Draft Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
October 19–20, 2015 Public Meeting
Docket Number: EPA–HQ–ORD–2015–0588
HSRB Website: http://www2.epa.gov/osa/human-studies-review-board

Committee Members:	(See EPA HSRB Members List—Attachment A)	
Date and Time:	Monday, October 19, 2015, 1:00–5:00 p.m. EDT Tuesday, October 20, 2015, 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:	Gary L. Chadwick, Pharm.D., M.P.H, C.I.P. Kyle L. Galbraith, Ph.D. Jewell H. Halanych, M.D., M.Sc. Randy Maddalena, Ph.D. Kenneth Ramos, M.D., Ph.D., Pharm.B. Suzanne M. Rivera, Ph.D., M.S.W. Helen H. Suh, Ph.D. Jun Zhu, Ph.D.

Monday, October 19, 2015

Commencement of Public Meeting and Review of Administrative Procedures

Before the meeting was called to order, the use of the Adobe® Connect webinar system to solicit comments from the public via webinar was discussed and explained. Mr. Jim Downing (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor [OSA], EPA [or Agency]) convened the meeting at 1:02 p.m. and welcomed Board members, EPA colleagues and members of the public.

Mr. Downing noted that in his role as DFO under the Federal Advisory Committee Act (FACA), he 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 welcomed a new member—Dr. Helen Suh—to the HSRB. Dr. Suh is an Associate Professor of Health Sciences at Northeastern University whose research focuses on environmental epidemiology.

Mr. Downing informed Board members 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. Copies of all meeting materials will be available at www.regulations.gov under docket number EPA–HQ–ORD–2015–0588,

and supporting documents are available on the HSRB website at www2.epa.gov/osa/human-studies-review-board. Time is scheduled for public comment. Mr. Downing noted that no individuals had preregistered to provide public comments.

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 at www.regulations.gov and on the HSRB website at www2.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 available at www.regulations.gov and on the HSRB website at www2.epa.gov/osa/human-studies-review-board. Mr. Downing then turned the meeting over to the HSRB Chair, Dr. Liza Dawson.

Introduction of Board Members

Dr. Dawson welcomed the Board members and asked them to introduce themselves, providing their names, affiliations and areas of expertise. The Board members completed their introductions.

Welcoming Remarks

Dr. Thomas Sinks (OSA, EPA), Director of OSA, provided opening remarks. Dr. Sinks welcomed the Board members on behalf of EPA and expressed appreciation for their attendance. He recently joined EPA to serve as Director of OSA, which is the office that provides administrative oversight for the Board. He—along with Dr. Toby Schonfeld, the Human Subjects Research Review Official, Mr. Downing, and other OSA staff—reports to the EPA Science Advisor, Dr. Thomas Burke. Dr. Sinks thanked the Board members for preparing for and participating in this meeting; he also acknowledged the efforts of EPA staff, particularly members of the Office of Pesticide Programs (OPP), in preparing for this meeting. Dr. Sinks looked forward with anticipation to the Board's comments on the two topics for this meeting. Dr. Dawson thanked Dr. Sinks for his comments.

Session 1: Completed Study from the U.S. Department of Agriculture Describing Laboratory Evaluation of Bite Protection from Repellent-Impregnated Clothing for the United States Military

Background

Dr. Dawson introduced the first session and asked Mr. Kevin Sweeney (OPP, EPA) to present EPA's science review.

EPA Science Assessment

Mr. Sweeney explained that the study determined whether or not 0.9 percent etofenprox treatment provided bite protection when mosquitoes were exposed to treated fabric. Compared to skin-applied repellent studies reviewed by the Board, this study differed because it was a laboratory study, a different repellent effect was studied, bite protection was the efficacy measure used, and the subjects received mosquito bites. This study protocol was reviewed by the HSRB on April 9, 2014, and revised to reflect EPA and HSRB comments. The revised protocol, as well as a further revision, was approved by Western Institutional Review Board (WIRB). The first protocol amendment approved an additional subject because of low control bite-through values. The second protocol amendment approved retesting an alternate subject because of low bite-through values as a result of incorrectly maintained mosquitoes. An additional change, which was acceptable but should have been filed as an amendment, was that 0.9 percent rather than 1.0 percent etofenprox-treated uniform fabric was used to allow wider certified limits in fabric production. The revised protocol also included an additional treatment of 75 washes (75x). The study objective was to determine the bite protection level of etofenprox-treated U.S. Military Fire Resistant Army Combat Uniforms initially treated at an application rate of 0.9 percent weight/weight and assessed after 0 (0x), 20 (20x), 50 (50x) and 75x washes. The results of the research were compared to the

U.S. Department of Defense's (DoD) specifications for minimum bite protection levels: 85 percent (0x), 80 percent (20x) and 70 percent (50x).

As discussed in the April 2014 HSBR meeting, the registrant agreed to evaluate skin irritation prior to commencing the study. A 28-day skin irritation study on rabbits with etofenprox-treated fabric showed no skin irritation. The acute toxicity of the test material is estimated to be a dermal LD_{50} of greater than 2,100 mg/kg body weight and an oral LD_{50} of greater than 5,000 mg/kg body weight. Assuming an 80-kg subject and 100 percent etofenprox absorption from eight treated sleeves, the equivalent dose rate is 9.5 mg/kg, resulting in a margin of exposure (MOE) less than 210 and an EPA level of concern less than 100.

Mr. Sweeney described the experimental design, endpoints and measures, and the statistical analysis plan. As shown in a video, sleeve tests were conducted by the subjects placing gloved hands in control or treated sleeves made of coat or trouser fabric, taping the sleeves to the gloves, sliding each arm into a test cage containing an average of 200 female mosquitoes preselected from stock cages, using a 15-minute test interval, and harvesting the mosquitoes. Eight subjects, four male and four female, wearing each type of sleeve, were exposed to two species of mosquitoes, *Aedes aegypti* and *Anopheles albimanus*, each tested separately, for a total of 16 replications per fabric type. More frequently than for the control arm, successful feedings for the pesticide arm resulted in the intoxication of mosquitoes and their knockdown to the floor of the test cage. The measure of repellent effects was determined by percent bite protection, where the presence of blood in a mosquito's abdomen was a confirmed "mosquito bite," and percent bite protection was calculated as (1 − [treatment rate of blood-fed mosquitoes]/[control rate of blood-fed mosquitoes]) × 100 percent. The statistical analysis plan was to determine the mean level of bite protection and associated 95 percent confidence intervals (CIs). The statistical analysis plan deviated from the protocol because instead of analyzing the data using a generalized linear model (GLiM) with a log link to determine CIs, a *t*-distribution CI was used. GLiM-based CIs were judged inappropriate because of subject-to-subject variation.

The bite-through and bite protection results of the study were presented by Mr. Sweeney. For controls, the mean percent fed was 89.5 and 71.2 percent, respectively, for *A. aegypti* and *An. albimanus*, indicating the large number of landings and successful feedings for controls. The mean and CI range bite protection results for *A. aegypti* met the DoD reference protection levels for all materials and number of washes except 0x trouser, where the minimum CI was 80.9. The mean and CI range bite protection results for *An. albimanus* met the DoD reference protection levels for all materials and number of washes. Mr. Sweeney concluded that the study was scientifically sound and the data from this study can be used to assess the bite protection of etofenprox-treated uniforms against mosquitoes.

Board Questions of Clarification—Science

Dr. Dawson invited Board members to ask questions for clarification. In response to a question from Dr. Randy Maddalena about whether fabrics were washed individually or together, Mr. Sweeney indicated that all the fabric was washed together and sleeves then were made from the fabrics. No sleeve was tested more than once. Dr. Gary Chadwick asked whether individual subjects underwent all of the tests during a single period. Mr. Sweeney responded that for each subject, all of the tests with one species were performed in a single day, and all of the tests with the second species were performed on a second day.

Dr. Dawson, noting no further questions of clarification, asked Ms. Maureen Lydon (OPP, EPA) to present her ethics review.

EPA Ethics Assessment

Ms. Lydon provided an ethics assessment with regard to recruitment, inclusion/exclusion criteria, the consent process, protocol deviations and amendments, institutional review board (IRB) oversight, implementation of test procedures, responsiveness to EPA and HSRB comments, completeness of documentation, and substantive acceptance standards. Recruiting was conducted consistent with the

protocol. Subjects were recruited through a printed advertisement in the *Gainesville Sun*, the local newspaper, and by posting the advertisement on University of Florida bulletin boards. The HSRB previously reviewed the advertisement, which included a phone number where respondents could leave messages. Thirty one individuals responded to the advertisement. The study director used the approved script to screen the 31 respondents. After preliminary telephone screening, the study director identified 28 eligible potential subjects, with 3 respondents excluded based on age. All the subjects met the approved inclusion/exclusion criteria, including exclusion of children and pregnant and lactating women.

Eight initial subjects were chosen at random, including four males and four females, ages 20 to 57, and the remaining subjects were alternates. An informed consent meeting was held by the study director with each subject; a representative of the study sponsor attended each meeting to pay subjects for their participation in the consent meeting. At the consent meeting, the respondents completed self-certification forms confirming that responses provided during the telephone screening were accurate. The study director explained study procedures and information on the consent form. Subjects were advised of the target number of mosquitos per cage and that controls would result in the highest bite through rate. The study director noted that the mosquitos were disease free and explained that if the subjects felt ill or had any concerns over reactions to bites, they could contact the nurse or study director. Their contact information was included on the consent form. After the detailed explanation of procedures, the study director escorted the subject to the conference room, where the video of the testing process was set up. A member of the study director's trained staff played the video of the testing process. The subjects could ask questions at any time. After the video was viewed and questions answered, the study director asked the sponsor's representative to return to the conference room to pay the subject for participating in the consent meeting. The subject then left with the unsigned consent form. Sufficient opportunity was provided for candidates to consider whether or not to participate. The subject called the study director to schedule an appointment for their test. On the day of testing, subjects entered the laboratory with their signed consent form and verbally confirmed their intent to participate. Female subjects took a pregnancy test on the first day of testing, the negative result of which was verified by a female staff member.

