Manual Pouring of Two Solid Formulations Containing an Antimicrobial. Meeting materials for these two topics will be available in advance of the meeting at http://www2.epa.gov/osa/human-studies-review-board.

On December 13, 2016, the Human Studies Review Board will review and finalize their draft Final Report from the October 19-20, 2016 meeting. The draft report will be available prior to the conference call at http://www2.epa.gov/osa/human-studies-review-board.

Meeting minutes and final reports. Minutes of these meetings, summarizing the matters discussed and recommendations made by the HSRB, will be released within 90 calendar days of the meeting. These minutes will be available at http://www2.epa.gov/osa/human-studies-review-board. In addition, information regarding the HSRB's Final Report, will be found at http://www2.epa.gov/osa/human-studies-review-board or from Jim Downing listed under FOR FURTHER INFORMATION CONTACT.

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Dated: October 4, 2016

Thomas A. Burke, PhD, MPH,
EPA Science Advisor,