Draft Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
January 12–13, 2016, Public Meeting
Docket Number: EPA–HQ–ORD–2015–0588
HSRB Website: www.epa.gov/osa/human-studies-review-board

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

Date and Time:	Monday, January 12, 2016, 1:00–5:45p.m. EST Tuesday, January 13, 2016, 1:00–5:30 p.m. EST (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. Jun Zhu, Ph.D.
	Consultant:	Kendra Lawrence, Ph.D., BCE, PMP
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the Meeting Agenda (see Attachment C), unless noted otherwise.	

Tuesday, January 12, 2016

Convene Public Meeting

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 expressed his appreciation to the Board members for their time and efforts preparing for the meeting and thanked EPA Office of Pesticide Programs (OPP) colleagues for their efforts in preparing for the meeting as well.

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 informed Board members that several interesting topics would be discussed during the meeting. He noted that agenda times are approximate, and although the material to be covered in the meeting will be extensive, 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.govunder docket number EPA–HQ–ORD–2015–0588, and supporting documents are available on the HSRB website at www.epa.gov/osa/human-studies-review-board.

Following EPA presentations, time has been allocated for the Board to ask questions of clarification. Time also has been allocated 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.govand on the HSRB website at www.epa.gov/osa/human-studies-review-board. The HSRB also will prepare a final report in response to questions posed by the Agency, which will include the Board's review and analysis of materials presented. The final report will be available at www.regulations.govand on the HSRB website at www.epa.gov/osa/human-studies-review-board.

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, including Dr. Edward Gbur, Jr., HSRB Vice-Chair, completed their introductions. Dr. George Fernandez was unable to attend the meeting but had provided his comments in writing in advance.

Opening Remarks

On behalf of EPA's program on human subjects research ethics and oversight, Dr. Toby Schonfeld, EPA Human Subjects Research Review Official, welcomed the participants. She expressed her appreciation for the work of the Board members and OPP representatives in preparing for the meeting.

Finalize the Draft Final Report from the HSRB October 2015 Meeting

Dr. Dawson stated that the draft report from the October 2015 meeting was nearly complete. Two issues had been discussed and resolved at the Board's December 2015 meeting. The first recommended how a study protocol should justify the study's design. The second regarded the timing of pregnancy testing for female subjects. Drafting of the language to reflect the Board's decisions on those issues had been deferred at the December meeting. A version of the draft final report with language reflecting the Board's resolution of those two issues had been provided to the Board prior to this meeting.

Dr. Dawson asked for comments from the Board members. Hearing none, finalization of the draft final report from the HSRB October 2015 meeting was put to a vote. The Board members agreed unanimously to approve the draft.

Assessing Intermittent Pesticide Exposure From Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos (TCVP), Authored by M. Keith Davis, J. Scott Boone, John E. Moran, John W. Tyler and Janice E. Chambers. *Journal of Exposure Science and Environmental Epidemiology* (2008) 18, 564–570

EPA Science Review Highlights

Mr. Wade Britton (OPP) provided an overview of the research published in the article titled "Assessing Intermittent Pesticide Exposure From Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos (TCVP)" (also referred to as the Davis study). The Davis study measured TCVP exposures in children and adults that could occur from contact with pet dogs wearing TCVP-containing flea collars. It was conducted by the Center for Environmental Health Sciences, College of Veterinary Medicine, Mississippi State University (MSU). The research included two studies, conducted in 1998 (Study 1) and 2002 (Study 2). In Study 1, TCVP residues were measured by rubbing/petting dogs' fur with a gloved hand. There were 23 pet dogs included in this, one from each of the 23 participating households. The sampling was conducted by volunteer technicians from MSU veterinary school. Study 1 also measured dog plasma cholinesterase. In Study 2, TCVP residues were collected by rubbing/petting dogs' fur with a gloved hand, using the same methods employed by Study 1. TCVP residues were also estimated by passive dosimetry or T-shirts worn by children and the use of urinary biomonitoring of participating children and adults. Study 2 involved 1 child and 1 adult from each of the 22 participating families and 22 pet dogs. The glove residue data are the only data proposed for use in EPA's risk assessment; the other parts of the study do not indicate risks of concern and involve intentional exposure of children, and therefore have not been relied upon.

Ms. Maureen Lydon (OPP) explained the rationale for HSRB review of the research. Studies 1 and 2 meet the regulatory definition of research. Because of collection of urine and T-shirt samples, Study 2 obtained data about individuals and so meets the regulatory definition of human subjects research. Although the families involved in the studies already used flea collars, the researchers provided specific flea collars to the participating families and asked that their dogs wear them during the studies; as a result, the research constitutes intentional exposure. EPA may rely on the research to improve the protection of public health. EPA wants to rely only on one sub-set of data from this research, the TCVP residue data collected by technicians using cotton gloves to rub the treated dogs. These data did not involve children. However, the data were collected as part of broader research that involved children and, as a result, specific federal regulations must be considered before EPA potentially can rely on the TCVP glove residue data. Code of Federal Regulations (CFR)Title 40, part 26,subpart Q, § 26.1703, prohibits EPA from relying on data from any research involving intentional exposure of any human subject who is a pregnant woman, a nursing woman or a child. 40 CFR § 26.1706 provides an exception that EPA only can rely on such research if it is crucial to making a decision to impose a more stringent regulatory restriction than could be justified without the data, and the TCVP glove residue data could result in a more stringent regulatory restriction than with existing data. To rely on the TCVP glove residue data, OPP must complete the following three steps: (1) obtain the views of the HSRB, (2) provide an opportunity for public comment, and (3) publish a full explanation of its decision to rely on the data.

Mr. Britton presented EPA's science review of the research. With regard to the sampling procedure, glove residue samples were collected in studies 1 and 2. MSU veterinary students collected

samples by rubbing dogs in a marked 10x4 inch area with 100 percent cotton gloves for a continuous 5-minute period. Before being used to collect fur residues, each glove was washed with laundry detergent, 3 times without detergent, and then pre-extracted. Three samples were collected per dog per sample day in the following order to prevent cross-contamination: the back near the base of the tail, at the neck with the collar removed, and at the neck with the collar in place, rubbing over the collar. A single glove was used for each of the three the sampling sites. The technicians rubbed with firm pressure, in back-and-forth motions. For Study 1, 23 dogs were sampled, three separate times, over nine sample time periods: prior to collar placement; at 4 hours post-collar application; and at 3, 7, 14, 28, 56 and 112 days post-collar application, for a grand total of 621 individual samples. For Study 2, 22 dogs were sampled, three separate times, over three sample time periods: prior to collar placement and at 5 and 12 days post-collar application, for a grand total of 198 individual samples. With regard to sample handling, immediately following sampling, gloves were inverted, removed and placed into a clean, labeled glass sample jar. During analytic method development, various concentrations were applied to different gloves to check the recovery rates and extraction parameters. The glove samples and spiked gloves were stored at 4º C in the time period between sample collection and analysis to ensure sample integrity.

With regard to analytical methods, the entire glove was analyzed for TCVP. After sampling, gloves were extracted with acetone using an accelerated solvent extractor by Dionex: 5 minutes at 75ºC and 1,500 psi; static for 2 minutes; flush 50% of volume; static for 2 minutes; purge with nitrogen for 150 seconds; and a final purge for 60 seconds. For every 20 samples, 3 spiked gloves were included at the time of sampling and extracted with the samples. After extraction, the extract was evaporated under a nitrogen stream using an N-EVAP, transferred to graduated test tubes, and adjusted to 10 mL with acetone. All glove samples were analyzed with an HP5890 gas chromatograph equipped with an electron capture detector and RTX-5 Amine column. Oven temperature was ramped at a rate of 3ºC/min from 205ºC-225ºC and held for 5 minutes, followed by a second ramp of 5ºC/min to a final temperature of 290ºC. ECD injector and detector temperatures were set to 290ºC and 325ºC, respectively. The limit of detection (LOD) was 2 ppb and the limit of quantification (LOQ) was 6 ppb. With regard to quality control, during method development, various concentrations (0.5–2500 mg) were applied to different gloves to check for recovery rates and extraction parameters. The percent recovery obtained during these tests ranged from 85% to 102%, with a mean of 95%.

With regard to statistics, analysis of variance calculations for glove residues were performed with the General Linear Model (GLM) procedure of the SAS® System for Windows, Version 9.1, using the 0.05 level of significance. Each glove data set was analyzed separately for each collar or age group using one-way analysis of variance for a randomized complete block design (where household is the blocking factor). The glove data were also examined for the presence of statistically significant correlations using Spearman's correlation coefficient. The calculation was performed using the CORR procedure of the SAS System for Windows, Version 9.1 at 0.05 level of significance. Statistical methods used by the study authors were scientifically appropriate, although the Linear Mixed Model (MIXED) procedure in SAS would have been preferred since it offers a richer selection of variance-covariance structures (e.g. AR(1)) for modeling longitudinal data than the GLM procedure of SAS). However, EPA is proposing using only the estimate of overall mean glove residues for all post-application sampling times. The difference between MIXED and GLM procedures in modeling covariance structures will not significantly influence the estimation of overall mean for all sampling days. EPA intends to rely only on the glove residue data, and not the T-shirt or urinary biomonitoring data; also EPA does not intend to use the confidence interval for purpose of the glove residue data for purpose of risk assessment.

As for a summary of results, for Study 1, the mean glove residues reported for all sampling times were 14,300 µg/glove over the collar, 4,300 µg/glove on the neck with the collar removed, and 130

µg/glove in the tail region. Glove residues decreased from all 3 sampling sites (86% decline) throughout 112 days following a peak at 7 days, 24,000 ± 4,000 µg/glove sampled by rubbing over the collar. Similarly, residues around the neck without the collar in place and in the tail region decreased 94% and 71%, respectively. For Study 2, the mean residues for all gloves analyzed post-treatment were 19,000 µg/glove over the collar, 8,000 µg/glove on the neck with the collar removed, and 80 µg/glove in the tail region. The residues obtained over the collar, and around the neck without the collar in place declined 30% from 5 to 12 days post-collar application, while residues obtained from the tail region remained fairly constant. Peak transferable residues collected over the collar at 5 and 12 days post-collar application were of a similar magnitude to those observed in study 1 at 7 and 14 days, respectively.

For purpose of risk assessment, EPA has added the reported residues from on the neck, over the collar and summed these with the tail; the under the collar residues have not been added since the label directs the user to fasten the collar in place. The use of these mean residues indicate post application risks of concern. As such, the use of maximum values would only worsen the present risk of concern identified; for purpose of risk quantification, EPA relied on the reported application rate of 4.8 grams per dog. EPA used this rate to define the limit and at this limit, risks of concern were identified.

The Davis study glove residue collection methods are consistent with pet fur transferable residue collection methods conducted around the time of the Davis study. They used a repeated petting motion to a single sample collection site (occasionally multiple collections sites were used) with a cotton gloved hand, a defined number of petting motions/strokes (5 - 10 strokes per sample collection point), and a defined period of time was typical of studies at that time (ranging anywhere from 5 - 10 minutes per sampling period). The residue collection method is intended to be a reproducible method for determining transfer following contact with an exposure source. The analytical methods used were scientifically valid with extraction recoveries ranging from 85% to 102%. While the MIXED statistical procedure would have been preferred, the method used has no impact as the EPA intends to use the mean of all sampling times.

In conclusion, pending HSRB review, EPA is considering relying on the glove residue data for risk assessment. Data have been determined to be scientifically valid and are appropriate for use in risk quantitation. Glove residue data from the Davis study may result in a more protective risk assessment and, therefore, would be needed to support a more stringent regulatory decision.

Board Questions of Clarification—Science

Dr. Dawson invited Board members to ask questions of clarification regarding the EPA Science Review. Dr. Gbur asked for clarification about how the standard error term was calculated, presented as 4,000 µg/glove (on slide19 of the EPA presentation) referring to Study 1 glove residue data results. Mr. Bayazid Sarkar (OPP) explained that it was the standard error of the mean based on page 568 of the research article; EPA does not have the raw data from the study. EPA is not using the standard error part in the risk assessment. Dr. Gbur asked whether the decrease in residues cited in the science review was numerical rather than represented by the standard error, and Mr. Sarkar confirmed this.

Dr. Randy Maddalena asked about efforts to access the raw data from the study. Ms. Lydon indicated that she and Mr. Bill Jordan (OPP) had interviewed the principal investigator (PI) of the study, Dr. Janice Chambers. Dr. Chambers had indicated that she would attempt to locate the raw data and would contact EPA if she was successful. Dr. Chambers had anticipated that she would not be able to locate the data and had not contacted EPA prior to this meeting.

Dr. Maddalena noted that the investigators had purchased the collars and used them "as is," without cutting them to fit smaller dogs. Had the collars been cut to fit a smaller dog, the application rate would decrease, and the estimates of the exposure rate per unit area would be expected to increase. Mr. Britton concurred that if the transferable residue measurements remained the same, the estimates of fraction available residue (FAR) would increase, thus increasing estimates of human exposure. Mr. Jeffrey Dawson (OPP) added that the FAR from the uncut collar already indicated a risk of concern. If the collar was cut and the FAR increased, the exposure and risk would increase.

Dr. Maddalena noted that EPA's standard operating procedure for calculating the FAR is to use the maximum observed transferable residue, whereas for this study, EPA had used the average over the exposure period. There was a brief discussion on this point. Mr. Dawson responded that collars differ from other pet products in that they are designed for use over a longer time period. If EPA had used the maximum transferable residue, the risk finding would have been worse, but the conclusion from a regulatory standpoint would have been the same. Mr. Britton added that an average exposure is compatible with the standard operating procedure for assessing cancer risk.

EPA Ethics Review Highlights

Ms. Lydon presented EPA's ethics review. The first topic discussed was the Agency's rationale for the HSRB review. In order to improve the protection of public health, pending public comment, EPA intends to rely only on the TCVP glove residue data from Study 1 and Study 2 in its risk assessment and to potentially impose a more stringent regulatory restriction than the Agency otherwise could without the data. Study 2 also involved the collection of data based on T-shirts worn by children, and urine samples from children and adults participating in the study. With the exception of the dog plasma cholinesterase measurement, all of the data collected constitutes exposure assessment research. EPA cannot reasonably separate the different types of data in these studies as different types of human research. Because study 2 encompassed more than TCVP glove residue data and involved children wearing T-shirts and providing urine samples, study 2 constitutes research involving intentional exposure of children. For that reason, even though OPP does not wish to rely on the data involving children, OPP is submitting the research to the HSRB for review under 40 CFR § 26.1706.

The research was funded by EPA Science to Achieve Results (STAR) grants. EPA's Office of Research and Development (ORD) reviewed the grant proposal which involved human research and funding from EPA. EPA's ethics review refers to the ORD file because it contains draft consent forms used during Study 2 and recruitment information. The HSRB received the ORD file prior to the meeting, along with the other background materials. Primary Investigator Janice Chambers confirmed that the ORD file is pertinent to the research.