The study reports eight protocol deviations during 2015. The study director consulted with the WIRB on reporting guidance, and WIRB confirmed that the deviations did not require prompt reporting to the IRB (i.e., within 5 days). Ms. Lydon highlighted the one deviation that impacted the informed consent meeting. Deviation 1 was that the sponsor representative attended the informed consent meeting to pay the subjects for participating in the meeting. The protocol said the study director would perform the informed consent meeting; however, the sponsor representative honored confidentiality. No information about the subject's identity or participation in the study was disclosed by the sponsor representative as a result of her attending the consent interview. Also, the informed consent form indicated that information from the study would be given to the sponsor. Ms. Lydon noted that the protocol also did not state that the study director's trained staff would play a video of the testing process and answer subjects' questions, along with the study director, after the video. As a follow-up action to the protocol deviation, EPA requested that the study director and sponsor adhere closely to specifics of the consent meeting and informed consent process as outlined in approved protocols for future studies. Deviation 1 and the other seven deviations were determined not to negatively affect participants' rights or health and safety and not to adversely impact scientific integrity.

The protocol was amended twice after WIRB approval on May 28, 2015. The first amendment asked for approval of an additional subject to be tested to replace Subject 3, for a total of nine subjects. After testing for Subject 3 was completed, the data revealed that the mosquito bite rate for the non-treated control was extremely low for Subject 3; as a result, data from a ninth subject was needed. Subject 3 was compensated for the full amount of $250. The second amendment asked for permission to allow Subject 4 to be retested against one of the mosquito species. Subject 4 had one set of sleeves with very low bite through amounts for controls. The reason was that the mosquitoes had been incorrectly maintained and did not respond avidly. The subject was compensated $125 for retesting, which occurred 3 weeks after the original test.

EPA noted another protocol change that should be reported to the WIRB. The original protocol stipulated a treatment ratio of etofenprox/fabric of 1.0 percent weight/weight, but the study reported a treatment ratio of 0.9 percent. These amendments did not negatively affect the participants' rights, health or safety. As a follow-up action, EPA asked the study director and sponsor to ensure that all amendments are reported to and approved by WIRB in future studies.

IRB oversight was provided by WIRB, which approved the protocol and support materials, including revisions to address EPA and HSRB comments. EPA and WIRB approved the following additional changes to the protocol: inclusion of fabric specimens that had been washed 75x, additional test time of 15 minutes for each of two mosquito species using the 75x wash cycle specimens, and a corresponding increase in compensation from $200 to $250. WIRB approved language for the revised protocol, consent form and advertisement that reflected these changes. By revising the protocol, there was no need to test 8 new subjects with controls in the future for the specimens washed 75 times. WIRB approved the two amendments; and the study director consulted with WIRB on reporting deviations.

Tests were implemented without adverse incidents, no subjects withdrew from the research, and no adverse events or incidents of concern were reported.

The study director and sponsor were responsive to EPA's and the HSRB's comments on the protocol for the study. Ms. Lydon highlighted 14 comments on the protocol and how they were addressed. The details are in attachment 2 to the ethics review provided to the Board. The protocol test procedures were revised to explain that the lab technician or primary investigator would inspect arms for cuts or other skin conditions, clarify when pregnancy testing would occur, and explain that a female staff member would verify negative results. The protocol also was revised to state that subjects received no direct benefit from participating, articulate objective measures for stopping, and specify a standard method and message to notify participants of exposure if test mosquitoes were found to carry disease. The study exclusion criteria were expanded to exclude people with known sensitivity to the test material or other chemical products; exclude people with open cuts, scrapes or skin conditions on their hands or forearms; and to offer nitrile gloves to people with latex sensitivity or allergy. The informed consent form was revised to add a reference to the study procedures about female subjects' taking a home pregnancy test and to add a section heading that highlighted the name and number of the on-call nurse. The study director and research staff also updated their training, as recommended by the HSRB. Two other comments were addressed by the study director and sponsor: (1) instead of asking about shirt sleeve size in the recruitment interview, a range of sleeve sizes were made prior to the study and altered as necessary to ensure a snug fit; and (2) instead of providing full compensation to all of the participants, including those who left the study early, a payment system was established for fair compensation for time spent on the study and to pay subjects for each set of sleeves on which testing was initiated; the consent form states that if you begin the study, but don't complete it, you'll be paid $25 for each set of sleeves tested, regardless of whether the 15 minute test interval was completed.

Documentation was complete, with WIRB correspondence provided, so the requirements of 40 Code of Federal Regulations (CFR) §26.1303 were satisfied. Ms. Lydon described the ethical acceptance standards applied for the conduct of the study. EPA regulations governing the Agency's reliance on research prohibit reliance on data involving intentional exposure of pregnant or nursing women or of children (40 CFR §26.1703) and prohibit reliance on data unless EPA has adequate information to determine substantial compliance with Subparts A through L for 40 CFR 26 (40 CFR §26.1705) . The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) §12(a)(2)(P) also makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent. EPA found that all subjects were at least 18, and pregnant and nursing women were excluded. No significant deficiencies in the ethical conduct of the research were found. Amendments and deviations did not compromise safety, consent or rights of subjects. Subjects were fully informed, and their consent was fully voluntary. The Agency concluded that available information indicates that the laboratory evaluation of bite protections from repellent-impregnated clothing for the U.S. military was conducted in substantial compliance with Subparts K and L of 40 CFR Part 26.

Board Questions of Clarification—Ethics

Dr. Dawson called for questions of clarification regarding EPA's ethics assessment. Dr. Edward Gbur inquired whether selection of subjects was stratified by sex. Ms. Lydon described the procedure by which 20 potential subjects were assigned random numbers, and then the numbers were selected at random until four males and four females were selected. Dr. Gbur commented that the sex stratification procedure should be described because it differs from a randomized selection of subjects. Ms. Lydon responded that for future studies, EPA will recommend that sex-stratified selection of subjects be clarified in the protocol and final report.

Dr. Jewell Halanych indicated that page 10 of EPA's ethics review states that no female subjects were enrolled in the study, which is incorrect; no pregnant or nursing female subjects were enrolled. Ms. Lydon replied that this error will be corrected.

No additional questions of clarification about the ethics review were offered, and Dr. Dawson turned to 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.

Charge Question

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

Charge to the Board—Science:

- Is the research reported in the completed study sufficiently sound, from a scientific perspective, to be used to evaluate the bite protection level of etofenprox-treated military clothing?

Board Science Assessment

Dr. Dawson asked Dr. Maddalena to provide his science assessment. She also asked Dr. Gbur to provide his comments and those of Dr. George Fernandez (who was not in attendance) on the statistical analysis. Dr. Maddalena stated that he had provided written comments to Mr. Downing, and Mr. Downing had sent those comments to the Board members via email. Dr. Maddalena stated that the Board reviewed the study protocol in April 2014, approved the protocol, and concluded that it would provide valid data. The protocol then was revised in accordance with EPA and HSRB comments. Deviations from the protocol were documented, mostly related to the number or quality of mosquitoes in the test chamber. In addition, some amendments to the study protocol occurred that were more ethical than scientific in nature. These amendments were documented and justified. All were approved except for the change in application rate from 1.0 to 0.9 percent weight/weight. Subject retention was good. Dr. Maddalena expressed no concerns about the quality of the data.

Dr. Gbur stated that the study used a simple *t*-distribution as the basis for determining CIs. This approach deviated from the analytical approach that the HSRB had suggested. The study authors had stated that GLiM-based CIs were not appropriate when subject-to-subject variation exists. Dr. Gbur disagreed with this statement. For mixed models, randomization of subjects is common. These models are more realistic, and their results are more readily interpretable than a *t*-distribution. In the analysis of a linear model, subjects can be treated as a random effect, which can be expanded to the general population, or a fixed effect, which is difficult to extend beyond the study population. The *t*-distribution is simpler than the concept of a fixed effect.

Dr. Gbur presented simulation results by Dr. Fernandez comparing *t*-distribution and GLiM means and CIs with eight subjects using SAS GLIMMIX (see Figure 1). Dr. Gbur pointed out that the means determined by both methods were similar, but the CIs were wider using a GLiM than a *t*-distribution. In this case, the overall conclusions would be the same, but the data would have wider generalizability if the GLiM analysis were used. Dr. Gbur did not recommend the *t*-distribution as a general approach for this type of study. If the GLiM analysis is used, the data can be used to answer other questions, such as how many times can uniforms be washed before they need to be replaced.

Figure 1. Simulation Results Comparing *t*-Distribution and Generalized Linear Model (GLiM) Means and Confidence Intervals (CIs)*

Overall Bkg Rate,%	True % Prot	Mean % Prot T	Half Width T CI	Coverage T CI	Mean % Prot GLiM	Half Width GLiM CI	Coverage GLiM CI
10	70	68.3	12.3	95	69.6	14.0	99
	85	84.2	8.2	95	84.7	8.7	98
	95	94.8	4.3	94	94.9	4.6	99
	98	97.9	4.2	93	97.9	3.3	98

Overall Bkg Rate,%	True % Prot	Mean % Prot T	Half Width T CI	Coverage T CI	Mean % Prot GLiM	Half Width GLiM CI	Coverage GLiM CI
25	70	69.5	7.0	94	69.8	9.6	99
	85	84.7	4.8	95	84.8	5.8	99
	95	94.9	2.7	94	94.9	2.9	99
	98	98.0	1.6	94	98.0	1.8	98

Overall Bkg Rate,%	True % Prot	Mean % Prot T	Half Width T CI	Coverage T CI	Mean % Prot GLiM	Half Width GLiM CI	Coverage GLiM CI
50	70	69.9	4.5	95	70.0	6.3	100
	85	84.9	3.2	95	84.9	3.8	99
	95	95.0	1.8	95	95.0	1.9	98
	98	98.0	1.2	94	98.0	1.2	98

Overall Bkg Rate,%	True % Prot	Mean % Prot T	Half Width T CI	Coverage T CI	Mean % Prot GLiM	Half Width GLiM CI	Coverage GLiM CI
75	70	69.9	3.4	96	70.0	4.1	99
	85	85.0	2.5	95	85.0	2.7	98
	95	95.0	1.5	95	95.0	1.4	98
	98	98.0	0.9	94	98.0	0.9	97

* Note: Subject-Subject Background Variation (Logit SD) = 0.3, Subject-Subject Protection Variation (Logit SD) = 0, NrSims = 5000, Seed = 98135183.

Dr. Kenneth Ramos asked whether blood-fed mosquitoes that did not fall to the floor of the test cage were included in the count of blood-fed mosquitoes. Mr. Sweeney explained that all the mosquitoes in the test chamber were harvested, both those that remained airborne and those that fell to the floor, and checked for blood.

Dr. Ramos asked Mr. Sweeney to explain why the DoD reference protection levels decreased with the number of washes. Mr. Sweeney responded that the DoD reference protection levels were derived for permethrin-treated clothing. The differences between protection with wash level for etofenprox and permethrin reflect differences in performance between the two clothing treatments. Dr. Ramos suggested including a footnote explaining the derivation of the protection levels. He added that a future study should investigate the number of washes at which etofenprox protection fails, because protection was maintained at 75x. Mr. Sweeney responded that the study authors did not include higher wash numbers than 75 because they had expected failure at 50x.

Dr. Ramos was surprised that a subject was retested in the control arm and asked what criteria were used to define when a retest was required. Mr. Sweeney responded that a minimum of 20 percent bite-through criterion was used for controls. Dr. Ulrich Bernier added that it was difficult to determine an *a priori* criterion for minimum bite-through. When the data were inexplicably low for one species compared to the other, however, it was clear that the mosquitoes were reared inappropriately and were fatigued. High bite-through controls provide better data about protection. Dr. Ramos noted that the investigators would not have been concerned with low bite-through data in treated sleeves, only control sleeves, leading to the danger of introducing bias by discarding some data. Dr. Bernier responded that the same populations were used to test the treated sleeves as the controls, making it appropriate to not have proceeded past the control sleeves. Dr. Dawson suggested including a pre-specified criterion in the protocol for when to exclude data to avoid introducing bias. Mr. Sweeney concurred with the suggestion.

Dr. Gbur noted that the discussion of the results focused on the mean when making comparisons to the DoD reference protection levels, whereas it is equally appropriate to focus on the lower bound of the CI when evaluating protective effects to soldiers. Dr. Maddalena stated that it is not the Board's role to recommend reference protection levels to the DoD. Dr. Dawson clarified that the Board cannot make a judgment whether a given treatment is sufficiently protective for military personnel, but the Board could indicate that the lower bound of the CI is relevant to evaluating the success of the product.

The Board discussed two different types of statistical analyses: *t*-test and GLiM. Dr. Jun Zhu stated that the simulation showed that the results of the two analyses were not very different, although a *t*-test was not the appropriate analysis. She offered two possible responses of the Board to the deviation from the protocol: (1) ask the investigators to reanalyze their data or (2) discuss the deviation from the protocol in the Board's report. Dr. Dawson added a third option: the Board could recommend that EPA and DoD should not rely on the results unless the investigators reanalyze their data. The Board needs to determine whether the data can be relied on for decision making. Dr. Gbur responded that this study was fortunate in that, based on Dr. Fernandez' simulation, the results from the two statistical approaches were similar, but he would not recommend the method used to determine CIs. The *t*-test results might be valid for determining whether the data met a given reference level, but not for other objectives for which the data might be used. The Board could recommend that in the future, the investigators be more mindful of other "sub-objectives" for which the data might be used and analyze future data with a GLiM. Dr. Bernier responded that if a sub-objective was to determine the number of washes that treated uniforms can withstand until they are no longer protective, he was not certain that DoD would fund another longevity study on etofenprox after sponsoring a study of the longevity of permethrin.

Dr. Gbur indicated that for this study, he was willing to accept the *t*-test CIs without reanalyzing the data, but the Board should recommend that for future studies, the investigators be much more careful with their statistical analysis. Carryover effects might occur from conducting multiple tests in 1 day. These might be mitigated by varying the sequence of wash numbers tested, which was in the protocol comments. Dr. Zhu was in favor of the Board's recommending that the data be reanalyzed properly, and she held the opinion that a reanalysis would not be onerous. Dr. Dawson added that requiring the investigators to reanalyze their data would set a precedent for future studies. Dr. Gbur asked whether EPA was expecting an analysis by GLiM. Dr. Dawson responded that the plan for statistical analysis had not been determined; it was changed as an amendment. Mr. Sweeney clarified that when the protocol was

presented to the Board, the statistical plan had not been decided; use of the *t*-test was reported as a protocol deviation.

Dr. Larry Holden, the statistician who analyzed the data for the study, explained that when the data were collected, very severe subject-to-subject variability in bite protection was observed. Interpreting the data as planned would have yielded odds ratios, rather than a ratio of probabilities, which would have been difficult to compare to the military's reference levels. Dr. Holden indicated that he had attempted to reproduce Dr. Fernandez' results and had calculated approximately the same results whether variability was modeled as a fixed or random effect, which made him doubt the validity of the simulation results. When a random effect was added to a GLiM mixed model, severe convergence problems had ensued. Dr. Gbur suggested that Dr. Fernandez likely ran a different version of the model. Dr. Dawson asked the Board to consider what its recommendation should be if it determines that Dr. Holden's version of the software had challenges. Dr. Gbur responded that he did not want to set a precedent for using a *t*-test to determine CIs because other types of statistical analyses can reflect more closely how the experiment was done. The relevant question in this case, however, is whether reanalyzing the data will change the conclusions of the study, and in this instance, it appears that the data will remain above the reference protection levels. Asking the investigators to reanalyze the data would ensure that a precedent is set. Dr. Gbur suggested that the conflicting results between Dr. Fernandez' and Dr. Holden's simulations were the result of using different versions of the software and that Dr. Fernandez' analysis converged because he was using a more up-to-date version of the GLIMMIX procedure with SAS. Dr. Holden countered that the problem was not limited to a software issue; using a GLiM with a log link with random effects was not conceptually sound.

Dr. Dawson summarized the points made by the Board members in the discussion of the deviation from protocol of the statistical analysis: (1) in this particular case, the analysis is sufficiently sound to interpret the data to meet the study's objective; (2) a better approach to analyzing the data might exist, but there are complications with the software and mixed model methods, which the Board could discuss in its report for the benefit of future researchers; and (3) in the future, the best method to analyze the data should be used. Drs. Gbur, Zhu and Suh expressed their agreement with Dr. Dawson's summation.

Dr. Dawson added another recommendation for the Board's consideration: in future studies, the conditions under which analyses might need to be repeated should be specified. Dr. Gbur added that the issue of how data from participants who withdraw from a study should be considered also had arisen in other studies. Dr. Dawson noted that recruiting alternates, which was part of the study protocol, was a provision for subjects' withdrawing from the study.

Dr. Maddalena suggested that the Board also recommend that these types of experiments include a clearer description of the protocol to address insufficient biting pressure. Dr. Bernier responded that in future studies, the protocols will address insufficient biting pressure, but numerical criteria might be difficult to specify *a priori* because of such factors as fabric type. Dr. Dawson stated that removing a subject because of poor biting pressure introduces nonrandom control of results by the investigator and potential bias.

Dr. Dawson indicated that she had heard no major concerns from the Board about using the study data in decision making. Several comments were made about deviations from the protocol for the statistical analysis. The Board members raised the following two additional issues: (1) the need to specify how to use data from subjects who withdraw from the study; and (2) the need to address insufficient biting pressure in the protocol. Dr. Maddalena stated that the data were sufficiently sound within the limitations of the time of the study. Dr. Dawson clarified that no conclusions could be drawn from the data for more than 75 washes.

Hearing no further comments, Dr. Dawson asked Dr. Maddalena to present the statement in response to the charge question for voting by the Board. The response was read into the record by Dr. Maddalena:

> The Board concludes that the research reported in the completed study is sufficiently sound, from a scientific perspective, to be used to evaluate the bite protection level of etofenprox-treated military clothing within the limits of the number of washes tested.

All the Board members present approved the response. Dr. Dawson noted that the Board's other comments on the study will be included in its report.

Board Ethics Assessment

Dr. Dawson asked Dr. Chadwick to provide his ethics review.

Before providing his ethics assessment, Dr. Chadwick read the following charge question into the record:

Charge to the Board—Ethics

- Does available information support a determination that the research was conducted in substantial compliance with 40 CFR Part 26, Subparts K and L?

Dr. Chadwick congratulated Ms. Lydon on providing an excellent assessment of the ethics issues regarding the study. He commented that the protocol and its amendments were approved by the IRB. The HSRB had discussed and approved the protocol. All the subjects were adults; all were recruited from the general population of Gainesville, Florida; pregnant and lactating females were excluded from the study; and all the participants provided informed consent before participating. Minor deviations from the protocol occurred, but they were well characterized. The deviations caused no negative effects on the participants' rights, health or safety. No ethical barriers exist to EPA's relying on data from this study.

Dr. Dawson solicited comments on the ethics assessment from the Board members. Dr. Halanych reiterated her comment about the typographical error in EPA's ethics assessment, which states that no female subjects participated in the study.

Dr. Dawson indicated that she also was impressed with EPA's ethics review, which was very clearly presented.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Chadwick'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 HSRB unanimously approved the statement.

Mr. Downing expressed his appreciation to the Board for their participation. He mentioned that the Board is scheduled to reconvene at 1:00 p.m. on October 20, 2015, to address the protocol for testing of S.C. Johnson personal tick repellent products to support the use of the EPA repellency awareness graphic. Mr. Downing adjourned the meeting for the day at 3:39 p.m.

Tuesday, October 20, 2015

Commencement of Public Meeting and Review of Administrative Procedures

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.

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

Mr. Downing informed members that the topic on the agenda for this second day of the meeting is an insect repellent protocol. Mr. Downing indicated that there was a public docket developed for this meeting. Copies of all meeting materials will be available at www.regulations.gov under the docket number listed on the agenda, and supporting documents also are available on the HSRB website. . A public comment period will be provided. Mr. Downing informed the Chair that he had no public comments to share and no requests for public comments for this meeting.

Meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and must be certified by the meeting Chair within 90 days. The approved minutes will be available at www.regulations.gov and 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 at www.regulations.gov and on the HSRB website.

Dr. Dawson noted that Dr. Chadwick would be leaving the meeting early and not participating in the portal and that Mr. Downing would provide opening remarks in place of Dr. Schonfeld (EPA), who was not able to attend this session or provide opening remarks.

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.

Welcoming Remarks

Mr. Downing reflected on Dr. Sinks' comments from the previous day. Dr. Sinks is the new Director of the EPA OSA, the Office that oversees the HSRB. The OSA is supported by the EPA Office of Research and Development (ORD). He noted Dr. Schonfeld was unable to attend today's session because of a conflict with a meeting concerning the Common Rule for bioethics. In concluding his remarks, Mr. Downing turned the meeting over to Dr. Dawson.