Ms. Lydon discussed the role of the veterinary students in rubbing the dogs. The technicians who rubbed the dogs in Study 1 and Study 2 were students enrolled at MSU's College of Veterinary Medicine. PI Dr. Chambers confirmed that both the researchers and the Institutional Review Board (IRB) viewed the veterinary students as technicians in the study, not as human subjects. The ORD file states that "the samplers will be trained so that consistency in the sample collection is maintained among dogs and among samplers." The technicians wore gloves and stroked the animals in a standardized, prescribed manner: "in a marked 10 x 4 inch area with clean, white, cotton gloves for a continuous 5-min period." The dogs were rubbed in specific locations (near the base of the tail, at the neck with collar removed, and at the neck with the collar in place).Under 40 CFR § 26.1102(e), a "human subject" means a living individual about whom an investigator conducting research obtains data through intervention or interaction. Looking at the article and ORD file, the PI did not obtain data about the technicians, nor did

she intend to do so. The pattern of rubbing does not resemble the typical human-pet interaction nor provide information about how a person would normally interact with a pet. In summary, EPA noted during the meeting that the researchers were not collecting data about the technicians in this study and concluded that there is no indication from the research article, the ORD file or the interview with the PI that the study collected data about the veterinary students who worked as technicians in the study. Instead, the researchers collected data only about the residues on the glove as an indication of how much residue was available for transfer from the pet. Therefore, OPP agrees with the PI and IRB that the samplers were not human subjects in the Davis study.

With regard to the societal value of the Davis study, the objective was to assess the amount of exposure to TCVP that could occur in children and adults from the use of a TCVP-containing collar on a pet dog. EPA is considering some of the data from this research in its risk assessment for TCVP. Ms. Lydon discussed ethical considerations related to recruitment, independent ethics review, informed consent, respect for subjects and compensation. Regarding recruitment, the article states that "the studies were conducted in Oktibbeha County, Mississippi (USA), with volunteer households having pet dogs" and that "participating families were volunteers who routinely used flea control products on their pet dogs." "One child and one adult were selected from each participating family" for study 2, which included 44 subjects. The ORD/EPA file on the STAR grant states that: "Dogs selected for this study will be owned by professional (DVM) or graduate students enrolled in the College of Veterinary Medicine, or staff/faculty members of Mississippi State University with a child aged 4-10 years in the household who routinely plays with this dog." It goes on to state that, "Students or staff should be the most reliable group of owners (in contrast to the general public) in that they are accessible daily, their dogs can readily be treated and sampled when the students are in class or the staff members are at work, and as members of the academic community, the compliance and appreciation of the value of research should be high." The ORD/EPA file further states that: "Dogs participating in this study must be enrolled in the Small Animal Community Practice Health Maintenance Program, so that their health status and vaccination history are known." PI Janice Chambers confirmed that MSU's College of Veterinary Medicine is located in Oktibbeha County, Mississippi. Therefore, the recruitment area referenced in the ORD file and the article is the same.

Regarding the independent ethics review, the IRB for Research on Human Subjects at MSU reviewed and approved the sampling protocols and consent forms, and the EPA's Office of Research and Development, the National Center for Environmental Research and Quality Assurance (NCERQA) reviewed the STAR grant proposal focusing on this research. ORD supported the research dependent on the incorporation of NCERQA comments on the consent forms. A copy of the protocol was distributed to each participating household, informed consent was obtained from the adults, and children were informed verbally of the procedures and oral or written assent was obtained from them. The IRB for Research on Human Subjects at MSU approved all sampling protocols and informed consent forms. The ORD file contains a draft consent form for adults and a minor's assent form. The consent form states that the study involves research and identifies its purpose, expected duration, number of urine and T-shirt samples to be provided, states that research results will be coded, participants are free to withdraw, provides a contact for information, and specifies compensation of $150 for each participating household. The consent form also states that "no risks are anticipated to the participants." The implication is that since families already used flea collars on their dogs, there was no added risk from participating in the study. In the abstract that the researchers submitted to ORD, however, the research states that "the residues of insecticides available for intermittent transfer to children from the fur of dogs treated by either a spot treatment or a collar for flea control will be appreciable and of a magnitude necessitating inclusion in cumulative risk assessments of pesticides to children; secondly, that the fur rubbing procedure developed to quantify dislodgeable

residues provides a useful estimate of insecticide residues which could be transferred from the fur of dogs to children."

Ms. Lydon stated that EPA believes that although the families involved already used flea collars registered by EPA, in the interest of transparency, the researchers should have shared their hypothesis with the parents of the participating children and included it in the consent form. It is unknown whether the information was stated in the protocol provided to the families. The minor's assent form states that the researchers "will specifically obtain assent from the children recruited to our project...We will explain that the child's parent or guardian has given us permission to request his/her help participation in the research project. We will then explain the urine collection protocol and the T-shirt protocol to the children in language appropriate to the age of the child and obtain his/her assent to participate. We will not explain the connection to the pesticide residues on the dog so as not to alter the behavior of the child with the dog. We will obtain the children's assent orally because of the age range of the children involved."

Regarding respect for subjects, the researchers: did not reveal subjects' identities; obtained informed consent; provided light weight short-sleeve T-shirts to kids which would not embarrass them; gave written assurance that urine samples will only be used to quantify insecticide urinary metabolites; and provided compensation. Compensation included $100 equivalent of veterinary care provided by the Animal Health Center of MSU College of Veterinary Medicine and $150 to participating households in Study 2.

Ms. Lydon discussed standards applicable to the conduct of the research. Study 1 was conducted in 1998 and Study 2 was conducted in 2002, both before EPA's Rule for Protection of Human Subjects became effective in 2006. Thus, 40 CFR Part 26, subparts B through Q, did not apply when this research was conducted. However, EPA's codification of the Common Rule 40 CFR Part 26 subpart A was in place and applies to the underlying research which received EPA STAR grant funding. Key elements of the Common Rule include IRB oversight and prior approval, an acceptable informed consent process, risk minimization, a favorable risk-benefit balance, equitable subject selection, and fully informed and voluntary participation by subjects. In addition, § 12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)—which states that it is unlawful to use any pesticide in tests on humans unless they are fully informed of the nature and purposes of the tests, as well as of any reasonably foreseeable physical and mental health consequences, and that participants freely volunteer —existed at the time of these studies.

The substantive acceptance standards which apply to the research include: 40 CFR § 26.1703, which, except as provided in § 26.1706, prohibits relying on data involving intentional exposure of pregnant or nursing women or of children; 40 CFR § 26.1704, which except as provided in § 26.1706, prohibits reliance on data if research was fundamentally unethical or deficient relative to prevailing standards at the time; and FIFRA § 12(a)(2)(P), which makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent. 40 CFR § 26.1706 states that EPA may rely on data that are unacceptable under standards § 26.1703 through § 26.1705 only if EPA has: (1) obtained the views of the HSRB, (2) provided the opportunity for public comment, (3) determined that relying on the data is crucial to a decision that would impose a more stringent regulator restriction to protect public health than could be justified without the data, and (4) published a full explanation of the decision to rely on the data.

Regarding 40 CFR § 26.1703, Study 2 involved T-shirt and urine samples that came from children. EPA only wants to rely on the glove residue data from Study 1 and 2 which did not involve children. 40 CFR § 26.1703 does now allow reliance on research involving kids except as provided in

§ 26.1706. Regarding 40 CFR § 26.1704, clear and convincing evidence that the pre-rule research was fundamentally unethical or deficient relative to prevailing ethics standards does not exist, and the research complied with FIFRA § 12(a)(2)(P). Regarding 40 CFR § 26.1706, pending public comment, OPP may wish to rely on the TCVP glove residue data generated in Study 1 and 2. The data may be crucial to a potential EPA decision to improve public health protection by imposing a more stringent regulatory restriction than could be justified without the data. Under 40 CFR § 26.1706, EPA must complete the aforementioned required in order to rely on the data.

Board Questions of Clarification—Ethics

Dr. Maddalena asked whether it was known if pregnant women were in the household at the time of the study. Ms. Lydon confirmed that this was not known. Dr. Dawson added that when the study was conducted, the prohibition against exposing pregnant women had not yet been established; therefore, the researchers had no regulatory mandate to ascertain whether any of the members of the household were pregnant.

Dr. Dawson asked for clarification regarding whether the decision not to use the data on pesticide residues on children's T-shirts was made because these data were not useful for the regulatory process or whether they were not used because they were obtained from exposed children. Mr. Britton responded that the rationale was the former. The T-shirt residues were significantly below the glove residues; therefore, the glove residue data would drive the regulatory decision.

Public Comments

Mr. Downing indicated that no requests had been received by EPA in advance of the meeting to provide public comment. He asked whether any members of the public participating via teleconference would like to provide comments. Hearing no response, Dr. Dawson invited Dr. Maddalena to discuss the Board's response to EPA's scientific charge.

Board Discussion—Science

Dr. Maddalena stated that EPA would like to use the data in this study to determine how much applied active ingredient would be available if a person touches a dog wearing a TCVP-containing pet collar. He noted that EPA had provided justification for using the data that were not most stringent (i.e., use of mean glove residue measures versus the maximum reported residue measures). Data are missing from the study that might lead to lower estimates of exposure; however, the available data still elicit a closer look at current regulatory standards.

Dr. Maddalena noted the difficulty in separately evaluating the quality of the article, the quality of the science, and the appropriateness of the data for their use as stated in the Board's charge.
Dr. Maddalena read the Board's charge into the record, noting that the charge is very specific to pet collars treated with TCVP:

> Is this research scientifically sound, providing reliable pet fur transferable residue data for use in evaluating potential exposures of adults and children from contact with pets treated with tetrachlorvinphos-containing pet collars?

Dr. Maddalena stated that the study was of good quality. The science was solid, and the recoveries and quality assurance results were good. Because the raw data are not available, however, it is not clear how reliable the data are for estimating a FAR. Also unknown is whether the same application rate should be applied to all dogs and how the extra length of collar was handled for small dogs. No mean

for the transferable residue is available because the data only are available graphically. The Agency summed values for the rump and neck, assuming that this sum is representative for the average for the full body of the animal. Whether the transferable residue data might have been correlated with the type of hair or breed is unknown. In spite of these limitations, Dr. Maddalena recommended that if the data are used once for the purpose indicated in the charge questions, they satisfy this purpose.

Dr. Maddalena posed other general questions that cannot be answered from the information provided in the article. These include the following: (1) Are cotton gloves a good surrogate for skin? (2) Is the cotton glove likely to become saturated with TCVP during a given petting event depending on the duration of petting? (3) Is there any loss of active ingredient from glove to hand as a result of the glove being permeable?

Dr. Maddalena suggested that the Board decide whether to respond positively to the charge question. Dr. Maddalena stated that, if the Agency thinks the data are going to provide a trigger to do their job, then the quality of the data is good; the science is solid. But, from a scientific perspective, the numbers in the research article are not complete and the HSRB and EPA do not have access to the raw data.

Dr. Britton concurred with Dr. Maddalena's characterization that EPA intends to use the data for a specific purpose related to risk assessment. He also responded to Dr. Maddalena's general questions. Regarding whether a cotton glove is a good surrogate for skin, the method was not intended to measure the transfer from fur to skin; rather, it was intended to be a reproducible method for determining residue transfer from fur to any surface. Regarding saturation, equilibrium was approached in a petting study that measured the number of strokes required to reach these levels, but it is unclear how that data might be related to a method, such as the one in question, which uses a timed petting period. Finally, possible breakthrough of pesticide residues from glove to skin is unknown based on the article.

Dr. Dawson asked for comments from the Board. She asked OPP whether exposure above a certain level triggers action by the Agency to limit exposure to the public, with the nuances of greater or lesser exposures by a different route are less crucial for Agency decision making than reaching a certain trigger or threshold for Agency action. Mr. Dawson responded that the Agency is interested in sample collection methods and the reliability of the data, but tradeoffs exist when considering the uncertainty and unknowns associated with such data that we need to consider relative to whether or not we would use the data or not. In this case, he noted that the sampling method used was the standard at the time the study was conducted for collecting information such as this. In this case, the information is product-specific that allows us to get closer to a more realistic risk assessment. If we identify risk, the Agency seeks to be transparent about uncertainty, so that triggers, from a regulatory perspective, the need to do some sort of action. It could be that this information could be refined with a better designed study that answers a lot of questions that various HSRB members have discussed and EPA identified in the science review. So that's a possible path forward, or there may be other ways of managing the potential risk. Possible actions include managing potential risk by reducing the amount of active ingredient in the product, or removing products from the market. In response to HSRB questions, Dr. Dawson noted that reducing the active ingredient in the collar would presumably require a follow-up study to determine the resulting exposure. Mr. Dawson agreed, stating that, if the Agency went that route, EPA would have more input into the design of a follow-up study. Mr. Britton also indicated that, associated with this, EPA would typically require data supporting the continued efficacy of the product.

Dr. Dawson asked Dr. Gbur to clarify his conclusion from a statistical standpoint as to whether the data in the study are reliable enough to allow use in evaluating potential exposure. Dr. Gbur replied

that the lack of information about standard errors in the exposure numbers derived from the data in the study is a concern. No information was provided by the researchers about how the standard errors were generated. The lack of characterization of variability provides no indication about the reproducibility of the method.

Mr. Dawson responded that the calculated risk still is of concern whether the low or high end of the standard errors indicated graphically are used. Without using these data at all, the Agency would have to change its risk conclusions in the risk assessment. Dr. Maddalena noted that the default value for FAR is 2 percent. These study data change the estimate to 3 to 4 percent. Dr. Maddalena stated that it appears that this difference, despite the range of uncertainty, is enough to trigger the Agency's action. Mr. Britton explained that the 2 percent default value is based on liquid products. In the study review, for study 1, the FAR value of 0.3% would be used and for study 2, the value of 0.4% would be used; those values are well below our SOP default value of 2%. Beyond that, there were other active ingredient exposure data available for pet collar products that we considered for use in risk assessment. Since 2012, EPA has received other registrant submitted studies which are pet collar glove residue studies. Of those studies, the Davis study results in about three times greater residue transfer than the next closest active ingredient pet collar study. EPA intends to take the pet collar residue data into account in our SOPs.

Dr. Suzanne Rivera indicated that she has some concerns to raise during the ethics review portion, of the HSRB discussion but she observed that the science must be judged useful in order for the study to be considered ethical. Dr. Dawson responded that the science is sound, but the data are not as informative as the Board might like them to be. They still are useful to EPA to inform more stringent regulation. Ms. Lydon added that the Board's concern about completeness of the data does not indicate that the study was not conducted in an ethical manner.

Dr. Maddalena stated that he would like to word his response to limit the use of these data to the particular use specified. He characterized the glove residue data as being much too conservative for use in a detailed exposure or risk assessment versus a screening exposure assessment. Mr. Dawson suggested that EPA might have use for the study data beyond the current risk assessment, such as to inform future study design. Dr. Maddalena expressed doubt as to whether the data represent the best value to determine the FAR, but the Board's response could acknowledge that the Agency has considered the limitations of the data.