Session 2: Protocol for Testing of S.C. Johnson & Son Personal Tick Repellent Products to Support the Use of the EPA Repellency Awareness Graphic

Background

Dr. Dawson called Session 2 to order and invited Mr. Sweeney to make his presentation describing EPA's science review. Mr. Sweeney informed Dr. Dawson that Dr. Eric Bohnenblust would make the presentation.

EPA Science Assessment

Dr. Bohnenblust stated that i2LResearch submitted a protocol for testing insect repellent products against ticks in the laboratory to determine the complete protection time (CPT) of 18 skin-applied repellent products that are registered by S.C. Johnson & Son, Inc. to support the use of the EPA Repellency Awareness Graphic. The study will be conducted by i2LResearch USA Inc. in Baltimore, Maryland, and will test three tick species and include up to 30 human subjects per product (10 per species). This protocol will be slightly different from previous protocols that have been reviewed by the HSRB. This protocol proposes to test aerosol and lotion products at a dose of 1 g/600 cm^2 of skin area and spritz/pump sprays at a dose of 0.5 g/600 cm^2. A dosimetry phase is not proposed, but rather fixed doses. This is a departure from the design of repellent efficacy studies that have been reviewed and approved by EPA and the HSRB in recent years, which have experimentally determined the dose.

Dr. Bohnenblust noted that EPA's Repellency Awareness Program was finalized earlier this year. The purpose of the program is to raise public awareness about the health protectiveness of mosquito and tick repellents applied to the skin. It specifically serves to raise consumer awareness about the efficacy of skin-applied insect repellents, to increase EPA and consumer confidence in the efficacy claims on labels, and to improve consumer protection against vector-borne diseases, such as Lyme disease and West Nile virus. In regard to labels, the Repellency Awareness Graphic will contain pictures of the insects for which the skin-repellent will be effective, as well as the duration of protection that is afforded by the product. The purpose of the graphic is to ensure that consumers are clearly informed about the duration of repellent protection and can make informed choices about the repellent products they purchase and use.

Dr. Bohnenblust summarized the i2LResearch protocol. The study objective is to determine the CPT for up to 18 EPA-registered, skin-applied repellent products from S.C. Johnson & Son, Inc. against the adult model of three tick species using volunteer human subjects in the laboratory. The data obtained from this research can be used by EPA to support the addition of the Repellency Awareness Graphic to labels for skin-applied insect repellents, thereby allowing better protection of consumers from nuisance arthropod bites and bites that lead to arthropod-borne diseases. All the test materials to be used in this study are S.C. Johnson products and all are registered by EPA as skin-applied insect repellents. The products have been shown to have minimal-to-no acute dermal toxicity and are not skin sensitizers. The MOE estimates were performed by S.C. Johnson & Son, Inc. via the dermal route of exposure for each of the 18 products to be tested. Their results show that the MOEs are greater than EPA's requirement of 100, and the proposed exposures to the test subjects is of little concern for the three active ingredients (AIs) to be tested: DEET, picaridin and p-menthane-3,8-diol (PMD).

Dr. Bohnenblust stressed that the i2LResearch study will not include a dosimetry phase to determine the typical consumer dose. Instead, it proposes using standardized rates of 1 g/600 cm^2 for aerosol and lotion products and 0.5 g/600 cm^2 for spritz/pump sprays. The rationale behind this approach is that a set dose can be related to known consumer behavior based on past tests reviewed by the HSRB where dosimetry was employed for skin-applied insect repellent products. In addition, the HSRB determined during its April 2015 meeting that a dose of 1 g/600 cm^2 was appropriate for all product types. However, based on analysis of dosimetry results from repellent studies reviewed since 2006, EPA's recommendation is that the following doses be used for studies conducted under this protocol: aerosol/lotion at 1 g/600 cm^2 and towelette/pump spray at 0.5 g/600 cm^2. The data may be bridged from a pump spray to a towelette because pump spray and towelette formulations are usually similar and the pump spray is applied at a lower dose.

Dr. Bohnenblust summarized that the experimental design will consist of one tick species and 10 subjects (5 males and 5 females) per test. All 10 subjects will be treated with each of the 18 test substances. Two additional subjects (one male and one female) will serve as alternates for each test. The test subjects will be selected at random from a pool of potential subjects from the Baltimore, Maryland area. Each product, therefore, will be tested on up to 30 different subjects and up to 6 different alternate subjects. Because EPA requires active ingredients to be identified on the consent forms, the subjects

would not be blinded to the treatments. If subjects participate in more than one test, the tests must be separated by a minimum of 2 days. Subjects are required to wash after each test to prevent carryover and contamination. A positive control substance will not be used. Each subject will have one forearm treated with the repellent product to be tested, and the other arm will serve as the untreated control. Assignment of the test substance to the subject's arms will be randomized. The control arm will be used to qualify ticks that are active, and determine the attractiveness of the subject to ticks. The data collected from the control arm will not be used to calculate the median CPT. In order to define the test site, four lines will be drawn on both of the subjects' forearms as follows: (1) a release line 3 cm above the wrist bone toward the elbow; (2) a boundary line 3 cm above the release line toward the elbow (this will be the edge of the treated area); (3) a crossing line 3 cm above the boundary line; and (4) an upper boundary line 12 cm above the boundary line. The upper boundary line will not be used during testing and serves only to mark the boundary of the treated area.

Before starting the tests, the ticks will be tested to make sure they qualify to actively quest. To assess this behavior, ticks will be placed at the release line on the untreated control arm and then must cross the boundary line within 3 minutes. Treatments will be challenged with 1 tick every 15 minutes or 4 ticks per hour. Once qualified, the ticks will be placed at the release line on the treated arm. After the tick begins to move up the arm, it will be given 3 minutes to cross the boundary and crossing lines on the treated arm. Ticks are considered repelled if in 3 minutes they do not reach the boundary line or reach the crossing line. Ticks are considered to not be repelled if in 3 minutes they reach the crossing line. Eleven DEET products, 4 picaridin products and 3 PMD products will be used in the study.

To determine the efficacy of the products, CPT will be the unit of measure for evaluating the repellent effects. The CPT for each tick species will be calculated as the time from test substance application to the time of the first confirmed crossing. The time in hours for each individual test subject will be used to calculate the median CPT for each species separately. The lowest median CPT of the three species is the value that will be recorded on the Repellency Awareness Graphic. The study endpoint will be evaluated as a crossing. A crossing will be said to have occurred when a tick crosses the crossing line on the subject's treated arm within 3 minutes. A first confirmed crossing, used to determine repellent failure, is that which is followed by the subsequent tick's crossing in the next exposure period, or when the first subsequent tick is repelled but the second subsequent tick is recorded as not being repelled.

The statistical analysis will be calculated using Kaplan-Meier Survival Analysis software, which is advantageous in this study because CPTs are unlikely to follow a normal distribution pattern. The study proposes to use three tick species per product and 10 human subjects per test, which equates to 30 replicates per product. According to Kaplan-Meier established median confidence limits for a range of sample sizes, sample sizes larger than 10 would provide marginal increases in precision relative to the increase in the number of exposed test subjects. The Kaplan-Meier Survival Analysis has been accepted by EPA and the HSRB for the median CPT calculation in past efficacy studies using repellents and also is recommended by the World Health Organization for CPT calculations from these types of data sets. Therefore, a proposed sample size of 10 subjects per study represents a reasonable compromise between increasing precision and limiting costs.

Dr. Bohnenblust indicated that the protocol will contain a number of measures to ensure data reliability. Good Laboratory Practice Standards, as defined by 40 CFR Part 160, will be followed throughout all studies. Prior to the start of the test, the study staff will conduct a training session with the subjects, treat the skin of the exposed limb with the test substance, and take measurements of the limb. After placing ticks on the untreated and treated arms, the staff will monitor and record tick movement and the start and stop times for each exposure period. The study director and staff will track test substance samples and closely monitor the testing and data recording. Alternate subjects will be enrolled to ensure adequate sample size. A Quality Assurance Unit will be in place to monitor all study activities and data collection. The test subjects can take part only once in any 2-day testing period. If subjects are scheduled to participate in two studies within 1 week, there will be a minimum of 2 calendar days between test days.

Dr. Bohnenblust stated that EPA is satisfied that the following elements are adequately addressed in the protocol: (1) available toxicity studies with DEET, picaridin and PMD; (2) adequate characterizations of toxicological profile of the formulations; and (3) adequate data to support estimate of acceptable MOEs. Although generally acceptable, the pre-training, experimental design and data analysis require refinement and clarification. Specifically, the protocol should be explicit with regard to the training outline and specific topics to be addressed and should provide more details on the exact timing of the testing, rationale for the study sample size, a definitive randomization method, and clarification of multiple testing of individual subjects. S.C. Johnson and i2LResearch responded to EPA's recommendations and will revise the protocol accordingly.

Dr. Bohnenblust stated that if amended to address the concerns raised in the EPA review, the i2LResearch protocol titled "Testing of S.C. Johnson Personal Tick Repellent Products to Support Use of the EPA Repellency Awareness Graphic" is likely to yield scientifically reliable information that would satisfy the following scientific criteria from the framework recommended by the HSRB. It would produce important information that cannot be obtained except from research with human subjects. It also has clear scientific objectives, and the study design should produce adequate data to achieve those objectives.

Board Questions of Clarification

Dr. Dawson asked for questions of clarification.