Dr. Dawson asked Dr. Maddalena to draft a recommendation for the Board's response to the science charge question, circulate it to the Board members via email, and offer it for the Board's deliberation on the morning of the second day of this meeting. Details of the Board's concerns about the data can be included in the final report.

Board Discussion—Ethics

Dr. Dawson reminded the Board that the ethics review is retrospective; different standards apply than for a prospective review. The Board must determine whether the study violated the ethics standards that applied at the time the study was conducted. The Board also needs to consider the ethics of the study in light of the use to which the Agency intends to put the study's results, which is to protect the health of the public.

Dr. Rivera presented her ethics assessment, addressing each of the two ethics charge questions individually. The first question was the following: "Does the HSRB have any comments on EPA's determination that the samplers were not human subjects?" The samplers were the technicians/students who performed the petting of the dogs. Dr. Rivera indicated that she was not persuaded that the samplers

were not human subjects. The possibility of transfer of pesticide to the samplers existed because the gloves were cotton. If exposure to an experiment is the intervention part of the definition of human subjects, then it's worth discussing whether or not the samplers were exposed to the experiment and therefore experienced an intervention. She noted that there are many studies where there is an observation of behavior but we don't collect data beyond the observation. Therefore, she was not persuaded that the samplers were not human subjects because information about them was not collected.

Dr. Schonfeld responded that the IRB had not considered the samplers to be human subjects. If later review boards do not agree with the original IRB review, logistical issues are raised for researchers.

Dr. Rivera suggested that the act of asking the question of the HSRB might imply that there is some doubt as to whether or not the samplers were human subjects. Ms. Lydon noted that EPA does not view the samplers as human subjects. The researchers had not collected data about them as individuals. There was no reference to possible seepage through the glove in the article and no information that that had occurred. Ms. Lydon indicated that she was the author of the ethics charge questions. EPA's view is that the veterinary students were technicians and not human subjects under the definition in the federal human research rule, and the intent of posing the question to the HSRB was to determine whether the Board agreed. EPA is seeking comments about the issue from the Board that will assist the Agency in writing and publishing for comment, a summary of potential ethical issues with the study, as required under 40 CFR § 26.1706 if EPA intends to rely on the glove residue data.

The floor was opened to questions and comments from the Board members. The Board discussed whether the samplers should be considered human subjects in the study and therefore should have been given the protection of informed consent or were part of the research team. Dr. Gary Chadwick stated that in his opinion, EPA and the IRB were not correct in not considering the samplers to be human subjects. For example, farmworkers wear protective clothing, residues on their clothing are measured, and the farmworkers are considered human subjects. Dr. Chadwick asked whether the samplers gave informed consent to participate in the study. Ms. Lydon noted that her response only applies to the conditions associated with this particular study. She added that only the adults and children in the participating households gave informed consent. In this case, the samplers were petting the dogs in a prescribed manner and the IRB did not view them as human subjects. Dr. Jewell Halanych agreed strongly that the samplers were human subjects and suggested that they be placed in the category of a vulnerable population because of their status as students. Mr. Dawson explained that EPA viewed the petting as a clinical sample collection method that was not meant to mimic human behaviors. It would be the same if we asked someone to collect residues from a treated field and they went and picked parts of a plant to analyze what's in that plant. It's analogous to field researchers doing research who have a protocol and collect certain samples and leave the field, but they are not mimicking human behaviors which emulate the exposure pathway being considered in risk assessment. Dr. Rivera stated that she, Dr. Chadwick and Dr. Halanych understood conceptually the difference between being a member of a study team and a participant. She indicated that all individuals exposed to risk in research are treated as subjects and should be given the protection of informed consent. Dr. Dawson noted that there is some ambiguity about individuals collecting data and it's not surprising that we can see this issue in different ways. One view is human behavior as a component of what is being measured (e.g., pesticide sprayers who are wearing dosimetry) versus samplers collecting residues from a dog and being told to do so in a prescribed manner in order to collect data.

Regarding the risk level, Dr. Dawson stated that no one had an idea that the level of exposure would be so high until the study was performed. Patting with a gloved hand would have been thought to be less risky than patting a dog with bare hands, as dog owners do. Whether there was bleed through of

the pesticide through the glove is unknown, and no data exist to suggest it occurred. If it was reasonable to assume that risk to the samplers was low, then the mistake about whether they should have secured informed consent is less serious. In addition, Dr. Dawson offered the analogy that individuals who work in a laboratory performing assays might be exposed to chemicals but are not considered human subjects; they are workers who need protection. Dr. Rivera agreed that the potential harm to the samplers might not have exceeded risk incurred during everyday life.

Dr. Rivera suggested that a possible Board response to the charge question might be to state that questions were raised about whether the IRB might have been mistaken in not characterizing the samplers as human subjects although the risk to the samplers might have been relatively low, but that should not be a barrier to EPA using the study. Dr. Halanych concurred with this response. Dr. Chadwick stated, however, that the level of risk had not been determined. In addition, the technicians were asked to alter their behavior, although the altered behavior could be characterized as being work-related (as with a laboratory technician) or a behavioral change that you might ask a human subject to do. Dr. Dawson proposed that the Board respond that questions had been raised by some of the Board members as to whether the samplers should be considered human subjects; the Board decided, however, that the issue of whether the samplers were human subjects should not have a bearing on whether EPA should use the study. The Board agreed unanimously with the proposed response to the first ethics charge question, the text of which Dr. Rivera would draft, circulate to the Board members via email, and offer for the Board's deliberation on the morning of the second day of this meeting.

Dr. Rivera read the second ethics charge question into the record: "Does the HSRB have any comments on the ethical conduct of the research?" Dr. Rivera stated that the risks of exposure to the toxin were not disclosed to the participants in advance of the intervention. She noted the possibility that the rubbing procedure could have exposed the children to more pesticide than living with the animal. The researchers did not explain to the children the connection between the goal of the study and exposure to pesticide residues on the dog. FIFRA, which was enacted at the time of the tests, states that it is illegal to intentionally expose humans to pesticides unless they are fully informed of the nature and purpose of the test. Dr. Rivera stated that withholding the entire intention of the study to the children represented an incomplete assent process. The children enrolled in the study were of varying ages, however, and would have had varying capacities to understand the purpose and associated risks of the study. The children were not informed of the purpose of the study, but the adults were. Children gave their assent to participate, whereas the adults gave their consent.

Dr. Dawson clarified that the children and parents were not asked to perform additional interactions with the dogs or follow the rubbing procedure, which Ms. Lydon confirmed. Only the technicians/veterinary students were asked to rub the dogs in a prescribed manner. Also, the ORD file provided to the HSRB includes the draft consent form. The floor was opened to questions and comments from the Board members. The characterization of risks to the participants in the consent form was discussed. Dr. Dawson stated that the consent form in the ORD file had indicated that no risks were anticipated to the participants, but a note from an IRB reviewer asked the investigators to revise the form, and the PI had said that she would. The final consent form was not included in the file. Ms. Lydon stated that the PI would have been required to make the changes to the consent form requested by ORD in order to receive STAR grant funding. Dr. Dawson corrected her statement that it was ORD, not the IRB, who requested the changes to the consent form. Dr. Rivera stated that the Board's comments should mention that the degree to which risks were explained in the final consent form was uncertain because the final consent form was not available.

The decision not to inform children participating in the study about the study's aim was discussed. Dr. Chadwick stated that the children were not informed fully so as not to alter their behavior with their dogs. Dr. Dawson agreed that informing the children about chemicals in the flea collars might have altered their behaviors, resulting in decreased exposure on the T-shirts and undermining the experiment; the social good that comes from the data would then have been lost. Dr. Rivera noted that not fully informing the children was an intentional choice by the investigators, which might be interpreted as a deception so as not to confound the study by causing the children to behave differently. Assuming that was explained to the IRB and they considered the pros and cons of that approach, Dr. Rivera didn't feel the need to second guess it; given that the risk is low and these are pesticides (flea collars) that the children would have been exposed to anyway, it doesn't appear that any measurable harm resulted from it.

Dr. Rivera stated that she would draft a revised recommendation for the Board's response to the second ethics charge question, circulate it to the Board members via email, and offer it for the Board's deliberation on the morning of the second day of this meeting. Dr. Dawson noted that the charge did not instruct the Board to offer EPA advice regarding whether to use the study, but the Board's response could include the ethical concerns raised. The Board agreed unanimously with the approach to respond to the second ethics charge question by outlining the ethical issues that had been raised.

EPA Review of Five Completed Studies for Field Testing of S.C. Johnson Skin-Applied Mosquito Repellent Products to Support Their Use of the Insect Repellency Awareness Graphic

Overview

Dr. Eric Bohnenblust (OPP) provided an overview for the five completed S.C. Johnson studies, each testing a single insect repellent against mosquitoes in the field to determine, for the EPA Repellency Awareness Graphic, the median complete protection time (CPT) of five of their skin applied repellent products. The EPA Repellency Awareness Graphic, an EPA program to raise public awareness of the health protectiveness (efficacy) of mosquito and tick repellents applied to the skin, shows the typical length of time the product repels mosquitoes or ticks. The purpose is to increase EPA and consumer confidence in the efficacy claims on labels and improve consumer protection against vector borne diseases, such as West Nile virus and Lyme disease.

There were 5 S.C. Johnson completed studies on the agenda for the January HSRB meeting. All 5 studies were based on the same previously review protocol. In the interest of time, EPA first reviewed the 42 science and ethics slides that were applicable to all 5 completed studies. After that, EPA presented study-specific information on each of the 5 studies.

EPA Science Review Highlights

Dr. Bohnenblust discussed the previous review of the protocol applicable to all five studies. EPA's science and ethics review of March 31, 2015 found the protocol acceptable with minor changes. The HSRB review on April 23, 2015 concurred with EPA with minor changes. The amended protocol of June 26, 2015 was approved by IRB on July 7, 2015.

With regard to the methods overview, testing was conducted at locations in Wisconsin and Florida. Testing was conducted against mosquitoes with 20 different treated human subjects per product (10 per site) and two untreated control subjects per site. Several tests were run with unequal numbers of male and female subjects. SC Johnson indicated that they conducted a statistical analysis comparing complete protection time (in hours) of men vs. women in studies conducted in Wisconsin for a variety of

spray-on personal mosquito repellent products using standard SC Johnson test protocol. The sample size for each individual product was too small (N=10) to warrant a product-by-product comparison of genders, so protection times for all products were combined before statistical testing was done. The Mann-Whitney U test was used to compare females to males, resulting p values of 0.89. This high p value suggests that complete protection time is statistically equivalent for females and males.

With regard to the treatment application rate, aerosol products were tested at 1 g/600 $cm^2$and pump sprays were tested at 0.5 g/600 cm^2. Method of application was as follows: For aerosols – spraying, then spreading on skin using fingers; for pump sprays – using a pipette, then spreading on skin using fingers. Subjects were exposed to mosquitoes for a 5-minute period every 30 minutes, using post-application delays before starting exposure that were specific to N,N-diethyl-meta-toluamide (DEET) content. Five minute exposure periods were delayed until 2 hours post application for products containing 12 – 15.99% DEET, and 3 hours for products containing > 16% DEET. The exposure periods occurred until product failure or the study director terminated the study. With regard to endpoints and measures, mosquito Landings were used to evaluate repellency. Repellent failure was determined by the "First Confirmed landing." Mosquitoes that landed were collected and identified to species for each site. With regard to data analysis, the median CPT for each product at each site was calculated using Kaplan-Meier Survival Analysis using PROC LIFETEST.

S.C. Johnson had addressed the HSRB's previous comments on the protocol that were provided during the April 23, 2015 HSRB meeting. Dr. Bohnenblust reviewed each HSRB science comment and S.C. Johnson's response to each comment, as noted below.

1. Comment on potential for cross contamination: The protocol should specify steps that will be taken to insure that the treated area on subjects is not impacted by activities that take place before or during the experiment (*i.e.*, rubbing sleeve or pant leg across the treated area).

S.C. Johnson Response: Subjects were not transported using a vehicle after the test substance was applied, and subjects were reminded not to touch or contact the treated skin in any manner. Any inadvertent contact with the treated area was reported to the study staff and documented in the raw data.

2. Comment on landing pressure: The protocol includes untreated control subjects with each test to insure that there is sufficient landing pressure to provide valid results. The Board recommends that the Agency and S.C. Johnson consider how a quantitative estimate of landing pressure can be determined without increasing the likelihood of bites if landing pressure is excessive (*e.g.*, recording the time of each landing, the time to reach 5 landings, or the total landings in 5 minutes) and how that information can be used to normalize or interpret CPTs measured under different landing pressure conditions.

S.C. Johnson Response: Study staff recorded the time to reach five landings if less than five minutes. Because all studies were performed at the same two sites, landing pressure appears to be fairly consistent across sites, therefore normalization is not required.

3. Comment on delayed start: The Board recognizes the advantages of delaying the exposure to mosquitoes for subjects treated with products that are known from previous experience to last for a long time. However, the protocol needs to provide more information about the criteria used to determine how long to wait before starting the test cycles (5 minute exposure at 30 minute intervals). Regardless of how long the subject's exposure is delayed, the protocol should require a

minimum number of completed cycles to insure valid results. For example, following a delayed exposure, the subject should complete at least three exposure cycles before getting a confirmed landing.

S.C. Johnson Response: Exposures were delayed until two hours after application for products contained 12-15.99% DEET and three hours for products containing more than 16% DEET. All subjects were exposed to mosquitoes for at least three exposure cycles before a confirmed landing was recorded. In addition, delaying exposure periods reduced the exposure of the subjects to potential bites from mosquitoes.

4. Comment on randomization: The randomization mechanism should be described in more detail and rationale should be given for any given choice of randomization within the protocol. For example, it is not clear whether/how cross-substance relations are to be evaluated in the data analysis and why randomization among test substances is needed. An explanation of this would be helpful. In addition, when the conditions support use of arm rather than leg for exposure, then it may be more important to consider handedness when selecting what arm to treat, rather than randomly assigning to left or right hand, so the subject can have their dominant hand to remove landing mosquitoes before they bite.

S.C. Johnson Response: One test substance was tested on each day, therefore randomizing the treatment was not necessary. The mechanism for randomizing the arm was not provided in the studies; however, after discussions with S.C. Johnson, they indicated that the mechanism for randomizing the arm to be treated was based on the random selection of test ID numbers. Subjects assigned odd numbers had their left arm treated, and subjects with even numbers had their right arms treated. In addition, the protocol notes that aspirating mosquitoes is not difficult even with a non-dominant hand. The untreated control subjects were allowed to choose which arm to expose.

5. Comment on sample size determination: A sample size calculation would be useful here to inform the power of testing and the width of confidence intervals. Power and sample size calculation can be implemented using existing SAS procedures. Information about appropriate sample size calculations is included in the EPA document "Product performance Test Guidelines OPPTS810.3700: Insect Repellents to be Applied to Human Skin."

S.C. Johnson Response: After discussions with S.C. Johnson, they indicated that they did not conduct a sample size calculation or power analysis, but the table which summarizes the effect of sample size on the confidence interval for median CPT presented in the protocol for testing repellents against ticks to the Human Studies Review Board at the October meeting would apply to these studies because both studies use 10 subjects. In the past, HSRB had positive reviews about the sample size of 10. EPA also believed that a sample size of 10 will provide a reasonable width of the confidence interval for the median based on past studies testing repellents.

6. Comment on sources of variation: The protocol does not currently specify the conditions that might cause the CPT data from the two sites to differ; however, the researchers should consider collecting information to explain any large and potentially significant differences in the CPT values between otherwise matched studies conducted at two different sites.

S.C. Johnson Response: The researchers identified mosquitoes to species, recorded habitat characteristics, climatic conditions, and the time to five landings on the untreated control subjects, information which could explain large and significant differences in median CPT.

S.C. Johnson had also addressed EPA's previous science comments on the protocol. EPA commented that product application was not fully described in the draft protocol. In the revised version, the exact method of determining the amount of product applied to each subject was described in §14.0 and 7.1.8.2.

EPA also asked S.C. Johnson to: "Describe how the data will be analyzed if the number of test subjects at the end of the test is less than ten. In other words, what if subjects withdraw? If alternates replace them, how will Johnson account for this change of subjects in the data analysis?" For the revised protocol, S.C. Johnson clarified that for subjects that withdrew before receiving their first confirmed landing, their CPT was considered to be the time at which they withdrew. These "right censored" subjects are indicated by a + on the survival curve graphs. Subjects that withdrew were not replaced with alternates.

EPA's third science comment on the draft protocol was as follows: "The protocol states that up to 10% of the exposure periods in a test may have less than the minimum landing (biting in the protocol) pressure of five mosquitoes landing in five minutes or less. Will treatment exposures occur during periods of insufficient landing pressure? If treatment data are collected during these periods, how will they be used in CPT calculation? If they are not used, how will the lack of data points be considered in the K-M analysis and calculation of Median CPT?" For the revised protocol, S.C. Johnson clarified that when the minimum landing pressure was not achieved in an exposure period, those exposure periods were used in the study report.

EPA Ethics Review Highlights

Ms. Lydon provided an ethics assessment applicable to all five studies, prior to discussing the study-specific information. During the ethics review of all five studies, Ms. Lydon addressed the topics of: recruitment; the informed consent process; pregnancy testing; training; mitigation of hazards; compensation; responsiveness to EPA and HSRB comments; the independent ethics review; and completeness of documentation.

For recruitment, S.C. Johnson contracted with recruitment firms. Using an approved phone script for the initial call, the recruitment firms screened 392 subjects. Using approved inclusion/exclusion criteria, and taking into account subjects' availability and interest, the firms scheduled 170 subjects for S.C. Johnson to contact. EPA highlighted for the HSRB that S.C. Johnson notified EPA that they had provided some incorrect information with regard to Table 6 in the completed studies for Mark 3, 4 and 5; S.C. Johnson will update these studies. S.C. Johnson double counted three additional subjects in table 6 for the studies mentioned. EPA shared the updated information as provided by S.C. Johnson: The total number of subjects initially contacted by the recruitment firm was 6,950; the total number of subjects interviewed by the recruitment forms was 392; and the total number of subjects screened by the SCJ study staff was 170. Using the approved follow-up screening script, eligible and interested subjects who were available for both the training and test dates were enrolled for each study.

The pool of candidates generally represented the demographics of U.S. repellent users, but not all targets were met because of subject availability for training/test days, and subjects withdrawing or not showing up on scheduled training or test days. Table 5 in each completed study provides the

demographics of subjects who were enrolled versus those who actually participated in each study. Table 6 in attachment 2 to the ethics review memos summarizes data on subject recruitment. Table 7, also in attachment 2, summarizes data on subject participation.

With regard to the informed consent process, S.C. Johnson (SCJ) adhered to the inclusion/exclusion criteria from the approved protocol. Interested subjects who met the inclusion/exclusion criteria met with Study Director or Principle Investigator at training session. Subjects were provided the informed consent document (ICD) and asked to read it. SCJ emailed consent forms to subjects in advance of training if they were provided an email address. SCJ asked subjects if they had questions and answered them. If subjects wished to enroll, they signed ICD and were given a copy.

Pregnancy testing was carried out consistent with the approved protocol section 2.3.12, reviewed by the HSRB. Testing for each study was conducted on the training day, and if the test day occurred more than 48 hours after the training, the pregnancy test was repeated on the morning of the test day. No pregnant or nursing female subjects participated in the study. The HSRB reviewed this approach without comment at the April 22-23, 2015 HSRB meeting.

With regard to training, the subjects were trained to aspirate blood-seeking mosquitoes prior to participating in the study. In WI, training took place in a laboratory and in FL, a field. Training was consistent with approved protocol. A study staffer demonstrated how to aspirate mosquitoes. After subjects watched at least 8 mosquitoes captured and aspirated properly, they tried it themselves. Subjects did this until the study staffer felt they were proficient and could participate in the field test. For the FL training in the field, subjects wore bug suits and gloves for protection during the training, consistent with protocol.

The protocol and completed study identifies five hazards associated with these studies and precautions taken to mitigate the hazards. Hazards included adverse reactions to test substances, exposure to biting mosquitoes, exposure to mosquito-vectored diseases, general risks of being in the field, and unanticipated loss of confidentiality. Pages 18 – 19 of each study describe the precautions taken to mitigate hazards. A few examples of precautions include excluding participants with known allergies to mosquito bites, training subjects to remove mosquitoes from skin before subjects could be bitten, and limiting exposure to one forearm. For untreated control subjects who were at greater risk of being bitten, when they received five lands within the 5-minute exposure (the minimum necessary to ensure adequate mosquito landing rate), they covered their exposed limbs by rolling down their sleeve. In the U.S., mosquitoes can transmit various disease-causing organisms to humans, notably the West Nile virus. All subjects were instructed as to what symptoms of these diseases may look like, so they could seek informed medical care in the unlikely event they contracted any of these diseases and became symptomatic.

The study was conducted in areas where the presence of mosquito-borne disease had not been detected by health or mosquito abatement staff during the prior month. The Study Director continually monitored for emerging reports of mosquito borne diseases in the area of the test locations prior to the test date and within two weeks following the test date. The Study Director consulted the USGS, CDC and State Health Department websites to monitor reported mosquito borne disease in areas for the county where the test location resided. Food and beverages were provided on site, and tent enclosures were provided to keep mosquitoes away from subjects between exposures; shade was provided to protect them from direct sun. In addition, ample seating was provided to subjects participating in testing. Subjects were instructed to inform study staff immediately if they experienced skin reactions or injury or felt unwell; such subjects would immediately be given appropriate care, and could withdraw from testing.

Subjects were told that they could withdraw from the study for any reason without penalty. Other precautions to mitigate hazards on pages 18-19 of each study.

Subjects were compensated consistent with the protocol for participation in training and testing, and alternates were compensated as well. Compensation included: $60 for participating in training, even if the subject withdrew from training; $15 per hour of participation on the test day; $18 per hour for each additional hour on the test day beyond first 8 hours; and $50 provided to an alternate if not needed on the test day.

S.C. Johnson was responsive to HSRB and EPA previous ethics comments in revising the draft protocol, informed consent document and telephone screening scripts. The details are discussed in attachment 3 to the ethics review memo already provided to the HSRB. The benefits section of the consent document was revised to indicate that payment is not considered a benefit. Family members of S.C. Johnson were excluded. Stopping rules were expanded. The study sponsor expanded the language in protocol section 11.2.6 to address this comment. The sponsor added the following language: "If the test subjects asks to withdraw, if any adverse reactions or sensitivity such as redness, edema, itching, or pain to the test substance are observed or reported, subjects exhibit hypersensitivity to insect bites and/or any medical management is needed, the test subject will be removed from the test immediately." The protocol was revised to provide details on the demographics of the recruiting pool which would be representative of U.S. repellent users. The comment was made that prospective subjects should be given the option of reading the consent document themselves. The study sponsor revised section 2.4.1 of the protocol to include the new language which states that, "Prior to participating in any aspect of the test, each potential subject who has expressed interest in participating in the study and has met the inclusion/exclusion criteria will meet with the Study Director or Principle Investigator at the scheduled training session. At this session, the subjects will be provided with copies of the Informed Consent Document and will then be asked to read the entire document." In addition section 2.4.2 was also revised to state *"After the potential subjects have completed reading the consent, The Study Director or Principle Investigator will ask the subjects if they have any questions regarding the information in the consent form, the study and their role in the study. Any questions will be answered."* The screening document was revised to make it clear that the subjects could request a copy of the consent document in advance for their review. S.C. Johnson confirmed that, since most of the test subjects asked for a copy of the consent document at this point, their practice was to send the consent form via email to all eligible test subjects. Given the changes above, it was determined that additional questions to confirm understanding of the informed consent document were not necessary; all test subjects could read and speak English, all test subjects were given ample time and opportunity to read the consent form and ask questions about it, and study staff asked each test subject if they had any questions about the consent document. Any questions were answered.

Subjects were told to provide their own transportation to and from the test site. The protocol and consent document were revised to explain how compensation would be handled if subjects participated in the training but not the study. In section 2.2.6 of the protocol, the sponsor added the following language: "Test subjects that choose to withdraw or asked to withdraw from the training session will still be paid $60.00 for attending all or part of the training session." In section 2.2.7 of the protocol, the sponsor added, "Test subjects that choose to withdraw or are asked to withdraw from the study on the test day will still be paid for the hours which they participated on that test day (however, this will not affect payment for any previous test days in which the subject may have already participated)." The same topics were addressed in the compensation section in the final consent form. Finally, these topics were also addressed in sections 12.2.5 and 12.2.6 of the final study.

A comment was made to discuss whether repeat tests should be limited and to include a plan for follow-up with subjects after the study. The protocol did not limit the number of repeat tests per person. S.C. Johnson provided the following explanations: All products which are subject to this protocol are registered by EPA and have been previously evaluated for safety. There were and are no anticipated hazards from repeated use. Since the protocol dictated that a minimum of two full calendar days would occur between treatments, it was not expected that residual active ingredient would be present in a later study. The protocol called for exposure to be controlled by exposing the test subjects to no more than the typical use rate. Exposure was further minimized by instructing each participant to wash their treated limb at the conclusion of the study. Test subjects were monitored during the study, so if an adverse reaction was noted, they could be removed from the study and avoid subsequent exposure. As of December 10, 2015, S.C. Johnson had not received any reports of adverse reactions after the test.

A plan was developed to be able to contact subjects after the study as necessary. The study sponsor expanded protocol section 11.2.4 to state, "The Study Director and recruitment firm will keep on file the phone numbers and addresses for each study participant as a means to contact them if needed." This statement follows the pre-existing language that, "Subjects will be informed both verbally and in writing of any significant new findings, such as detection of mosquito borne disease in the area or product contamination, discovered during the course of the testing which may influence their continued participation." Section 11.2.8 was expanded to state, "Study staff will monitor and contact test participants if any mosquito borne disease cases are reported in the test area within two weeks following the test date." Language was already included in protocol section 11.2.9 and in the consent form providing a 24 hour contact number that test subjects could use for any research-related issues or concerns. Follow-up was deemed necessary only if S.C. Johnson came into possession of new information about which the test subjects should be notified consistent with the protocol. On the topic of following up with subjects, prior to S.C. Johnson finalizing the protocol, OPP told S.C. Johnson that the expanded information described above was sufficient.

In response to a different comment, S.C. Johnson expanded the protocol to provide a process to contact subjects in the event that new information is discovered. The study sponsor expanded protocol section 11.2.4 to state, "The Study Director and recruitment firm will keep on file the phone numbers and addresses for each study participant as a means to contact them if needed." This statement follows the pre-existing language that, "Subjects will be informed both verbally and in writing of any significant new findings, such as detection of mosquito borne disease in the area or product contamination, discovered during the course of the testing which may influence their continued participation." Section 11.2.8 was expanded to state, "Study staff will monitor and contact test participants if any mosquito borne disease cases are reported in the test area within two weeks following the test date.

In response to other comments, S.C. Johnson provided a justification for excluding non-English speakers and information on the demographics of the recruitment pool at each site, and recruitment strategies. The original section 2.2.3 of the protocol did not provide details on the demographic targets. The revised section 2.2.3 provides details on the demographic targets. With regard to the requested justification language, the protocol was revised to state: "This pool will generally represent the demographics of US repellent users. Current repellent product labels are in English, so to target users familiar with and that understand the product labels, we will be recruiting English speaking subjects. This research does not offer benefits to the subjects, so limiting recruitment to English speakers does not result in equity-of-access issues. In addition, the language that someone speaks does not directly affect attractiveness to mosquitos. SCJ will target recruiting a minimum of 10% bilingual (English and another

language) to help not restrict recruitment to only English speakers." After this language, the revised protocol includes 2015 Neilson data related to U.S. repellent users.

The consent document was revised in response to concern regarding S.C. Johnson's plan to handle claims similar to workers' compensation claims. In the consent form, the study sponsor deleted the worker compensation claim language that concerned the HSRB and revised the applicable section to read as follows: "Compensation for Injury: In the unlikely event that you are injured as a result of your participation in this study, medical care will be made immediately available. The sponsor will reimburse you for the costs of this care. If you believe you may have suffered any physical or mental side effects as a result of your participation, please contact the Study Investigator using the phone number on page 1 of this document. All adverse effects will be followed until resolution is reached. There are no plans to provide other compensation beyond that which is listed in this informed consent document. You will not lose any of your legal rights or release the Sponsor, the study doctor, the study staff, or study site from liability for mistakes or intentional misconduct by signing this consent document."Finally, the consent form was revised in response to request to clarify the statement that the study is confidential. The sentence in question stated that, "This study is considered confidential." After this sentence, the study sponsor clarified that "The details of the study should not be discussed or disclosed with others not involved with the study. All data collected on individual subjects is also confidential."

The requirement for an independent ethics review was satisfied because Schulman Associates IRB (SAIRB), an accredited and independent IRB, approved the revised protocol, the informed consent document, and the phone script for initial and follow-up calls. Documentation was completed, SAIRB correspondence was provided, and the requirements of 40 CFR § 26.1303 were satisfied.

Board Questions of Clarification—Science

Dr. Kenneth Ramos asked whether the two different dosing regimens were part of the original protocol. Dr. Bohnenblust responded that they were. Mr. Kevin Sweeney (OPP) added that the dosing regimens were determined for comparison with existing data sets and for verisimilitude with actual use.

Dr. Maddalena asked about including data when the landing pressure was too low. Dr. Bohnenblust replied that the situation only occurred in one study and did not affect results.

Board Questions of Clarification—Ethics

Dr. Halanych asked about the timing of pregnancy testing. Ms. Lydon responded that if the training occurred more than 48 hours before exposure, S.C. Johnson confirmed that female subjects were tested again on the morning of the test day.

Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic, GLP Study Number 865E1, J. Palm, September 24, 2015. Test Substance: MARK-3 OFF! Deep Woods Sportsmen Insect Repellent I (Maximum Strength Pump Spray Deep Woods OFF! EPA Reg. No. 4822-276)

EPA Science Review Highlights

Dr. Bohnenblust presented EPA's science review of the MARK-3 study. The MARK-3 study, which tested an EPA-registered 98.25% DEET pump spray, was conducted on July 29, 2015, in

Wisconsin and September 10, 2015, in Florida with 10 treated subjects (six females and four males at the Wisconsin site) and two untreated subjects at each site. The mean application rate was 101 percent of the target, and the application rate ranged from 97 to 104 percent. The study was ended after 20 exposure periods at the Wisconsin site because landings on the untreated subjects were not adequate (<5 landings per 5 minutes) and after 19 exposure periods at the Florida site at the discretion of the study director.

At the Florida site, five landings occurred on all untreated control subjects during all exposure periods. At the Wisconsin site, less than five landings occurred on one subject in exposure periods 19 and 20 and on the other subject in exposure periods 14 and 19.The time to five landings ranged from 17 seconds to just under 5 minutes during all exposure periods where 5 landings occurred. In Wisconsin, 70 mosquitoes were collected, and the *Aedes* genus predominated (five species total). In Florida, 302 mosquitoes were collected, and *Aedes* also predominated, but more species were detected (11 total).

The Kaplan-Meier Survival Analysis was used to calculate the median CPT. For those subjects who did not experience first confirmed landing (FCL) by the end of the study, their CPT values are conservatively assumed to be the post-treatment duration of the study in a given site. At the Florida site, 4 subjects did not receive an FCL, and 2 subjects did not receive an FCL at the Wisconsin site. The median CPT was 12.0 for the Wisconsin site (range 4.5–12.0) and 12.0 for the Florida site (range 8.5–12.0), yielding a median CPT for the graphic of 12 hours.

EPA concluded that the methods used in this study were adequate to produce scientifically reliable results. The methods were based on the protocol reviewed and accepted by the EPA and HSRB on April 23, 2015 as amended to incorporate EPA and HSRB recommendations before testing began. The data in the study are acceptable to support a median CPT of 12.0 hours against mosquitoes for the EPA Repellency Awareness Graphic on the label for Mark-3.

Board Questions of Clarification—Science

Dr. Gbur asked how the overall median was calculated from the two site-specific median CPTs. He asked why the data from the two sites were not pooled to determine an overall median for the graphic. Dr. Bohnenblust replied that the median CPT used for the graphic was the lower of the two site-specific medians. Mr. Sarkar added that this approach was used rather than calculating a median from pooled data from both sites because it is more protective of human health.

Dr. Ramos pointed out an error in the report, where 2014 was written instead of 2015 for the date the protocol used to conduct the study was reviewed by the board.

Dr. Ramos asked why the number of mosquitoes collected at each site was so different. Ms. Julie Palm (S.C. Johnson) explained that the number collected included aspirated mosquitoes and any additional mosquitoes collected by staff. A Consultant to the Board, Dr. Kendra Lawrence (U.S. Army Medical Material Development Activity) asked for more details about the collection of additional mosquitoes. Ms. Palm replied that the mosquitoes were collected from the protective suit of the untreated controls. The goal of collecting additional mosquitoes was to obtain a large number to identify in the laboratory.

Dr. Ramos asked why data were tallied in Tables 3 and 4 of the EPA Science Review when they were analyzed separately by site. Mr. Sarkar responded that after receiving the total data, EPA requested the site-specific data and will request site-specific data in future studies. Ms. Palm added that no specific reason exists for providing totals.

Dr. Ramos asked for details about blinding subjects to the product applied. Ms. Palm responded that per the protocol, test subjects were blinded to the product used, but if a subject asked, they were informed about which product was being used.

Dr. Ramos asked about the origin of the five-landings-in-5-minutes minimum landing pressure. Mr. Sweeney responded that the rate was derived from historical studies, determined with input from EPA's Science Advisory Board, and discussed by the HSRB in 2010 and is included in EPA guidelines; for most of the S.C. Johnson studies, the pressure was higher than the minimum rate. Ms. Lydon added that the minimum landing pressure was included in the protocol.

Dr. Ramos inquired about possible use of the untreated control data to normalize the data. Dr. Bohnenblust responded that the protocol does not specify how the untreated control data were to be used.

Dr. Lawrence asked about the option given to treated subjects to brush away instead of aspirate mosquitoes. Ms. Palm replied that it was judged more important to avoid bites than to ensure that all mosquitoes were collected, and this was stressed in the training.

Dr. Maddalena asked why testing at both sites was reported to end at 12 hours when testing began 2 hours post-treatment and the study was ended at 20 exposure periods at the Wisconsin site but 19 exposure periods at the Florida site. He also asked how terminating the testing early might affect the CPT. Dr. Bohnenblust responded that if the study was terminated early, subjects without a first confirmed landing were assigned a CPT equal to the exposure period. Ms. Palm added that the median would already have been determined before the test was terminated.

Dr. Maddalena asked how the absence of mosquito-borne disease was confirmed. Ms. Lydon explained that the study was conducted in areas where the presence of mosquito-borne disease had not been detected by health or mosquito abatement staff during the prior month. The Study Director continually monitored for emerging reports of mosquito borne diseases in the area of the test locations prior to the test date and within two weeks following the test date. The Study Director consulted the USGS, CDC and State Health Department websites to monitor reported mosquito borne disease in areas for the county where the test location resided. Ms. Lydon explained that this was described in the slides that were general to all five studies.

EPA Ethics Review Highlights

The EPA slides applicable to all Mark studies which are under review were discussed during the January 12, 2016 HSRB meeting and were not repeated per study. Ms. Lydon presented the results of EPA's ethics assessment specific to the MARK-3 study. For the MARK-3 study, 44 subjects enrolled, eight of whom did not show up; 24 subjects were assigned to participate in the test with 12 alternates/extras. Twenty-one subjects completed the testing. No amendments were made to the protocol, but two deviations were documented, neither of which negatively affected subjects' rights, health or safety. SCJ adhered to IRB instructions and protocol in documenting the deviations. No adverse events or incidents of concern were reported during or after test implementation.

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

EPA finds that the study is in compliance with the acceptance standards. All subjects were at least 18, and pregnant and nursing women were excluded; no significant deficiencies in ethical conduct of the research existed; deviations did not compromise the health and safety, consent, or rights of subjects; and subjects were fully informed, and their consent was fully voluntary, without coercion or undue influence. EPA concludes that available information indicates that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Board Questions of Clarification—Ethics

There were no questions of clarification from the Board on the EPA Ethics Review.

Public Comments

Mr. Downing indicated that no requests had been received by EPA in advance of the meeting to provide public comment. Members of the public participating via teleconference were asked to provide comments. Hearing no response, Dr. Dawson invited Dr. Ramos to discuss the Board's response to EPA's scientific charge.

Board Discussion—Science

Dr. Ramos stated that the study was completed following the approved protocol. He agreed with the general conclusions offered by S.C. Johnson and EPA. He indicated, however, that the mosquito collection method detracted from the overall value of the study. The collected mosquitoes were not necessarily reflective of those landing on the treated subjects. Pooling the data resulted in a loss of any indication of potential bias.

Dr. Dawson asked for comments from the Board. Dr. Lawrence expressed concern about how the data on mosquito species were presented, which implied that they were collected from treated subjects, and noted that it was unclear whether mosquitoes were collected systematically from untreated controls across sites.

Dr. Lawrence noted that telling subjects what product was being used if they asked was a deviation from the protocol. She also commented that testing was performed differently at the different sites: Wisconsin testing used one species of laboratory-bred mosquitoes, and Florida testing took place in a field environment. Dr. Ramos clarified that the difference was true only for training, not testing.

Dr. Lawrence stated that she would have preferred if a power analysis had been performed to determine the appropriate number of subjects, particularly when some tests used fewer than 10 subjects. Dr. Ramos responded that a power analysis was performed for the tick repellent protocol, and eight subjects was determined to be sufficient for this field test with mosquitoes. Dr. Lawrence countered that the two studies involved different organisms and different conditions. When making public health recommendations, she stressed the importance of having the best data available; therefore, power calculations are necessary.

Dr. Gbur noted a discrepancy between the total number of mosquitoes in Tables 3 and 4 and in Tables 11, 12 and 13.

Dr. Dawson read the charge to the Board:

> Is the study sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?

Dr. Ramos responded that despite the weakness of the study identified, the answer to the charge question should be "yes." Dr. Dawson suggested that any concerns about the study be raised in the Board's final report, to which Dr. Ramos agreed.

Dr. Dawson invited Dr. Jun Zhu to provide her comments on the statistical analyses used in the study. Dr. Zhu indicated that the Board's concerns about experimental design had been adequately addressed. Regarding possible gender differences in CPT, the *p* value was very high, indicating no significant differences between genders. Mr. Sarkar added that the test for possible gender differences was done combining data from all products because of small sample sizes. Dr. Gbur stated that the Mann-Whitney U test could have been performed on data with sample sizes as small as 10. Dr. Zhu indicated that she would include this in her report.

Dr. Dawson asked for additional comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Ramos' proposed response to the charge question that the study was sufficiently sound to be used by EPA and that issues exist, but they are not significant. The Board members agreed unanimously with the proposed response.

Board Discussion—Ethics

Dr. Halanych provided her assessment that the available information support a determination that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L.

Dr. Dawson asked for comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Halanych's proposed response to the charge question. The Board members agreed unanimously with the proposed response.

Adjournment

Mr. Downing indicated that the meeting would reconvene on January 13, 2016, at 1:00 p.m. Eastern Standard Time. The meeting would begin with a discussion of the Board's responses to the science and ethics charge questions on the TCVP study. Dr. Dawson indicated that Dr. Maddalena and Dr. Rivera would send the text of the proposed responses to the Board members via email prior to the meeting.

Mr. Downing adjourned the meeting for the day at 5:49 p.m.

Tuesday, January 13, 2016

Convene Public Meeting

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

the Board members for their time and efforts preparing for the meeting, and on behalf of himself and the HSRB, thanked OPP colleagues for their efforts in preparing for the meeting.

Mr. Downing noted that in his role as DFO under 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 informed Board members that four interesting topics would be discussed during the second day of the meeting. He noted that agenda times are approximate, and although the material to be covered in the meeting will be extensive, 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 www.epa.gov/osa/human-studies-review-board.

Following EPA presentations, time will be allocated for the Board to ask questions of clarification. Time also has been allocated 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 www.epa.gov/osa/human-studies-review-board. The HSRB also will prepare a final report in response to questions posed by the Agency, which will include the Board's review and analysis of materials presented. The final report will be available at www.regulations.gov and on the HSRB website at www.epa.gov/osa/human-studies-review-board.

Introduction of Board Members

Mr. Downing conducted a roll call of the Board members and asked them to introduce themselves, providing their names, affiliations and areas of expertise. The Board members, all of whom also were present on the previous day, completed their introductions.

Opening Remarks

On behalf of EPA's program on human subjects research ethics and oversight, Dr. Toby Schonfeld welcomed the participants. She commented on the rich and robust discussion of the previous day and anticipated another fruitful discussion.

Assessing Intermittent Pesticide Exposure From Flea Control Collars Containing the Organophosphorus Insecticide TCVP (continued from January 12)

Board Discussion—Science (continued)

Dr. Maddalena proposed the following approach for the section on HSRB Detailed Recommendations and Rationale:

> The section on **HSRB Detailed Recommendations and Rationale** would reiterate the limitations of the study that we discussed during the meeting and recommend translating the mean glove residue data reported in Figures 1 and 2 of the paper to numerical values, combine results from the two studies, calculate "Fraction Available Residue" (Far) at each sampling time point (assuming 4.8 g active ingredient per treatment), then clearly justify the selection of the average Far over the lifetime of the collar (120 days) or the average over the period of maximum Far (values measured between 3 and 15 days).

In addition, Dr. Maddalena proposed the following response to the science charge question:

> The research is scientifically sound and, if used appropriately, the pet fur transferable residue data from the rubbing protocol can provide useful information for evaluating potential exposures of adults and children from contact with dogs treated with tetrachlorvinphos containing pet collars.

Dr. Dawson asked for comments from the Board. An editorial correction was made by a Board member that "Far" should be written "FAR." Mr. Dawson stated that the proposed response was well-written, but he observed that the language of the recommendations and rationale was very prescriptive for risk assessment purposes, going beyond the charge to the Board. He proposed instead that the Board consider discussing the limitations of the data, and then stating the following: "The Agency should consider these limitations when the information is used for risk assessment purposes." He noted that EPA had identified some of the same issues with the data, as had the Board. Dr. Maddalena expressed his concern that the transferable residue data might be used in inappropriate ways. Dr. Dawson added that the Board needed to explain why the question of whether the data can be used cannot be answered with a simple "yes" or "no." The Board needs to distinguish between what is scientifically optimal and what the Agency needs to make a regulatory decision that will be protective of human health.

Dr. Dawson asked for additional comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Maddalena's proposed response to the charge question that the study was sufficiently scientifically sound to be used appropriately by EPA. The limitations of the data would be discussed in the Board's report. The Board members agreed unanimously with the proposed response.

Board Discussion—Ethics (continued)

Dr. Rivera proposed the following response to the first ethics charge question requesting comment on EPA's determination that the samplers were not human subjects:

> Questions were raised by several committee members about the PI's and IRB's determinations that the samplers were not human subjects in the study; rather they were viewed as study staff. Some members of the board asserted that the student/technicians, by virtue of being potentially exposed to the pesticide as part of the conduct of the study, should have been considered human subjects. Furthermore,

> if they had been treated as subjects, they might have been considered "vulnerable" due to their status as students. It was noted that the insect repellant collars were commercially available at the time, and that the potential exposure to the pesticide residues through petting the dogs for 5 minute periods wearing cotton gloves was likely much less than average exposure of a pet owner. There is no information available about whether there was any "bleed through" of pesticide from cotton gloves to the skin of the samplers and therefore the actual exposure is unknown. Considering all of these factors, the committee felt that the risks of exposure were not greater than those experienced in everyday life. Thus, even if the determination regarding the status of the samplers as study staff rather than subjects was mistaken, the committee did not believe this resulted in any material harms and so this question should not prevent the EPA from using the pet fur transferable residue data derived from the study for making a decision to impose a more stringent regulatory restriction than could be justified without the data.

Dr. Dawson asked for comments from the Board. Dr. Maddalena asked whether data exist quantifying possible breakthrough with gloves. Mr. Dawson replied that no data exist from the Davis study, but data on breakthrough have been collected in other studies, such as analyzing rinses of the hands of exposed workers who wore gloves; typically, breakthrough is not significant. Dr. Dawson noted that if breakthrough was significant, dose-response relationships from such data would not be accurate.

Dr. Dawson asked for additional comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Rivera's proposed response to the first ethics charge question. The Board members agreed unanimously with the proposed response.