Dr. Ramos asked for clarification of Section D, page 10, of the protocol in reference to the definition of a first confirmed crossing, which described two 15-minute intervals or one 30-minute interval. Dr. Bohnenblust responded by referencing slides 30 and 31 of the presentation. The first tick after the first crossing will be the next 15-minute period. The second tick after the first crossing, if the first tick does not cross, will be the 30-minute period. Dr. Ramos suggested that clarifying this section would be helpful. Dr. Ramos also asked for the rationale for using the specific species of ticks and why the carrier of Rocky Mountain spotted fever (RMSF), which is a well-known tick-borne disease, was not included in the species tested. Dr. Bohnenblust responded that the three tick species are vectors of disease that EPA has commonly requested. More than one species of *Dermacenter* transmits RMSF, and *D. variablis* would transmit it as well. This protocol is using the *Ixodes scapalaris*, *Amblyomma americanum* and *D. variabilis* strains that are commonly used. In response to a question by Dr. Ramos about whether coverage is suggested with other species, Dr. Bohnenblust responded that species with similar behaviors imply similar responses. Dr. Ramos suggested that a citation that supports this assertion be provided. He also asked for clarification concerning the population to be tested in the Baltimore area and the Nielsen survey to identify repellent users. Dr. Dawson responded by referring to Section 2.3.4 (page 55) of the EPA science and ethics review document. i2LResearch will use a recruitment firm, and the pool is intended to represent the demographics of U.S. repellent users. They will recruit English-speaking subjects and rely on 2015 Nielsen data to determine the 10-percent bilingual criterion. Dr. Ramos queried about the reliability of the Nielsen survey. Mr. William Jordan (OPA, EPA) explained that the Nielsen surveys are conducted by a national consumer research firm and companies rely heavily on these data, which are considered a reliable means of determining a user base. Dr. Ramos asked about the rationale for choosing 2 calendar days between tests. Dr. Bohnenblust stated that EPA recommended the 2-day timeframe because it is not unreasonable to assume that repellent is cleared after 2 days as the compounds are short-lived. Dr. Ramos questioned the use of the term "rate" in regards to the dose of substance, and Dr. Bohnenblust replied that "application rate" often is used to mean the amount of product per unit area. Dr. Ramos requested clarification of the first-aid qualifications of personnel. Dr. Dawson commented that i2LResearch employees are first-aid qualified and deferred the response to either the company's Executive Director, Kristine Styer, or the study director, Dr. Tim Ford. Dr. Ford responded that the employees are certified in cardiopulmonary resuscitation (CPR) and first-aid with re-certifications every 2 to 3 years. They will serve as the first responders, and other health professionals will be on standby.

Dr. Gbur wanted to know if the Nielsen survey responses on repellant usage were available and if there is information on how the data were collected. Ms. Lydon of EPA stated that she did not have a

copy of the survey questions and requested that a representative from i2LResearch or S.C. Johnson respond. Mr. Dan Hollas from S.C. Johnson replied that the data analyzed were not from a dedicated Nielsen survey for repellant response, but were extracted from a broader survey. He added that Nielsen uses a variety of sources, and retail sales data are included. Dr. Gbur commented that not knowing the response rate is a concern.

Dr. Suh asked whether participant selection (male and female) would be stratified according to gender and if there are any known differences in response based on gender. She wondered if there would be sufficient power in the study to assess the efficacy if there is bias based on gender. Mr. Sweeney responded that gender differences are not expected, and that EPA generally has not seen them in these types of studies. Dr. Suh asked whether the sample size is adequate if there are gender differences. Mr. Sweeney replied that additional testing would be performed to elucidate the matter if differences are observed.

Dr. Maddalena questioned the absence of a positive control in the study. Mr. Sweeney responded that each subject served as his/her own control. Several questions regarding the use of the positive control and its interpretation in the study results were discussed. Dr. Maddalena verified that randomization of the arm is being used with multiple tests on the individual subject.

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

EPA Ethics Assessment

Ms. Lydon provided an ethics assessment with regard to the value to society, recruitment, inclusion/exclusion criteria, the informed consent process, responsiveness to EPA comments, risk minimization, and substantive acceptance standards. The proposed study will determine the CPT of up to 18 EPA-registered insect repellent products against ticks. Up to three different Active Ingredients (AIs) in a variety of products, all previously registered and assessed by EPA, will be tested for duration of efficacy. The AIs and most of the products involved are already on the market being used by consumers. Product-specific efficacy testing is required to support the use of EPA's Repellency Awareness Graphic on product labels. Consumers who use tick repellents to avoid tick bites cannot readily assess the duration of repellency. If EPA's Repellency Awareness Graphic is added to the label, consumers can make informed decisions by knowing the length of time that each product repels ticks. From EPA's perspective, that provides a valuable service to consumers.

Participants will be recruited through advertising using digital and social media. At EPA's request, a recruitment firm also will use Spanish-language advertisements and an online Spanish newspaper that advertises in the recruitment area. Subjects will be recruited from the Baltimore, MD area, where the testing lab is located. The advertisement will contain a link to a study-specific secure website where interested respondents can learn more about the study and complete a prescreening qualification form. Once completed, the prescreening qualification form will be uploaded to a secure and encrypted portal accessible only to i2LResearch staff. The recruitment firm or i2LResearch will contact the individuals from the pool to determine whether they meet the basic inclusion criteria. They will be asked some basic eligibility questions and told about the study using the telephone script, which provides the details of the content of the initial call. Eligible or interested respondents will receive a follow-up call from i2LResearch to review the study steps; identify the 2 hour training, inclusion/exclusion factors and compensation; and offer to provide the consent form 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 language for the protocol. As one part of training, the consent form will be provided to subjects and reviewed. Six questions will be asked of subjects to ensure their understanding, and eligible interested subjects will sign an informed consent form and receive a copy of the signed form.

The 15 inclusion/exclusion criteria listed in Section 2.6 of the protocol are complete and appropriate with two exceptions. EPA has asked that exclusions be added for sensitivity to tick bites or latex and for individuals with skin disease or skin problems, such as eczema, psoriasis or atopic dermatitis. Ms. Lydon noted that one inclusion criterion is that each participant must read and speak English fluently. The rationale for this criterion is that the current repellent product labels are in English and that the language that a person speaks does not affect the individual's attractiveness to ticks. To target users who understand product labels, the study director will recruit English-speaking subjects with a minimum of 10 percent bilingual subjects. Because the research offers no benefits to subjects, limiting recruitment to English speakers with 10 percent bilingual speakers is not expected to result in any equity-of-access issues.

The proposed consent process with EPA comments included was noted as satisfactory. Each potential subject who has expressed interest in participating in a study and met the inclusion/exclusion criteria will meet with i2LResearch for a 2-hour training session prior to each study. Subjects will be provided the informed consent form, given time to read it, and have the opportunity to ask questions. The training will include a review of the study, the subject's role, the potential length of the study on any given test day and inclusion/exclusion criteria. Questions about the study will be discussed and answered to ensure the subject's understanding. I2LResearch will tell all subjects that if they'd like to speak privately with the study director, they can do so at the end of the training. Female subjects must take a pregnancy test within 48 hours prior to the test day. During the training, the subjects will have their forearm measured and will be shown how to position their arm during testing. The procedure of each 15-minute test interval also will be explained. All eligible subjects will sign the informed consent form and be provided a copy.

The revised informed consent form includes all elements required by regulations. To confirm understanding of the consent form, subjects will be asked six questions, which EPA has revised. These questions are different from the questions previously provided to the Board. S.C. Johnson and i2LResearch support these revised questions. The questions are: (1) What will study staff place on your arm, monitor, take off and discard in order to collect study data? (2) What type of product will be applied to your arm and remain on your arm during the exposure period of the study? (3) How long could one test day last? (4) What are the potential discomforts or hazards from this study? (5) Do you have the freedom to quit or withdraw from the study at any time? (6) If you quit or withdraw from the study, for how many hours will you be paid? If the subject indicates that he or she does not understand a question, the relevant information would be reviewed again to help ensure comprehension.

EPA provided 19 detailed comments on the protocol and support materials to i2LResearch and SC Johnson. They agreed to address all of them. The protocol test procedures were revised to include details of training and the recruitment process, including a Spanish-language advertisement and use of an online Spanish newspaper as part of the recruitment process. Given the potential length of the study day, EPA asked that breaks be provided during the test day, and breakfast, lunch and dinner be provided to the subjects; lunch and dinner are scheduled for 15-minute periods approximately 5 and 10 hours, respectively, after arrival at the laboratory, and a third 15-minute break will be provided approximately 15 hours after arrival. Testing staff also will encourage subjects to walk around the laboratory and stretch between exposure intervals to minimize discomfort or fatigue due to the length of the test day. EPA requested an increase in proposed compensation. Given that the training is two hours, EPA recommended that subject be paid $30 for each training session, instead of $25. Test subjects who withdraw will be paid $30 for attending all or part of each training session. For each test day, participants will be paid $104 ($13 per hour) for any length of participation up to 8 hours. Exceptions are noted in the protocol. If a test goes beyond 8 hours, participants will receive time-and-a-half ($19.50 per hour) for testing time for any overtime hours, up to an expected maximum of 19 hours. Originally subjects were to be paid $11 an hour.

The protocol also includes information about payment for alternates and visits to i2LResearch for the pregnancy test. EPA asked that the length of the 2-hour preparatory time on test day be reduced to essential activities only. The timing of the pregnancy test was revised to occur within 48 hours prior to the test day instead of on the test day due to the potential length of the test day. The consent form and

relevant procedures were revised at EPA's request to (1) include questions prepared to ensure understanding of the consent form; (2) clarify when and how often the consent form will be signed if the subject is participating in more than one study; and (3) include a section on the Test Material; a detailed description of training; a description of the provision of breaks; a description of the provision of breakfast, lunch and dinner; and a description of possible discomfort or fatigue from a long test day as a risk. Phone scripts for initial and follow-up contact were revised to clarify the length of the test day and training, explain the use of code numbers for privacy, update compensation figures, and highlight the freedom to withdraw. The follow-up contact script was revised to reflect the same changes and indicate the provision of breaks and meals. EPA asked that support be provided to help bolster the subject's arm when it is being held at a 45-degree angle during the test. Information about the location of and directions to the hospital closest to the laboratory will be identified prior to the test date. New information or results will be shared with subjects "in a timely manner."

The protocol was revised to address risks and risk minimization and describe appropriate measures to minimize the five types of hazards. Regarding the risk of adverse reaction to test substances, participating subjects must be users of insect repellent products. The subjects must not be hypersensitive to repellent or latex or skin care products. The subject must be free from skin disease, skin problems such as eczema, psoriasis, or atopic dermatitis. i2LResearch will watch for unanticipated problems or adverse effects. I2L will have at least two first-aid qualified staff members and supplies on site. In the case of medical emergency, i2L staff will call 911, ask for emergency assistance, and follow instructions given by the emergency dispatcher. As discussed in the revised language, subjects will be told that if anyone experiences any skin reaction, experiences an injury, or simply feels unwell, he or she should inform i2L 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. Subjects may also ask for standard first aid items or request first aid assistance at any time.

Regarding risk of exposure to ticks, the participating subjects must have no known allergies or sensitivities to tick bites. Staff members will be trained to move or remove ticks from subjects before they have the opportunity to bite. Tick exposure will be limited to one tick at a time, and only on the area of the forearm. Next, to greatly reduce, if not eliminate, the risk of contracting any tick-borne diseases, the study will be conducted with laboratory-reared ticks, which are not known to harbor any pathogens. This will be documented with confirmation from the supplier lab.

With regard to risk of unanticipated loss of confidentiality, all efforts will be taken to maintain the confidentiality of the pregnancy tests results. The results will be kept confidential, will not be recorded, and will not be disclosed to anyone other than the test subject, the verifying employee, and/or the Study Director. Each subject will be assigned a code number. Only subjects' code numbers will appear on data sheets. The subjects' names will not appear in the report. The study records will be maintained at the testing facility in locked cabinets and electronic files kept on a password-protected computer server. To try to address fatigue and physical discomfort from the length of the test day, the study sponsor will provide breakfast, lunch and dinner to participating subjects assuming the test day extends to those meal times. The study director will provide up to three 15 minute breaks to each test subject per test day and opportunities to stretch throughout the test day, as well as support for the subject's arm as it's held at an angle during the exposure period. Also, there will be a two-day break between test days.

In terms of benefits, subjects derive no direct benefit from the study. The primary direct beneficiary is the sponsor. Another beneficiary is the consumer who uses tick repellents. If EPA's Repellency Awareness Graphic is added to the product label, the consumer will know how long the tick repellent will be effective in repelling ticks. Ms. Lydon stated that, with the proposed revisions to the protocol, EPA believes that risks have been effectively minimized and that the risks are reasonable in light of the expected benefits from the knowledge to be gained.

Ms. Lydon said that Schulman Associates IRB (SAIRB) reviewed and conditionally approved the protocol and informed consent materials in an independent ethics review. Final approval is conditional, pending HSRB review. SAIRB has accreditation from the Association for the Accreditation of Human Research Protection Programs, is registered with the Office for Human Research Protections, and is independent of the investigators. EPA believes that the revised protocol, if implemented as revised, provides respect for subjects. To protect subjects' privacy, identification number codes will be used to identify subjects on all data sheets, instead of names. Female subjects will take the pregnancy test in a private setting. After the test, each female subject will be asked privately by a female researcher if she wishes to continue in the study. If not, she is free to leave. If yes, she will be asked to show the result to the female researcher to allow her to verify the negative result on the test. The results will be kept confidential, will not be recorded, and will not be disclosed to anyone other than the test subject and the study director or principal investigator. With regard to payment for participating in the study and training, the revised level of compensation is appropriate. The freedom to withdraw or quit is highlighted in both the initial and follow-up telephone screening calls, as well as during the training session and on the consent form. In the unlikely event that medical care is needed as a result of the study, the sponsor will reimburse the subjects for costs of any medical care not covered by insurance.

Ms. Lydon described the ethical standards applied for the conduct of the study. This proposal is for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. The primary ethical standards applicable to the conduct of this research are 40 CFR Part 26, Subparts K and L, and FIFRA 12(a)(2)(P). Attachment 1 to the EPA ethics review contains a point-by-point evaluation of how this protocol addresses the requirements of 40 CFR Part 26, Subparts K and L. Findings in EPA's ethics review included that i2LResearch and S.C. Johnson & Son, Inc. agreed to address EPA's comments; there are no deficiencies relative to 40 CFR Part 26, Subparts K and L, or to FIFRA §12(a)(2)(P); and the protocol meets the applicable requirements of 40 CFR Part 26, Subparts K and L.

Board Questions of Clarification

Dr. Dawson asked for questions of clarification.

Dr. Kyle Galbraith requested details on the conduct of the pregnancy test within the 48-hour time period prior to the test day. Ms. Lydon confirmed that the 48-hour timeframe is based on prior approaches used by study sponsors, as well as an attempt to reduce the length of the (18-hour) test day.

Dr. Chadwick asked about the 10-percent bilingual criterion and the scientific and/or ethical rationale for the desired balance (50/50) of recruitment by gender. Ms. Lydon responded that the intent is to have a recruitment pool that represents the demographics of repellent users in the United States. The 10-percent number resulted from Nielsen's data, which showed that 10 percent of repellent users, and 13 percent of dollars spent on repellents, come from the Hispanic population. Dr. Chadwick commented that recruitment of bilingual subjects does not guarantee that Hispanics would be recruited. Ms. Lydon confirmed that EPA is comfortable with the revised protocol as proposed. Dr. Suzanne Rivera expressed concern about the issues of language and ethnicity/representation of the heterogeneous U.S. population, noting that the intent of the 10-percent bilingual criterion appears to justify the exclusion of non-English speakers for a non-scientific reason.

There were no additional questions about the ethics review, and Dr. Dawson turned to Mr. Downing to call for public comments.

Public Comments

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

Charge Questions

Dr. Dawson read the following charge questions into the record:

If the S.C. Johnson & Son, Inc. and i2LResearch protocol is revised as suggested in EPA's review and if the research is performed as described—

Charge to the Board—Science:

- Is the protocol "Testing of S.C. Johnson & Son, Inc. Personal Tick Repellent Products to Support Use of the EPA Repellency Awareness Graphic" likely to generate scientifically reliable data, useful for estimating the complete protection time of various EPA-registered S.C. Johnson & Son, Inc. skin-applied tick repellents in the laboratory against three species of ticks?

Charge to the Board—Ethics:

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

Board Science Assessment

Dr. Dawson asked Drs. Ramos and Zhu to provide their science and statistics reviews.

Dr. Ramos said that many of his issues have been discussed. The study is generally well designed and has the potential to provide useful information. The protocol, however, misses some opportunities because some of the decisions made for the optimization of the protocol detract from the scientific quality of the study. The major point of contention relates to the inclusion of controls in the study; the absence of a substance control, particularly for toxicity, is a weakness in the design because it does not allow a true assessment of the effectiveness of the substance being studied and does not provide a way to validate the dosage measure. Dr. Ramos indicated that he would like to hear more about the rationale for excluding controls.

The protocol includes a statement that steps would be taken to ensure that the ticks would not bite, but it is not explained how this could be guaranteed.

Dr. Ramos expressed concern about how first aid qualifications would be handled, and proper specifications should be added to the protocol. When dealing with potentially allergenic substances and when charged with assessing the health status of skin, the researchers carry some liabilities. Individuals with appropriate training are required to assess the health status of skin and to understand histories of allergies and hypersensitivities.

The decision to move the pregnancy test to 48 hours prior to the test day was made to help reduce the length of the test day. The 48-hour timeframe, however, could mean that a woman possibly could be undergoing the testing while she is pregnant. Dr. Ramos stressed that the pregnancy test should be conducted on the day of testing.

Dr. Ramos also suggested that the break times be reconsidered, observing that three 15-minute breaks in an 18-hour day may not be adequate.

Dr. Zhu said that the protocol is clearly written and indicates that randomization regarding which arm is to be treated would be decided on a coin toss. Dr. Zhu thought that a random number generator would be a better approach.

Dr. Zhu requested clarification about the Kaplan-Meier Confidence Limits for a Range of Sample Sizes Table provided as part of the Statistical Analysis Plan. Dr. Tom Roswell spoke on behalf of S.C. Johnson & Son, Inc. and explained that the table is based on the upper and lower confidence levels for the Kaplan-Meier median and that those levels always are based on the positional value. He added that the construction of the confidence levels remains invariant regardless of the individual CPT value levels, and that the positional limits do not change based on CPT values. The CPT values are referred to in the EPA science and ethics review document. Dr. Gbur stated that what is being considered is the distribution of the order of statistics and asked for clarity about the notion of relative precision in the sentence accompanying the table that reads, "Sample sizes larger than ten would provide only marginal increases in precision relative to the increase in the number of exposed test subjects." He wondered what would change if 9 or 11 subjects were used. Dr. Roswell replied that he provided representative samples (10, 12, 15, and 20) for the table, rather than including a larger number of potential samples, and referred to the "Percent of values above LCL" column, which does not increase proportionally to the changes in the "Sample size" column. He provided 12 because the minimal value is the next smallest value (where the minimal value becomes different from 10) and 11 has the same minimal value as 10. For the lower confidence level to be sufficiently far from the minimum, the sample size has to be substantially increased. Dr. Zhu asked if this method had been used in other studies. Dr. Roswell replied that it was used for the mosquito study that was reviewed at the HSRB's meeting in April 2015. Dr. Dawson distilled the discussion into two questions: Was the calculation done via a recognizable method? Is the sample size sufficient? Dr. Gbur suggested that Dr. Roswell and S.C. Johnson & Son, Inc. provide more detail about the table and its accompanying text. Dr. Zhu added that an alternative way of presenting the position ("Percent of values above LCL" column) would be helpful.

Dr. Zhu requested clarification about the following sentence in the Experimental Design statement: "The data collected from the control arm will not be used to calculate the median Complete Protection Time." Mr. Sweeney said that the term "untreated" would be preferable to "control arm," and the focus is to ensure that the ticks are attracted to the subjects and orient and move up the arm; as soon as the tick is qualified, it will be moved to the treated arm. Dr. Gbur commented on the tick's activity on the untreated arm and wondered how the quantified data would be used for the treated arm. Dr. Dawson reiterated Dr. Gbur's query by asking how a tick's activity would be determined without a quantitative measure. Mr. Sweeney responded that a tick becomes qualified if it makes it to a certain point up the arm within 3 minutes.

Dr. Dawson asked for comments from the Board.

Dr. Gbur referred to pages 55–57 of the peer review memo and asked if the percentages were being applied to characteristics of the entire population of recruits, rather than to a set of subjects used for a particular set of tests. He was answered affirmatively. Dr. Gbur asked about randomization, pointing out that up to 18 demographic combinations are possible, with only 10 subjects for a particular test; because not all the combinations would be filled for a given test, some tests could contain no one from a particular demographic designation. Dr. Dawson referred Dr. Gbur to page 11 of the EPA science and ethics review document, which states that for each testing period, 12 test subjects (6 male and 6 female) would be selected and randomly assigned to a test section. Dr. Gbur commented that the protocol does not include information about how the demographics are broken down beyond gender considerations, such as by age and ethnicity. He was referred to page 55 of the peer review memo, which clarifies that the pool of subjects, rather than individual tests, is being matched to the demographics. Dr. Dawson highlighted three reasons that researchers are concerned about representativeness and inclusion: fairness, differences expected among subgroups, and that differences between groups are not suspected but may emerge in the course of the study. Of these three, the first two reasons are not a concern for this protocol, but heterogeneous subjects are preferred because it is good to have representative populations "just in case." She added that a good representation of the population overall should be sought. Dr. Gbur agreed but noted that to reliably test differences among subgroups for a specific product, a larger sample size would be needed. An EPA staff member thanked Dr. Dawson for her clear exposition and said that with this

study, EPA would be able to look across a large data set of 18 products and three tick species to see patterns of sensitivities and differences based on gender or age.