Dr. Rivera proposed the following response to the second ethics charge question asking whether the HSRB had any comments on the ethical conduct of the research:

> Committee members observed that the records from correspondence with EPA staff regarding the study suggest the consent form was amended to include disclosure to parents about the risks of pesticide exposure, although the final approved consent form was not provided. A question was raised about the decision made to provide incomplete assent to the minor subjects following parental permission. Study documents suggest this was an intentional choice ("We will not explain the connection to the pesticide residues on the dog…"), which was made, according to study documents, in order to avoid confounding the results by causing alterations in the children's behavior around their dogs. Board members noted that the amount and type of information provided to children in an assent process will vary depending on the age of the child; the children enrolled in the study were between the ages of 3 and 11 years old and therefore would have had varying levels of capacity to process the information about the study. It was noted that the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), which existed at the time of these studies, states that it's unlawful to use any pesticide in tests on humans unless they are fully informed of the nature and purposes of the test. Although some board members viewed the assent as incomplete in this case, because parents are presumed to have given fully-informed permission, and given that the insect repellant collars were commercially available at the time and already in use in the households recruited to the study, the committee felt that the risks of exposure were not greater than those experienced in everyday life. Thus, the committee did not believe this

resulted in any material harms and so this question should not prevent the EPA from using the pet fur transferable residue data derived from the study for making a decision to impose a more stringent regulatory restriction than could be justified without the data.

Dr. Dawson asked for comments from the Board. Ms. Lydon suggested that in the third sentence of the response, the Board be explicit about the study document to which it is referring (i.e., the draft minor's assent form). In addition, the response later states that the "assent appears to have been incomplete…" She suggested that the Board again be explicit that it is referring to the draft minor's assent form. Dr. Dawson agreed that the Board would determine to which form and assent it was referring and be explicit in its response.

Dr. Dawson asked for additional comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Rivera's proposed response to the second ethics charge question with the clarifications that were discussed. The Board members agreed unanimously with the proposed response.

Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic, GLP Study Number 873E1, C. Talbert, October 21, 2015. Test Substance: MARK-8 OFF! Deep Woods Insect Repellent V (OFF! Insect Repellent Formula, EPA Reg. No. 4822-167)

EPA Science Review Highlights

Dr. Bohnenblust presented EPA's science review of the MARK-8 study. The MARK-8 study, which tested an EPA-registered 25% DEET aerosol product, was conducted on August 10, 2015, in Wisconsin and August 25, 2015, in Florida with 10 treated subjects and two untreated subjects at each site. The target application rate was 1.0 g per 600 cm^2 plus or minus 10%.The mean application rate was 102 percent of the target, and the application rate ranged from 92 to 113 percent. The study was ended after 17 exposure periods at the Wisconsin site and at the discretion of the study director at the Florida site after 14 exposure periods.

Deviations from the protocol occurred in the studies. Under documented Deviation 4, in the Florida study, the test substance was applied at 113% of the target volume to subject 207, and the calculated volume was higher for subject 219 but actual application was less than target volume. S.C. Johnson responded that the test substance was applied at a higher than calculated volume; however, the test substance repelled mosquitos for a similar length of time on other subjects so this did not affect the study. Deviation 6 documented that, at both study sites, the first exposure period occurred 2 hours after treatment instead of 3 hours post treatment. S.C. Johnson responded that this did not affect the study results; it increased the amount of data collected. Deviation 3 documented that the 6^{th} and 7^{th} exposure periods in the Florida study were canceled because of heavy rain and lightning. S.C. Johnson responded that, if a first confirmed landing occurred in the next exposure period after the rain delay, then the time of failure would either be the first confirmed landing prior to the rain delay or the first delay exposure.

Kaplan-Meier survival analysis was used to calculate the median CPT, and CPTs for subjects who did not experience a first confirmed landing by the end of the study (two subjects in Florida and four in Wisconsin) were assumed to be the post-treatment duration of the study at the given site. The results of the study were that landing pressures were sufficient during all exposure periods at the Florida and Wisconsin sites. At both the Wisconsin and Florida sites, five landings occurred on all untreated control subjects during all exposure periods. One untreated subject withdrew after the fifth exposure period and

was not replaced. The time to five landings ranged from 11 seconds to 3 minutes during all exposure periods across both sites.

In Wisconsin, 118 mosquitoes were collected, and the Aedes genus predominated (four species total). In Florida, 178 mosquitoes were collected, and Aedes also predominated, but more species were detected (seven total). The median CPT was 8.25 for the Wisconsin site (range 6.0–10.0) and 8.0 for the Florida site (range 3.5–8.5), yielding a median CPT for the graphic of 8 hours.

EPA concluded that the methods used in this study were adequate to produce scientifically reliable results. The methods were based on the protocol reviewed and accepted by the EPA and HSRB on April 23, 2015 as amended to incorporate EPA and HSRB recommendations before testing began. The data in the study are acceptable to support a median CPT of 8.0 hours against mosquitoes for the EPA Repellency Awareness Graphic on the label for MARK-8 product.

Board Questions of Clarification—Science

Dr. Ramos asked Dr. Bohnenblust to restate how the first confirmed landing was determined in the case of rain delay, which he did. In the event of a rain delay, if a confirmed land occurred in the exposure period immediately following a rain delay, the first confirmed landing was determined to be the exposure period when the rain delay began. Dr. Gbur stated that the method by which the CPT was assigned to individuals after a rain delay was confusing. He noted that all three subjects who had landings immediately after the rain delay ended received a CPT of 4.5 hours (i.e., the rain delay time period).

Dr. Ramos asked whether S.C. Johnson had commented on the median CPT from the MARK-8 study as opposed to the CPTs for other repellent products. Dr. Bohnenblust responded that S.C. Johnson had not provided any additional information about the differences.

Dr. Ramos asked if a subject withdrew from the study, whether it was handled the same way as in other studies. Dr. Bohnenblust replied that withdrawals were handled the same in all studies.

Dr. Dawson suggested that the lower end of the confidence interval might be more meaningful than the median in determining the CPT for the graphic, noting the large difference between 3.5 and 8 hours. This difference might provide information about how the type of mosquito affected the CPT. A Board member noted that in addition to differences by mosquito species, individuals might differ in their attractiveness to mosquitoes. Dr. Bohnenblust responded that the value of 3.5 hours might be an outlier, and the median was used rather than the mean to reduce the effects of outliers. He added that the graphic is meant to be used qualitatively for comparative purposes rather than as a guarantee of protection.

EPA Ethics Review Highlights

Ms. Lydon presented the results of EPA's ethics assessment specific to the MARK-8 study. For the MARK-8 study, 57 subjects were enrolled, 20 of whom did not show up for training; 24 subjects were assigned to participate in the test with 12 alternates/extras. Twenty-three subjects completed the testing. Two subjects withdrew, 1 on the training day and 1 on the test day. In Wisconsin, one control subject withdrew after the fifth exposure interval (4.5 hours post-exposure) "feeling ill". The subject contacted the study director after the test day regarding other testing. When the study director asked about the illness, that subject informed the study director of the nature of the illness, which was unrelated to the testing. S.C. Johnson adhered to the protocol with regard to the subject who felt ill, but in future draft protocols, EPA will ensure that the protocol states that if a subject feels ill and withdraws, the study sponsor will contact the subject the next day to determine his or her health status.

No amendments were made to the protocol, but six deviations were documented. EPA identified follow-up actions associated with three of the deviations (#1, 4 and 6). Deviation 1 involved a male subject who was referred to the study director by another test subject rather than being contacted in the initial screening. The male recruit was treated the same as if he were recruited via by the recruitment agency. The subject was interviewed, and completed the consent form and required pre-test training. The late addition of the male subject allowed for the appropriate number of male to female test subjects. However, in future protocols, EPA will address the possibility of referral by other test subjects in the recruitment process. Deviation 4 involved incorrect entry of raw data on arm measurements into the dose calculation spreadsheet for two subjects. For 2 subjects (207 and 219) SCJ measured their arms for the test as discussed in the protocol. However, the measured value from the original raw data sheet was not accurately entered into the calculation spread sheet used to identify the target dose. For example, see language below from Deviation 4 explanation: "Subject 207: The measurement for the upper left arm is 28.5 cm, and subsequent calculated dose was 0.83g. The measured value from original raw data sheet looks like 23.5 cm and not 28.5. Using this value (23.5) in the dose calculation, the target dose amount would have calculated out to be 0.78g." OPP scientists indicated that the incorrect dose would not have affected the health and safety of the subjects. However, EPA will follow-up with the study sponsor to reiterate the importance of ensuring that correct arm measurements are clearly and accurately documented in future studies so that correct doses are calculated and administered to subjects. EPA will ask the study sponsor to identify safeguards that can be put in place to address this.

Regarding Deviation 6, "Section 10.6.6 called for the first exposure to be 3 hours post treatment for DEET formulas with an active ingredient amount of 16.0% and above. There was only a 2 hour post treatment delay before the first exposure for this study." Subsequent to their study submittal to EPA, S.C. Johnson corrected their write-up on "impact on the study/results" to read: "There was no negative impact on the results of the study by having two extra data collections added to the start of the exposures." The subjects were exposed to mosquitos during two extra data collections. This did not negatively affect the subjects' health or safety, but for future studies, EPA will request that the sponsor ensure adherence to the appropriate start times for first exposures consistent with the protocol.

S.C. Johnson adhered to IRB instructions and protocol in documenting the deviations, and the deviations did not negatively affect subjects' rights, health or safety. Although two subjects withdrew, one because of illness, the illness was not linked to the study. In summary, there were no adverse events or incidents of concern reported during or after test implementation.

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

EPA finds that the study was in compliance with the acceptance standards. All subjects were at least 18, and pregnant and nursing women were excluded; no significant deficiencies in ethical conduct of the research existed; deviations did not compromise the health and safety, consent or rights of subjects; and subjects were fully informed, and their consent was fully voluntary, without coercion or undue influence. EPA concludes that available information indicates that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Board Questions of Clarification—Ethics

There were no questions of clarification from the Board on the EPA Ethics Review.

Public Comments

Mr. Downing indicated that no requests had been received by EPA in advance of the meeting to provide public comment. Members of the public participating via teleconference were asked to provide comments. Hearing no response, Dr. Dawson invited Dr. Ramos to discuss the Board's response to EPA's scientific charge.

Board Discussion—Science

Dr. Ramos noted that the variance between sites was striking. Because the Board does not have access to all of the raw data, interpreting the variance is not feasible. He asked why the variance in CPT was so different from other studies and whether the formulation of the product could affect the variance. Ms. Palm responded that many factors—including location, species and subjects—can determine the duration of the CPT. These factors might affect the range and median. Mr. Sweeney added that the species composition of the mosquito population can vary by location, which is why two sites were studied, and the Florida mosquitoes might have been more aggressive. Dr. Lawrence stated that another significant difference was the rain delay that occurred at the Florida site, which might have changed environmental conditions (e.g., humidity, temperature) that might affect mosquito behavior and factors that might affect how the repellent acts on the skin (e.g., sweating, skin temperature). Dr. Ramos noted that in this study, variance also was greater in the number of mosquitoes collected. Dr. Lawrence responded that the number of subjects was small, which made the effects of odd events more obvious, and one of the untreated controls withdrew, which left fewer data for comparative purposes. Dr. Gbur stated that terminating three subjects after the rain delay would not have affected the median, but it did affect the confidence limits and therefore the perception of variability. There is no way determine whether the variability is real because of the rain delay. The median for the Florida data was only 0.5 hour less than the upper limit, indicating that the data were skewed, whereas the median was closer to the middle of the range of the Wisconsin data. Dr. Gbur expressed doubt about the appropriateness of the approach taken to assign CPTs after the rain delay but noted that the median was not affected. Mr. Sarkar acknowledged that the rain delay could have affected the variability of the data.

Dr. Ramos stated that if the study did not have sufficient power, the predictive value of the median is decreased. Dr. Lawrence had raised questions about relying on the power calculations of the tick study. Dr. Lawrence recognized the value of the graphic and conducting studies with comparable data but emphasized the need to consider the organism and the effects of conducting field versus laboratory studies when deciding whether to conduct power calculations. She noted that power calculations are recommended in EPA's guidelines.

Dr. Dawson invited Dr. Gbur to provide his comments on the statistical analyses used in the study. Dr. Gbur stated that S.C. Johnson had responded to most of the design and analysis issues raised. He commented, however, that S.C. Johnson had collected a large amount of environmental and demographic data but not analyzed them.

Dr. Gbur questioned the rationale behind choosing a sample size of 10.

Dr. Gbur also discussed the approach taken to determine the median CPT. The smaller of the medians from the two sites was chosen for the graphic, and in this study, the medians were not very different. This approach is adequate if EPA's objective is a single estimate of a median CPT, but it does not indicate variability.

The Board discussed whether supplementary data on variability should be provided to consumers in the graphic and by what mechanisms. Dr. Dawson noted that the Board's charge was to respond on the adequacy of the data from the study to support the median CPT for the repellency graphic. In future studies, the Agency might opt for a different approach and seek to generate information that might be useful to the consumer, such as the effects of environmental conditions and species. The label might contain a qualification that different species and different weather conditions might result in different protection times. Dr. Zhu raised concern about objectivity in assessing variance and asked what criteria the Board might use to determine that the confidence interval was too wide. Dr. Gbur stated that some of the information collected by S.C. Johnson might affect how consumers would use the product.

Dr. Ramos read the science charge question into the record:

> Is the study sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?

He stated that his view was that the Board's answer to the charge should be "yes." The strengths and limitations of the study should be highlighted in the Board's report to guide future decision making.

Dr. Dawson asked for additional comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Ramos' proposed response to the science charge question. The Board members agreed unanimously with the proposed response.

Board Discussion—Ethics

Dr. Rivera provided her assessment that the available information support a determination that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L. To the best of her understanding, the researchers obtained approval from an IRB, materials related to that approval were submitted to EPA, no children were included in the study, and precautions were taken to exclude pregnant and nursing women. Therefore, Dr. Rivera proposed that the Board respond to the charge that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L. In addition, she proposed that the Board state that if the scientific reviewers were satisfied with the study's design, the report about the conduct of the study suggest that the data are appropriate to be used to estimate the duration of protection.

Dr. Dawson asked for comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Rivera's proposed response to the ethics charge question. The Board members agreed unanimously with the proposed response.

Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic, GLP Study Number 866E1, E. Laznicka, October 21, 2015. Test Substance: MARK-4 OFF! Active Insect Repellent I (Unscented OFF! Insect Repellent, EPA Reg. No. 4822-380)

EPA Science Review Highlights

Mr. Sweeney presented EPA's review of the science of the MARK-4 study. The MARK-4 study, which tested an EPA-registered 15% DEET aerosol product, was conducted on August 5, 2015, in Wisconsin and September 22, 2015, in Florida. The target application rate was 1.0 g per 600 cm^2 plus or minus 10%. The mean application rate was 102 percent of the target and the application rate ranged from

95 to 114 percent. One subject received 114 percent of the target amount but no protocol deviation was reported. S.C. Johnson should report this to the SAIRB consistent with their reporting procedures. Landing pressures were sufficient during all exposure periods at the Florida and Wisconsin sites. Five mosquitoes landed on an untreated control subject in less than one minute in five out of six exposure periods. Time to five mosquito landings ranged from 21 seconds to nearly 2 minutes across both untreated control subjects through eight exposure periods. At the Wisconsin site, there were 10 subjects (five males and five females), two untreated control subjects (one male and one female), and two alternates (one male and one female), and no protocol deviations were reported. At the Florida site, there were eight treated subjects (two males and six females), two untreated control subjects (one male and one female), and no alternates. The fourth exposure period in the Florida study was canceled because of rain, and the fifth was started early because of incoming weather. The results showed that eight of 10 subjects at the Wisconsin site reported a first confirmed landing through 10 hours post-treatment. The study director stopped the study at 10 hours with two subjects remaining. One received a landing at 10 hours while the other did not.

In the Florida study, protocol deviation 3 reported missed exposure period #4 due to rain and that exposure period #5 began 5 minutes early due to oncoming weather. Two landings occurred in exposure period 3. Subject #333 received an unconfirmed landing and continued in the study. Subject #334 received a first confirmed landing (FCL) and was removed from the study. In exposure period 5, a FCL was received by one subject (#329) and an unconfirmed landing by another subject (#321). Subject #333 did not receive a FCL in exposure period 5 and continued in the study through exposure period 7. Protocol deviation 3 discussed corrective actions; for the subjects receiving the FCL and landing in exposure period 5, respectively, the CPT was determined to be exposure period 3, which was 3.5 hours post-treatment. Subject #329 was removed from the study but Subject #321 remained in the study until a FCL occurred at 5.0 hours post-treatment. However, a CPT of 3.5 hours was the value reported.

With regard to results, seven of eight subjects reported a first confirmed landing through 5.5 hours post-treatment. The Study Director stopped the study at 5.5 hours post-treatment because only one subject remained without a first confirmed landing. All subjects completed the study.

Kaplan-Meier survival analysis was used to calculate the median CPT, and the CPTs for subjects who did not experience a first confirmed landing by the end of the study (3 subjects) were conservatively assumed to be the post-treatment duration of the study at the given site. The median CPT was 7.5 for the Wisconsin site (range 4.0–10.0) and 5.0 for the Florida site (range 2.5–5.5).The study was acceptable, and the data support a median CPT for the graphic of 5 hours.

Board Questions of Clarification—Science

There were no questions of clarification from the Board on the EPA Science Review.

EPA Ethics Review Highlights

Ms. Lydon presented the results of EPA's ethics assessment specific to the MARK-4 study. For the MARK-4 study, 41 subjects enrolled, 14 of whom did not show up; 22 subjects were assigned to participate in the tests with seven alternates/extras at the Wisconsin site. Twenty-two subjects completed the testing and no one withdrew.

One incident of concern was reported. Within 2 weeks following the Wisconsin test date of August 5, 2015, there were two cases of birds that tested positive for West Nile virus. The birds were collected in Kenosha County, WI on August 14, 2015 and August 17, 2015 at two locations at least 10

miles away from the Wisconsin test location. The Wisconsin State Health Department released the positive test results for West Nile virus on August 24, 2015. Before the testing of the MARK-4 product and for two weeks following the last test date, the study investigators had been monitoring the detection of mosquito-borne diseases via the Wisconsin State Health Department website, which typically is updated weekly. After obtaining the information on the two birds, the Study Investigators began the process to contact test participants that West Nile virus had been detected in the test area within two weeks following the test date(s). Consistent with the protocol, an IRB-approved notification letter was sent to the test subjects with return receipt requested and included post cards for the subjects to send back to confirm receipt. (The draft letter was included in Attachment 4 to EPA's ethics review memo.) The letter informed the test subjects about the diseased birds; described virus symptoms (provided by the Centers of Disease Control and Prevention) and when they might appear; asked subjects to contact S.C. Johnson if the subjects experienced virus symptoms and provided a phone number; and noted that if they experienced symptoms, subjects might seek medical care, the costs of which S.C. Johnson would reimburse. S.C. Johnson confirmed that all subjects received their notification letters. As of December 2015, S.C. Johnson had not been contacted by any subject experiencing symptoms. Regarding reporting of incidents, S.C. Johnson followed the protocol in informing subjects and provided all information required by protocol. EPA recommended that in future draft protocols for repellent studies, EPA should ensure that the protocol is clear with regard to what it means to "monitor" test participants if any mosquito borne disease cases are reported in the test area within two weeks following the test date.

EPA also took the initiative to recommend that, in future protocols and consent forms, language be included specifying that the study sponsor will cover the costs of medical care resulting from a subject's participation in the study rather than reimburse the subject for medical costs.

One amendment to the protocol was a change in study director (due to a 10 week sabbatical), and four deviations were documented. EPA identified follow-up actions associated with one of the deviations. Deviation 3 noted that the fourth exposure period was cancelled due to heavy rain and the fifth exposure began 5 minutes early due to oncoming weather. As described on page 23 of the study, "the protocol did not address how to determine repellent break down point in the event of rain delay, so conservative logic was developed and used for all MARK studies where a rain delay occurred. If a land occurred during an exposure period immediately following a rain delay, the break down period was determined to be (the) period when the rain delay began."

As follow-up, EPA will ensure that future draft protocols for repellent studies address how to determine repellent breakdown points in the event of a rain delay, and the protocol will discuss cover for the subjects in the event of a rain delay. S.C. Johnson adhered to IRB instructions and the protocol in documenting the amendment and deviations; the deviations did not negatively affect subjects' rights, health or safety.

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

EPA finds that the study was in compliance with the acceptance standards. All subjects were at least 18, and pregnant and nursing women were excluded; no significant deficiencies in ethical conduct of the research existed; deviations did not compromise the health and safety, consent or rights of subjects; and subjects were fully informed, and their consent was fully voluntary, without coercion or undue

influence. EPA concludes that available information indicates that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Board Questions of Clarification—Ethics

There were no questions of clarification from the Board on the EPA Ethics Review.

Public Comments

Mr. Downing indicated that no requests had been received by EPA in advance of the meeting to provide public comment. Members of the public participating via teleconference were asked to provide comments. Hearing no response, Dr. Dawson invited Dr. Maddalena to discuss the Board's response to EPA's scientific charge.

Board Discussion—Science

Dr. Maddalena asked why there was no mention of the EPA repellency graphic in the science charge question. Mr. Downing responded that all of the science charge questions for the five studies of field testing of S.C. Johnson personal mosquito repellent products to support their use of the EPA Repellency Awareness Graphic should be the same.

Dr. Maddalena asked two questions about the application rate of the aerosol spray: (1) how could the researchers be sure that overspray was not significant? (2) If treatment involves spreading the spray onto the arm, how sure are the researchers that product was not lost to the gloved hand that spread the spray? Ms. Palm responded that, regarding the first question, the researchers sprayed close to the skin to minimize overspray. Regarding the second question, the researchers used only two fingers to spread the product evenly, which was important to the test, and this was done for all products. Dr. Maddalena noted that if product had been lost to the two fingers, the error would have been on the side of a conservative estimate of the median CPT.

Dr. Maddalena expressed concern about deviations of the study. At the Florida site, the treated subject sample size was small and not gender-balanced. Also at the Florida site, the rain delay might have affected the median CPT.

Dr. Gbur provided his comments on the statistical analyses used in the study. He observed that many of his comments were the same as those for the MARK-8 study. S.C. Johnson had collected a large amount of environmental and demographic data but had not analyzed them. He also commented on the sample size, rain delay, use of the lower median of the two sites instead of a combined data analysis for both sites to determine the median, and possible differences in median CPT between male and female subjects that might have been detected if the statistical test had been performed individually on the data for each product. Dr. Gbur had analyzed the Wisconsin data for the MARK-4 study gender differences by the Mann-Whitney U test, and he had found a significant difference in the CPTs of male and female subjects. He also noted that the Florida and Wisconsin median CPTs were very different, with the Florida CPT being much shorter. It is possible that the large site-to-site difference in this product's CPTs was attributable to the lower DEET content. The difference between the sites raises the issue that the median CPT in the graphic might be too high for some locations in the United States. EPA might consider a different approach in the future to ensure that the public understands possible variability in protection. For its intended use, however, the data from the study is adequate.

Dr. Dawson asked for comments from the Board. Dr. Dawson asked Dr. Gbur about the applicability of the Mann-Whitney U test to small sample sizes. He stated that his statistical tables stopped at three; therefore, he was unable to perform the test on the Florida data, which had only two males, but was able to perform it on the Wisconsin data. Mr. Sarkar asked for more information about the tables that Dr. Gbur had used, and Dr. Gbur indicated that he would send him a reference for the statistical reference books and tables that he had consulted. Dr. Dawson asked for clarification from Dr. Gbur about his concerns about possible site-to-site and gender variation in the median CPT. Dr. Gbur explained that for some populations and some areas of the country, the median CPT determined in the study might be too large or too small.

Dr. Maddalena suggested that the Board recommend a threshold for the difference between two sites that would trigger testing at a third site. Dr. Gbur stated that this could be a recommendation for future studies, but the study was robust enough to determine the complete protection against mosquitoes provided for the tested repellent.

Dr. Dawson proposed that in future studies, a multivariate analysis could be performed on variables that might affect protection times. The results of the analysis could inform the selection of sites to provide the most information. Dr. Gbur was concerned that sample size might not be sufficient for a predictive model. He proposed looking for trends retrospectively in the data for such factors as gender, temperature and wind speed.

Dr. Maddalena stated that his recommendation was that the Board respond in the affirmative to the science charge question if a reference is included to the EPA Repellency Awareness Graphic. Dr. Maddalena read the science charge question into the record:

> Is the study sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?

He suggested adding "in support of the EPA Repellency Awareness Graphic." Dr. Dawson proposed that the Board highlight in its report the issues cited above that are applicable to the five studies. Dr. Ramos emphasized that the Board's response should be consistent across the five studies.

Dr. Dawson asked for additional comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Maddalena's proposed response to the science charge question, which included a reference to the EPA Repellency Awareness Graphic. The Board members agreed unanimously with the proposed response.

Board Discussion—Ethics

Dr. Kyle Galbraith stated that based on the information provided, the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L. The protocol was reviewed and approved by an IRB. The letter that was sent to subjects about the bird cases of West Nile virus was reviewed by the IRB. Minors and pregnant and nursing women were excluded.

Dr. Dawson asked for comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Galbraith's proposed response to the ethics charge question. The Board members agreed unanimously with the proposed response.

Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic, GLP Study Number 864E1, J. Palm, September 24, 2015. Test Substance: MARK-2 OFF! Deep Woods Sportsmen Insect Repellent II (UNSCENTED DEEP WOODS OFF! EPA Reg. No. 4822-397)

EPA Science Review Highlights

Mr. Sweeney presented EPA's review of the science of the MARK-2 study. The MARK-2 study, which tested an EPA-registered 30% DEET aerosol product, was conducted on August 3, 2015, in Wisconsin and August 18–19, 2015, in Florida. The target application rate was 1.0 g per 600 cm2 plus or minus 10%. The mean application rate was 100 percent of the target amount and the application rate ranged from 94 to 111 percent. One subject received 111 percent of the target amount and no protocol deviation was reported. S.C. Johnson should report this deviation consistent with SAIRB reporting procedures.

Landing pressures were sufficient during all exposure periods at the Florida and Wisconsin sites. At the Wisconsin site, there were 10 subjects (five males and five females), two untreated control subjects (one male and one female), and five alternates (one male and four females). At the Florida site on August 18, there were only five treated subjects (one male and four females); one untreated control (male), who was paired with a treated subject; and no alternates. At the Florida site on August 19, there were only five treated subjects (two males and three females); one untreated control (female), who was paired with a treated subject; and one alternate (the untreated male from August 18).

In Wisconsin, in five of the six exposure periods, five mosquito landings were recorded by the untreated control subjects in one minute or less. The time to five mosquito landings ranged from 12 seconds to 2½ minutes across both untreated control subjects through 16 exposure periods. In Florida, on August 18th, five mosquito landings occurred on an untreated control subject in less than one minute in 10 of the exposure periods; in greater than one minute but less than two minutes in six exposure periods; and at 3½ minutes in the last exposure period. On August 19th, five mosquito landings occurred in less than one minute in 14 of 15 exposure periods. In Wisconsin, protocol deviation #1 described changes to the number and sex ratio of alternates.

In Florida, protocol deviations 2, 3, 4, 5, and 6 were reported. Protocol deviation 6 reported that the study started at two hours post-treatment instead of at three hours post-treatment. Protocol deviations 2, 3, and 4 addressed changes to number, sex ratio, and alternate subjects. Protocol deviation 5 reported missed exposure period #5 due to rain on August 18th. There were no landings in either exposure periods 4 or 6. This did not have an impact on the study outcome.

Nine of 10 subjects at the Wisconsin site reported a first confirmed landing through 9.5 hours post-treatment. The study director stopped the study at 9.5 hours because only one subject remained without a first confirmed landing (FCL). All subjects completed the study. Four out of five subjects at the Florida site on August 18 reported a first confirmed landing through 10 hours post-treatment. The study director stopped the study at 10 hours because only one subject remained without a FCL. On August 19, four of five subjects at the Florida site reported a first confirmed landing through 9 hours post-treatment. One subject withdrew at 8.5 hours, and his CPT was recorded as 8.5 hours (censored). The study director stopped the study at 9 hours post-treatment because all subjects had reported a first confirmed landing (FCL).

Kaplan-Meier survival analysis was used to calculate the median CPT, and CPTs for subjects who did not experience a first confirmed landing by the end of the study (2 subjects) were conservatively

assumed to be the post-treatment duration of the study at the given site. The median CPT was 7.5 for the Wisconsin site (range 4.0–9.5) and 8.5 for the Florida site (range 4.5–10). The study was acceptable, and the data support a median CPT for the Repellency Awareness Graphic of 7.0 hours.

Board Questions of Clarification—Science

Because the exposure started 1 hour earlier than specified in the protocol, Dr. Chadwick asked whether the CPT included the earlier start time. Mr. Sweeney replied that it did.

Dr. Dawson asked whether the 111 percent dose applied to one subject had been reported to the IRB. She also noted that many deviations typically occur in studies, and she asked whether the basis for EPA's statement that this deviation should have been reported was a result of procedural requirements of the IRB or regulatory requirements, such as those of the Office for Human Research Protection, which requires reporting only those deviations that might put subjects or others at an increased risk of harm than was previously known or recognized. Dr. Chadwick noted that the International Council for Harmonization also has reporting guidelines. Mr. Sweeney responded that per the protocol, the dose was supposed to have been 1g/600 cm^2 ± 10%. The deviation from the protocol in dosing outside of those limits should have been reported to the IRB. Ms. Lydon added that the SAIRB has specific reporting procedures, and EPA had based its statement that S.C. Johnson should have reported the deviation on the SAIRB's reporting procedures.