Dr. Dawson asked members if they had additional comments on this topic. Dr. Suh recommended that the analysis plan be more detailed—examining gender differences, including secondary analyses or end points that could elucidate trends, or providing information about results. Mr. Sweeney agreed.

Dr. Dawson called for additional comments on the science review and asked if any of the issues raised compromise the ability of the study to produce scientifically reliable data or if the discussion had clarified the protocol and its rationale. In response to a query by Dr. Ramos about how to assess the study if the responses to EPA concerns about sample size are not adequate, Dr. Dawson stated that it could be possible to identify the issues in which a response or change would be needed.

Dr. Ramos stated that two changes are needed in the protocol: (1) the timing of the pregnancy test; and (2) the qualifications of the personnel performing medical assessments of the subjects as part of the protocol. A third possible concern is the desirability of positive and negative substance controls. Dr. Galbraith said that there is not a widely accepted standard regarding the timing of pregnancy testing prior to enrollment and thought that 48 hours prior was reasonable, but he agreed that input from other members of the Board was desirable. Dr. Dawson reflected on the conduct of clinical trials in which pregnancy tests are given to enrollees during a reasonable screening schedule and agreed that the 48-hour window seems reasonable. Dr. Ramos stated that the product is a pesticide that has the potential to affect pregnancy-related outcomes; the substance is approved for use, but the potential for harm exists. Dr. Halanych pointed out that pregnancy tests can be negative for the initial 7 days of pregnancy, and if it is given on the same day as the test, it also should be given 7 days prior. Dr. Ramos indicated that a pregnancy test given on the same day as the test affords greater protection than 7 days prior. Dr. Gbur asked if the product label includes a pregnancy warning. Mr. Jordan replied that EPA routinely requires companies to test their products for reproductive effects in animal studies, and EPA staff do not recall any such risks associated with the S.C. Johnson product. Dr. Dawson summarized the possible approaches that the HSRB could recommend, including that the protocol remain with a 48-hour prior test, revert to same-day testing, or allow women to make the decision to take the pregnancy test on the test day or up to 48 hours prior to the test day with counseling about potential exposure risks. Board members agreed with this last approach.

Dr. Dawson asked for further comments on the issue of controls. Dr. Maddalena expressed partial agreement with Dr. Ramos, noting that studies published as peer-reviewed literature must have positive and negative controls; however, this study is meant only to answer a specific question and not be published. He provided an example of moving a tick from one arm to another with forceps. Dr. Dawson asked if the study should meet the same standards of scientific credibility, regardless of whether or not it is published. Mr. Jordan replied that he was confused about what would constitute a negative control; the goal is to understand the effectiveness of the insect repellent in repelling the tick. Dr. Dawson said that the negative control would involve performing all the same procedures that are used with the test substance using an inert substance as a control. Dr. Dawson wondered if from the Agency perspective or study design the use of a positive/negative control would pose any feasibility issues or present challenges in interpretation. Dr. Ramos responded that interpretation would be compromised without a control. Dr. Bohnenblust commented on the movement of ticks by researchers and said that moving a tick with a feather or content applicator is a common occurrence in the laboratory, does not change the tick's overall behavior, and is not anticipated to have any major effect.

Dr. Dawson summarized the new wording for the Board's recommendation that the protocol, once modified according to HSRB suggestions, is likely to generate scientifically reliable data. The suggestions relate to the controls; the pregnancy testing and medical personnel issues; safety and participatory burden concerns; and clarification about statistics.

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

The HSRB unanimously approved the statement.

Board Ethics Assessment

Dr. Dawson asked Dr. Galbraith to present his ethics review.

Dr. Galbraith stated that the protocol likely meets the applicable requirements of 40 CFR Part 26, Subparts K and L.

Dr. Galbraith noted that the final protocol and relevant IRB correspondence would need to be submitted to EPA and recommended that that any recruitment materials that are translated be certified by a qualified translator or translation service. Related to Subpart L, concerning unintentional exposure of human subjects (e.g., pregnant women, nursing women, and children), the protocol, consent form and recruitment script all clearly state that the human subjects must be ages 18 to 55, and they clearly exclude women who are breastfeeding from the research. Dr. Galbraith expressed support for the decision to provide women the option of completing the pregnancy test either 48 hours before the test with counseling about the precautions needed or on the morning of the test date. In general, risk components appear to be appropriate from the ethical standpoint, including the study design to minimize the risk of exposure to tick-borne disease. The protocol indicates that the study will use only laboratory-reared ticks that are not known to harbor any pathogens. Confirmation of this point would be received from the tick supplier laboratory, and Dr. Galbraith recommended that the name of the supplier be included in the materials provided to EPA.

Dr. Galbraith stated that the details provided in the response from S.C. Johnson & Son, Inc. and i2LResearch to the EPA science and ethics review and revisions to the consent form are sufficient. First aid support will be available onsite to address any research-related injury, the consent form contains a 24-hour telephone number for participants to contact the study director in the event of a research-related reaction after participants have left the testing facility. Participants can choose to participate in more than one testing period, but the protocol has been revised to allow a minimum of 2 calendar days between each session to minimize risk associated with fatigue. In response to page 17 of the science and ethics review, S.C. Johnson & Son, Inc. and i2LResearch indicate that they will provide supporting material on which participants can rest their arm during the testing.

Several areas that could be strengthened to reduce risks include that participants should be asked about dietary preferences for meals, and entertainment (e.g., television and DVDs) should be provided or participants should be encouraged to bring appropriate entertainment with them. The subject remuneration information on the consent form should be revised to indicate the protocol in the event of a research-related injury. The current consent form states that participants would be reimbursed in such an event, but a reimbursement process may be burdensome to subjects who have limited economic resources.

Dr. Galbraith appreciated the revised questions about the informed consent process.

Regarding subject selection, recruitment procedures are duly described, do not appear to be coercive in any way, and appear to minimize risk to participants by limiting subject selection to the 18 to 55 age group (excluding pregnant and breastfeeding women and those with allergies or sensitivity to latex or ticks). Dr. Galbraith noted the issue raised by Dr. Rivera about the exclusion of potential subjects who cannot read or speak English fluently, expressed sympathy with that concern, and said that Dr. Dawson had addressed the issue of the stratification of participants and why it is not necessarily important to open the study to non-English speakers.

Dr. Maddalena noted that subjects will be onsite for a long (18-hour) day and raised the issue of transportation for them.

Dr. Gbur commented on the exclusion of non-English speakers and wondered why the bilingual criterion is limited to 10 percent; if translators are provided for Spanish speakers, then they should be available for other potential bilingual subjects. Dr. Dawson clarified that the researchers are not providing translators for any bilingual subjects. Dr. Gbur wondered why advertisements would be placed in Spanish newspapers. Dr. Galbraith provided his understanding that the bilingual demographics are being drawn from the Nielsen survey, which demonstrated that Hispanics represent 13 percent of the product users, although Spanish-speaking subjects must understand English. Dr. Gbur asked if the ability to speak English was a real issue with foreign-language speakers. Dr. Galbraith said that in his laboratory experience, in studies that provide no direct benefit to the subject, researchers generally try to exclude non-English speakers; potential subjects do not miss out on a benefit by the fact of exclusion. For studies that provide direct benefit for the subject, researchers typically work with the overseeing IRB to ensure that an appropriate consent process is in place and translated materials are available. Dr. Gbur stated that the burden of providing written or in-person translation is on S.C. Johnson & Son, Inc. and i2LResearch, and he expressed that such a burden is minimal. Dr. Dawson said that she did not think that the fairness issue was a problem in this protocol; the research study does not provide direct benefits and subjects agree to provide some of their time for an hourly compensation rate. She reflected on Dr. Rivera's earlier comments and agreed that, if the inclusion of bilingual people is to serve as a surrogate for ethnicity or diversity, then the study would have greater transparency if people of a certain ethnicity are recruited. Dr. Galbraith agreed with Dr. Dawson and said that he would include this topic in his written report.

Dr. Galbraith asked for additional comments about remuneration. Dr. Schonfeld indicated that she is aware of one EPA laboratory's practices regarding remuneration for research-related injuries and medical care; the protocol's provision of remuneration on a reimbursement basis is consistent with the practices of that laboratory.

Dr. Dawson asked Dr. Galbraith to summarize his recommendations. Dr. Galbraith stated that the research, when modified as recommended by EPA and HSRB, is likely to meet the ethical requirements of 40 CFR Part 26, Subparts K and L, pending the following changes:

- Submit all the finalized materials to EPA after they have been reviewed by the IRB of oversight.
- Revise the pregnancy testing procedures in the protocol as discussed in the HSRB's science review discussion.
- Include information about the supplier of the ticks in the protocol.
- Ask participants about their dietary preferences and accommodate them during the testing day.
- Provide entertainment or encourage participants to bring their own entertainment, given the length of time they will spend at the facility.

Dr. Galbraith said that he will acknowledge the HSRB's discussion of the exclusion of non-English speakers in his written report, but he will not include it in the recommendations section.

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

The HSRB unanimously approved the statement.

Closing Remarks

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

Mr. Downing recognized Mr. Jordan, who has been the OPP's leader in human subjects research for many years and who is retiring from EPA at the end of 2015. He thanked Mr. Jordan for his contributions related to human subjects research. Mr. Jordan thanked Mr. Downing and said that it has been a fascinating and wonderful experience to participate and noted that he has missed only one HSRB meeting during the past 7 years.

Mr. Downing announced that the next HSRB meeting is scheduled for January 12–13, 2016, and the exact times will be posted in the *Federal Register*.

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

Gary L. Chadwick, Pharm.D., M.P.H., C.I.P.
Senior Consultant
HRP Consulting Group, Inc.
Fairport, NY

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

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

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

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

Members (continued)

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

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

Helen H. Suh, Ph.D.
Associate Professor of Health Sciences
Northeastern University
Boston, MA

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

Attachment B

FEDERAL REGISTER NOTICE ANNOUNCING MEETING

[*Federal Register* Volume 80, Number 185 (Thursday, September 24, 2015)]
[Notices]
[Pages 57607–57608]
From the *Federal Register* Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2015–24342]

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ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2015–0588; FRL–9934–66–ORD]

Human Studies Review Board; Notification of a Public Meeting

AGENCY: U.S. Environmental Protection Agency.

ACTION: Notice.

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

DATES: A public virtual meeting will be held on October 19–20, 2015, from 1:00 p.m. to approximately 5:00 p.m. Eastern Time each day. A separate teleconference meeting is planned for Monday, December 7, 2015, from 1:00 p.m. to approximately 2:30 p.m. for the HSRB to finalize its Final Report of the October 19–20, 2015 meeting.

ADDRESSES: Both of these meetings will be conducted entirely on the Internet using Adobe Connect. Registration is required to attend this meeting. Please visit the HSRB Web site: http://www.epa.gov/hsrb to register.

Comments: Submit your written comments, identified by Docket ID No. EPA–HQ–ORD–2015–0588, by one of the following methods:

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

Email: ORD.Docket@epa.gov.

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

Hand Delivery: The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue NW, Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding federal holidays. Please call (202) 566–1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site at: http://www.epa.gov/epahome/dockets.htm.

Instructions: The Agency's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information or other information the disclosure of which is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or email. The http://www.regulations.gov Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If

you send an email comment directly to the EPA without going through http://www.regulations.gov, your email address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, the EPA recommends that you include your name and other contact information in the body of your comment and with any electronic storage media you submit. If the EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, the EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact Jim Downing 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. General information concerning the EPA HSRB can be found on the EPA Web site at: http://www.epa.gov/hsrb.

SUPPLEMENTARY INFORMATION:

Meeting access: Access to these Internet meetings are open to all by following the information provided above.

Procedures for providing public input: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in Section I, "Public Meeting" under subsection D. "How May I Participate in this Meeting?" of this notice.

I. Public Meeting

A. Does this action apply to me?

This action is directed to the public in general. This Notice may, however, be of particular interest to persons who conduct or assess human studies, especially studies on substances regulated by the EPA, or to persons who are, or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act or the Federal Insecticide, Fungicide, and Rodenticide Act. This notice might also be of special interest to participants of studies involving human subjects, or representatives of study participants or experts on community engagement. The Agency has not attempted to describe all the specific entities that may have interest in human subjects research. If you have any questions regarding this notice, consult Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.**

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

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

Docket: All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA Docket Center, in the Public Reading Room. The Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue NW, Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding federal holidays. Please call (202) 566–1744 or email the ORD Docket at ord.docket@epa.gov for instructions.

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Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm). The Agency's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by early October 2015. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and other related documents that are available electronically, from the regulations.gov Web site and the EPA HSRB Web site at http://www.epa.gov/hsrb/. For questions on document availability, or if you do not have access to the Internet, consult Jim Downing listed under **FOR FURTHER INFORMATION.**

C. What should I consider as I prepare my comments for the EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data that you used to support your views.
4. Provide specific examples to illustrate your concerns and suggest alternatives.
5. To ensure proper receipt by the EPA, be sure to identify the Docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

D. How may I participate in this meeting?

You may participate in these meetings by following the instructions in this section. To ensure proper receipt by the EPA, it is imperative that you identify Docket ID number EPA–HQ–ORD–2015–0588 in the subject line on the first page of your request.

1. *Oral comments.* Requests to present oral comments during either conference call will be accepted up to Noon Eastern Time on Wednesday, October 14, 2015, for the October 19–20 meeting and up to Noon Eastern Time on Wednesday, December 2, 2015, for the December 7, 2015 conference call. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments during either call. Individuals or groups wishing to make brief oral comments to the HSRB on October 19 or 20, 2015, are strongly advised to submit their request (preferably via email) to Jim Downing, listed under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern Time, Wednesday, October 14, 2015, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Official to review the meeting agenda to provide an appropriate public comment period. Individuals or groups wishing to make brief oral comments to the HSRB during the December 7, 2015 teleconference should submit their request by Noon Eastern Time on Wednesday, December 2, 2015. The request should identify the name of the individual making the presentation and the organization (if any) the individual will represent. Oral comments before the HSRB are generally limited to five minutes per individual or organization. Please note that this includes all individuals appearing either as part of, or on behalf of, an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand the time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, further public comments may be possible.
2. *Written comments.* Submit your written comments prior to the 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 14, 2015, for the October 19–20 meeting, and by noon Eastern Time on Wednesday, December 2, 2015, for the December 7, 2015 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 using the instructions in Section I., under subsection C., "What Should I Consider as I Prepare My Comments for the EPA?" In addition, the agency also requests that persons submitting comments directly to the docket also provide a copy of their

comments to Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.** There is no limit on the length of written comments for consideration by the HSRB.

E. Background

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

1. *Topics for discussion.* On Monday, October 19, 2015, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding: A completed study from the U.S. Department of Agriculture Describing Laboratory Evaluation of Bite Protection from Repellent-Impregnated Clothing for the United States Military. At the continuation of the October meeting on Tuesday, October 20, 2015, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding: Protocol for Testing of S.C. Johnson Personal Tick Repellent Products to Support Use of EPA Repellency Awareness Graphic.

2. Then on Monday, December 7, 2015 the HSRB will finalize its Final Report for the October 19–20, 2015 meeting.

2. *Meeting minutes and reports.* Minutes of these meetings, summarizing the matters discussed and recommendations, if any, made by the advisory committee regarding such matters, will be released within 90 calendar days of the meeting. Such minutes will be available at http://www.epa.gov/osa/hsrb/ and http://www.regulations.gov. In addition, information regarding the HSRB's final meeting report, will be found at http://www.epa.gov/osa/hsrb/ or from the person listed under **FOR FURTHER INFORMATION CONTACT.**

Dated: September 17, 2015.
Thomas A. Burke,
EPA Science Advisor.
[FR Doc. 2015–24342 Filed 9–23–15; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
October 19, 2015 PUBLIC MEETING AGENDA

Internet Virtual Meeting
The meeting will be conducted at the following website:
https://epa.connectsolutions.com/hsrb

And on the phone: 866-299-3188 (access code: 2025647189)

Monday, October 19, 2015

HSRB WEB SITE http://www2.epa.gov/osa/human-studies-review-board
Docket Telephone: (202) 566–1752
Docket Number: EPA–HQ–ORD–2015–0588

12:50 p.m. **HSRB members login online**

1:00 p.m.* **Convene Public Meeting**—Jim Downing, Designated Federal Officer, EPA Human Studies Review Board, Office of the Science Advisor
Virtual Meeting Operations—Liza Dawson, Ph.D., HSRB Chair
Introduction of Board Members—Liza Dawson, Ph.D., HSRB Chair
Opening Remarks—Thomas Sinks, Ph.D., Director, Office of the Science Advisor, EPA

Completed Study from the U.S. Department of Agriculture Describing Laboratory Evaluation of Bite Protection from Repellent-Impregnated Clothing for the United States Military

1:20 p.m. **EPA Science Review Highlights**—Mr. Kevin Sweeney (Registration Division, OPP, EPA)
1:40 p.m. **Board Questions of Clarification**—Liza Dawson, Ph.D., HSRB Chair, EPA staff
2:05 p.m. **EPA Ethics Review Highlights**—Maureen Lydon (OPP, EPA)
2:25 p.m. **Board Questions of Clarification**—Liza Dawson, Ph.D., HSRB Chair, EPA staff
2:50 p.m. **Public Comments**
2:55 p.m. **Board Discussion**

Charge to the Board—Science:

- Is the research reported in the completed study sufficiently sound, from a scientific perspective, to be used to evaluate the bite protection level of etofenprox-treated military clothing?

Discussants: Randy Maddalena, Ph.D. (Ed Gbur, statistics)

*Agenda times are approximate and subject to change depending upon the discussion. [All times shown are Eastern time zone.]

Charge to the Board—Ethics:

- Does available information support a determination that the research was conducted in substantial compliance with 40 CFR Part 26, Subparts K and L?

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

5:00 p.m.* **Adjourn**

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U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
October 20, 2015 PUBLIC MEETING AGENDA

Internet Virtual Meeting
The meeting will be conducted at the following website:
https://epa.connectsolutions.com/hsrb

And on the phone: 866-299-3188 (access code: 2025647189)

Tuesday, October 20, 2015

HSRB WEB SITE http://www2.epa.gov/osa/human-studies-review-board
Docket Telephone: (202) 566–1752
Docket Number: EPA–HQ–ORD–2015–0588

12:50 p.m. **HSRB members login online**

1:00 p.m.* **Convene Public Meeting**—Jim Downing, Designated Federal Officer, EPA Human Studies Review Board, Office of the Science Advisor
Virtual Meeting Operations—Liza Dawson, Ph.D., HSRB Chair
Introduction of Board Members—Liza Dawson, Ph.D., HSRB Chair
Opening Remarks—Toby Schonfeld, Ph.D., Human Subjects Research Review Official, Office of the Science Advisor, EPA

Protocol for Testing of S.C. Johnson Personal Tick Repellent Products to Support Use of EPA Repellency Awareness Graphic

1:15 p.m. **EPA Science Review Highlights**—Mr. Kevin Sweeney, and Eric Bohnenblust, Ph.D. (Registration Division, OPP, EPA)
1:35 p.m. **Board Questions of Clarification**—Liza Dawson, Ph.D., HSRB Chair, EPA staff
2:00 p.m. **EPA Ethics Review Highlights**—Maureen Lydon (OPP, EPA)
2:40 p.m. **Board Questions of Clarification**—Liza Dawson, Ph.D., HSRB Chair, EPA staff
3:10 p.m. **Public Comments**
3:15 p.m. **Board Discussion**

Charge to the Board—Science:

If the S.C. Johnson & Son, Inc. and i2LResearch protocol is revised as suggested in EPA's review and if the research is performed as described:

- Is the protocol "Testing of S.C. Johnson Personal Tick Repellent Products to Support their Use of the EPA Repellency Awareness Graphic" likely to generate scientifically reliable data, useful for estimating the complete protection time of various EPA-registered S.C. Johnson skin-applied tick repellents in the laboratory against three species of ticks?

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Discussants: Kenneth Ramos, Ph.D. (Jun Zhu, Ph.D., statistics)

Charge to the Board—Ethics:

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

Discussant: Kyle Galbraith, Ph.D.

5:00 p.m.* **Adjourn**

*Agenda times are approximate and subject to change depending upon the discussion. [All times shown are Eastern time zone.]