EPA Ethics Review Highlights

Ms. Lydon presented the results of EPA's ethics assessment specific to the MARK-2 study. For the MARK-2 study, 54 subjects were enrolled, 20 of whom did not show up; 24 subjects were assigned to participate in the test with nine alternates/extras; and 23 subjects completed the testing.

No amendments were made to the protocol, and seven deviations were documented. EPA identified follow-up actions associated with deviations #2 and #6. The study documents deviation 2 in Florida, which includes the following information in part. In Florida, on the training date of August 17, 2015, only 5 of 11 males and 8 of 19 females showed up for their scheduled training. One male withdrew before training was complete. As a result, 12 subjects, 4 males and 8 females, were available as test subjects. The study director asked one male (who was untreated control on August 18th) to come to test session on August 19th as an alternate. It's understandable why study director asked untreated control if he could attend next test session as alternate. In future draft protocols for repellent studies, EPA should propose the inclusion of alternative recruitment approaches, as feasible, to plan for situations where subjects don't show up or withdraw unexpectedly.

As SC Johnson documented in the study, the protocol states that for DEET formulas with active ingredient amounts of 16.0% and above, the first exposure to the test system will be delayed to 3 hours post treatment. In this study, as documented in deviation 6, there was a two hour delay to the first exposure to the test system. This was an oversight of the study director. The subjects were exposed to mosquitoes during two extra data collections. This did not negatively impact the subjects' health or safety. However, for future studies, EPA will request that the study sponsor ensure adherence to the appropriate start time for first exposures consistent with the protocol.

Regarding the references in the raw notes, per section 13.5.6 of the completed study, any inadvertent contact of the treated skin reported by test subjects was appropriately documented in the raw data. This is consistent with protocol. As a result, the raw data refers to "minor rubs" and "abrasions." S.C. Johnson confirmed that these terms do not refer to any irritations or injuries. They refer to a treated

limb coming in contact with a foreign object which has the potential to transfer repellent off the treated limb.

S.C. Johnson adhered to IRB instructions and protocol in documenting the deviations, and the deviations did not negatively affect subjects' rights, health or safety. There were no adverse events or incidents of concern reported during or after test implementation.

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

EPA finds that the study was in compliance with the acceptance standards. All subjects were at least 18, and pregnant and nursing women were excluded; no significant deficiencies in ethical conduct of the research existed; deviations did not compromise the health and safety, consent or rights of subjects; and subjects were fully informed, and their consent was fully voluntary, without coercion or undue influence. EPA concludes that available information indicates that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Board Questions of Clarification—Ethics

There were no questions of clarification from the Board on the EPA Ethics Review.

Public Comments

Mr. Downing indicated that no requests had been received by EPA in advance of the meeting to provide public comment. Members of the public participating via teleconference were asked to provide comments. Hearing no response, Dr. Dawson invited Dr. Ramos to discuss the Board's response to EPA's scientific charge.

Board Discussion—Science

Dr. Ramos stated that all deviations associated with the protocol had been discussed. The study had the same general strengths and weaknesses as the other S.C. Johnson studies. Two differences were that: (1) it had been necessary to pair the untreated subject with a treated subject; and (2) at the Florida site, testing had taken place over a 2-day period. He asked for details on how mosquito collection occurred for the untreated-treated pair. Ms. Palm of S.C. Johnson recognized that pairing the untreated and treated subject was not ideal, but the decision to do so had been based on test subject availability. The untreated subject had maintained the required number of landings despite being paired with a treated subject. The untreated and treated pair monitored each other for landings, but the aspiration was performed by the subjects themselves. Regarding splitting the testing across 2 days, the Mann-Whitney U test was used to compare the data collected on each day, and no significant difference in the median CPT was found. Dr. Gbur asked whether the Mann-Whitney U test had been conducted for gender and other confounding factors for all of the individual studies. Ms. Palm responded that a statistical comparison only was performed on the data for the Florida site for the MARK-2 study because of the 2-day split.

Dr. Ramos stated that his view was that the Board's answer to the science charge question—which was the same as for the MARK-3, MARK-8 and MARK-4 studies—should be affirmative, noting the strengths and weaknesses inherent in the protocol design.

Dr. Dawson asked for additional comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Ramos' proposed response to the science charge question. The Board members agreed unanimously with the proposed response.

Board Discussion—Ethics

Dr. Halanych read the ethics charge question into the record: "Does the available information support a determination that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L?"

She stated her view that the answer is affirmative because the study used an established IRB that reviewed all important information; risks to subjects were minimized; researchers equitably selected subjects, sought and appropriately documented informed consent, made adequate provisions to ensure the safety of subjects, and protected the privacy and confidentiality of the data; and no children or pregnant or nursing women were involved.

Dr. Dawson asked for comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Halanych's proposed response to the charge question. The Board members agreed unanimously with the proposed response.

Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic, GLP Study Number 867E1, E. Laznicka, October 21, 2015. Test Substance: MARK-5 OFF! Family Care Insect Repellent IV (Unscented) (UNSCENTED OFF! SKINTASTIC SPRAY INSECT REPELLENT, EPA Reg. No. 4822-395)

EPA Science Review Highlights

Mr. Sweeney presented EPA's science review of the MARK-5 study. The MARK-5 study, which tested an EPA-registered 7% DEET pump spray, was conducted on July 28, 2015, in Wisconsin and September 29, 2015, in Florida. The target application rate was 0.5 g per 600 cm^2 plus or minus 10%. The mean application rate was reported as 100 percent of the target but calculated as 101.75 or 102 percent. The application rate ranged from 100 to 109 percent of the target amount.

With regard to mosquito landings on control subjects, at the Wisconsin site, the study did not record the untreated control landing pressure in the first exposure period; this was protocol deviation # 4. In Wisconsin, five mosquito landings were recorded in less than one minute on three of the five subsequent exposure periods. The time to five mosquito landings ranged from 35 seconds to 3¼ minutes across both control subjects through the five exposure periods.

With regard to mosquito landings on control subjects at the Florida site, five mosquitoes landed on an untreated control subject in less than one minute in five out of seven exposure periods. The time to five mosquito landings ranged from 30 seconds to 2½ minutes across both untreated control subjects through seven exposure periods.

At the Wisconsin site, there were 10 subjects (five males and five females) and two untreated control subjects (one male and one female). In Wisconsin, there were four female alternates and 0 male alternates. This was protocol deviation #1, which had no impact on the study outcome. All subjects at the Wisconsin site reported a first confirmed landing through 2.5 hours post-treatment. All subjects completed the study.

At the Florida site, there were 10 treated subjects (five males and five females) and two untreated control subjects (one male and one female). There was one male alternate and no female alternates, which constituted protocol deviation #1, which had no impact on the study outcome. Eight of 10 subjects at the Florida site reported a first confirmed landing through 3.0 hours post-treatment. The Study Director stopped the study at 3.0 hours post-treatment. All subjects completed the study.

Kaplan-Meier survival analysis was used to calculate the median CPT, and CPTs for subjects who did not experience a first confirmed landing by the end of the study (2 subjects) were assumed to be the post-treatment duration of the study at the given site. The median CPT was 2.0 for the Wisconsin site (range 1.5–2.5) and 2.5 for the Florida site (range 1.0–3.5). The study was acceptable, and the data support a median CPT for the Repellency Awareness Graphic of 2.0 hours.

Board Questions of Clarification—Science

There were no questions of clarification from the Board on the EPA Science Review.

EPA Ethics Review Highlights

Ms. Lydon presented the results of EPA's ethics assessment specific to the MARK-5 study. For the MARK-5 study, 44 subjects were enrolled, 10 of whom did not show up; 24 subjects were assigned to participate in the test with 12 alternates/extras; and 24 subjects completed the testing.

One amendment to the protocol was a change in study director (due to the original director taking a 10-week sabbatical), and four deviations were documented. The deviations did not raise any ethical concerns or deficiencies. S.C. Johnson adhered to IRB instructions and the protocol in documenting the amendment and deviations, and the deviations did not negatively impact subjects' rights, health or safety.

Regarding reporting of incidents, no subjects withdrew from the study, and there were no adverse events or incidents of concern reported during or after test implementation.

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

EPA finds that the study was in compliance with the acceptance standards. All subjects were at least 18, and pregnant and nursing women were excluded; no significant deficiencies in ethical conduct of the research existed; deviations did not compromise the health and safety, consent or rights of subjects; and subjects were fully informed, and their consent was fully voluntary, without coercion or undue influence. EPA concludes that available information indicates that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Board Questions of Clarification—Ethics

There were no questions of clarification from the Board on the EPA Ethics Review.

Public Comments

Mr. Downing indicated that no requests had been received by EPA in advance of the meeting to provide public comment. Members of the public participating via teleconference were asked to provide

comments. Hearing no response, Dr. Dawson invited Dr. Maddalena to discuss the Board's response to EPA's scientific charge.

Board Discussion—Science

Dr. Maddalena indicated that the same issues existed with the study as had been raised earlier for the other S.C. Johnson studies. He stated that the study was sufficiently sound, from a scientific perspective, to be used for the EPA Repellency Awareness Graphic.

Dr. Dawson invited Dr. Gbur to provide his comments on the statistical analyses used in the study. Dr. Gbur stated that Dr. Fernandez' comments on the statistics were the same as for the other S.C. Johnson studies. At Dr. Dawson's request, he offered a summary of those comments. The first point was that the median CPT as calculated using Kaplan-Meier survival analysis in SAS involved a generalization. Dr. Fernandez's second point was that the study design was adequate for the proposed goals, but the analysis could have been further enhanced by performing a stratified analysis by site and other factors. Dr. Dawson restated the second point that the current analysis was adequate for the EPA Repellency Awareness Graphic, but more information could have been gathered from the data with a more robust analysis.

Dr. Dawson asked for additional comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Maddalena's proposed response to the science charge question. The Board members agreed unanimously with the proposed response.

Board Discussion—Ethics

Dr. Chadwick discussed the Board's response to EPA's ethics charge. He stated that the researchers attended to everything that needed to be considered. The subjects were adults and not nursing or pregnant. Reasonable protections were provided for coercion, as well as subject welfare and safety. He concluded that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L, and can be used by EPA.

Dr. Dawson asked for comments from the Board. Hearing none, Dr. Dawson asked the Board to vote on Dr. Chadwick's proposed response to the ethics charge question. The Board members agreed unanimously with the proposed response.

General Scientific Issues Applicable to Future Mosquito Repellency Studies

Dr. Dawson suggested that the Board members use the remaining time to discuss general scientific issues that might be applicable to future studies.

Dr. Maddalena stated that if the most important measure was the median CPT, he recommended that studies be terminated after a CPT is determined for the sixth treated subject. This approach would balance the need to determine an outcome from the study with risks to subjects. Dr. Gbur disagreed with terminating studies early because the ability to determine additional covariates from the data would be lost. Dr. Dawson added that if the Board believes that the research is unreasonably risky, it would not be able to recommend that it be performed; the degree of riskiness of a study is not determined by the number of subjects. Mr. Sarkar stated that unless studies continue as indicated in the protocol, observed variability will be decreased artificially because of right censoring. EPA also uses the data to determine whether gender differences exist.

Dr. Gbur recommended that a sample size calculation be performed. Dr. Dawson agreed that the need for increased statistical power had been a strong view of the Board.

Dr. Gbur suggested that EPA consider requiring the sponsor to determine factors that might cause variation in the CPT. Dr. Dawson added that the Board members could suggest how to obtain more information from the studies in ways that would be reasonable and scientifically useful. Dr. Zhu proposed that the Board recommend that S.C. Johnson conduct further statistical analyses on the data to advance the field for future studies. Dr. Dawson responded that providing recommendations to the sponsor was beyond the Board's charge. Instead, the Board could suggest that EPA ask sponsors to perform such analyses in the future; the Agency would determine whether or not to act on the Board's advice.

Dr. Dawson suggested that EPA provide consumers with information that currently is not included on product labels. The Board members had expressed interest in providing more information to the consumer on how the products perform. Dr. Gbur indicated that S.C. Johnson had collected significant amounts of information that it might consider supplying to consumers. Dr. Gbur suggested that information on male/female and site location differences might be useful. In certain locations, for example, S.C. Johnson might choose not to market a pump spray that lasts only 2 hours. Dr. Zhu suggested that information on variability could be placed in a public venue so that it would be available to interested consumers. Dr. Dawson cited package inserts for drugs as a precedent for a regulatory agency providing more information to the public.

Dr. Dawson proposed that the Board members discuss three types of recommendations to the Agency: (1) analyses of data that already exist; (2) considerations for different study designs (e.g., sample size, weather events); and (3) what types of information should be communicated to the public. Regarding analyses of existing data, Dr. Gbur suggested exploring subject gender and age and also site differences. In addition, differences among products (e.g., aerosol vs. pump, percentage DEET) could be assessed. Dr. Lawrence noted that the data involve small numbers of subjects, and only analyses the Agency is confident about should be performed.

Regarding considerations for improved study design, Dr. Maddalena suggested that in future protocols, the data from the S.C. Johnson studies on no-shows be used to estimate the number of recruits needed. In addition, he suggested that a threshold be established for the difference between two sites that would trigger the need for a third site. Dr. Dawson noted an issue of timing that would be involved in establishing a third site subsequent to data collection and analysis and prior to the end of the mosquito season. In addition to no-shows, Dr. Gbur emphasized the importance of collecting data on landing pressure and mosquito species, as well as other factors that might affect the results as at a given site, such as time of day, time of season, climate, temperature and rain. Dr. Gbur suggested that in the future, studies conduct analyses to evaluate gender differences.

Regarding the type of information that could be communicated to the public, Dr. Gbur suggested that a range of responses rather than just a median could be provided. Dr. Lawrence responded that the aim of the EPA Repellency Awareness Graphic is to provide information to the public similar to an SPF rating on sunscreen, which involves very standardized testing and clear communication of a single number for SPF protection. Providing caveats about to the graphic would diverge from the intent of the graphic, which was to represent the results of repellency studies conducted by sponsors in a uniform manner and provide the CPT to the public in a clear and easily understood format. She emphasized the need for well-designed, adequately powered studies that would provide more confidence in the resulting CPT. Dr. Dawson cited circumstances under which the public might seek more detailed information than provided by the EPA Repellency Awareness Graphic, such as an outbreak of West Nile virus or

mosquitoes that appear resistant to a repellent. A median CPT of 8 hours with a large range might provide consumers with an exaggerated sense of confidence in a product.

Adjournment

Mr. Downing announced that the next HSRB meeting is scheduled for April 12–13, 2016, and the exact times and location (i.e., virtual vs. face-to-face meeting) will be posted in the *Federal Register*. Mr. Downing thanked OPP staff. Ms. Lydon mentioned that the list of topics had not yet been decided for the April meeting, but additional insect repellent studies may be completed. She also noted that a briefing session for Board members on agricultural handlers studies will take place in March 2016.

Mr. Downing adjourned the meeting at 5:09 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

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