Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
April 8–9, 2014 Public Meeting
Docket Number: EPA–HQ–ORD–2014–0189
HSRB Website: http://www.epa.gov/osa/hsrb

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

Date and Time:	Tuesday, April 8, 2014, 10:00 a.m. – 5:30 p.m. Wednesday, April 9, 2014, 9:30 a.m. – 3:00 p.m. (See *Federal Register* Notice—Attachment B)	
Location:	EPA, One Potomac Yard (South Building), 2777 S. Crystal Drive, Arlington, VA 22202	
Purpose:	The EPA HSRB provides advice, information and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Rebecca T. Parkin, Ph.D., M.P.H.
	Board Members:	Liza Dawson, Ph.D. George C.J. Fernandez, Ph.D. Kyle L. Galbraith, Ph.D. Edward Gbur, Jr., Ph.D. Sidney Green, Jr., Ph.D., Fellow, ATS Elizabeth Heitman, Ph.D. John C. Kissel, Ph.D. Randy Maddalena, Ph.D. William J. Popendorf, Ph.D. Kenneth Ramos, M.D., Ph.D., PharmB Leonard Ritter, Ph.D., ATS Linda J. Young, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the meeting Agenda (Attachment C), unless noted otherwise.	

Tuesday, April 8, 2014

Commencement of Public Meeting and Review of Administrative Procedures

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

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. Also in his role as DFO, he must work with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied. HSRB members were briefed on federal conflict of interest laws, and they have completed a standard government financial disclosure report. In consultation with the deputy ethics officer for OSA and the Office of General Counsel (OGC), Mr. Downing has reviewed the reports to ensure that all requirements are met.

Mr. Downing informed members that there are several interesting and challenging topics on the agenda for the meeting. He noted that agenda times are approximate, and the group will strive to have adequate time for Agency presentations, public comments and the Board's thorough deliberations. All speakers, including Board members and members of the public, should use their microphone and identify themselves before speaking, as the meeting is being recorded and broadcast on the Internet. Copies of all meeting materials will be available at http://www.regulations.gov under docket number EPA–HQ–ORD–2014–0189, and supporting documents are available on the HSRB website at http://www.epa.gov/osa/hsrb. Following the presentations, time has been scheduled for the Board to direct questions of clarification to EPA staff and the sponsors of the studies discussed. This time is to be used for points of clarification rather than Board discussion. A public comment period will be maintained, and remarks must be limited to 5 minutes. No members of the public had preregistered to make a public comment for the topics under consideration.

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

Introduction and Identification of Board Members

Dr. Parkin welcomed the Board members. Mr. Downing indicated that Dr. Jonathan Cohen (ICF International) would be participating in the meeting via teleconference; Dr. Cohen's participation was delayed, however, due to technical difficulties. Dr. Parkin asked Board members to introduce themselves, and members completed their introductions. Dr. Parkin next invited Dr. Glenn Paulson (Science Advisor, EPA) to offer opening remarks.

Opening Remarks

Dr. Paulson welcomed all in attendance. He indicated that one of the responsibilities of OSA is to provide support and administrative oversight for the HSRB. He joined Mr. Downing and Dr. Parkin in expressing appreciation to the Board members for their service in preparing

for, participating in and following up for this meeting. He recognized and appreciated both the time required and amount of material reviewed to prepare for deliberations during this meeting, as well as the time to prepare the Board's advice to EPA. Dr. Paulson welcomed the members of the public in attendance and those participating via the Internet and thanked EPA colleagues for their work organizing and preparing for this meeting.

Dr. Paulson next noted changes to the Board. He welcomed five new members, noting EPA's appreciation for their acceptance to serve on the HSRB. He thanked the new and continuing Board members for providing EPA with access to their diverse expertise in reviewing complex ethical and scientific issues. The five new members were introduced as follows:

- Dr. Liza Dawson is research ethics team leader in the Division of AIDS for the National Institutes of Allergy & Infectious Diseases (NIAID). In this role, she provides consultation and advice on research ethics issues for AIDS research programs, coordinates a portfolio of extramural bioethics grants, and reviews clinical trial protocols as part of the Institutes' scientific review committee.

- Dr. Kyle L. Galbraith manages the Human Subjects Protection Office at the Carle Foundation Hospital, a 345-bed facility in central Illinois. Dr. Galbraith is responsible for overseeing the operations of the hospital's Institutional Review Board (IRB); developing institutional policies for human subject protection; and educating researchers, support staff and IRB members on the responsible conduct of research, as well as other topics related to the ethical conduct of human subjects research. He serves on the IRB himself, as well as the hospital's Ethics and Conflict of Interest Committees. Dr. Galbraith participates in the hospital's ethics consultation service and also regularly lectures on clinical research ethics for the Medical Humanities and Social Sciences Program at the University of Illinois at Urbana-Champaign.

- Dr. Edward Gbur, Jr. is currently the Director of the Agricultural Statistics Laboratory at the Arkansas Agricultural Experiment Station. He also is Professor of Statistics in the College of Agricultural, Food and Life Sciences at the University of Arkansas.

- Dr. Randy Maddalena is a Research Scientist in the Indoor Environment Group at the Environmental Energy Technologies Division in the Lawrence Berkeley National Laboratory. The focus of his research is on environmental fate and transport processes and multipathway exposure assessment for organic chemicals, combining modeling, bench-scale studies and field observational studies. His research supports the development, evaluation and application of mathematical models that predict chemical fate in multiple environmental media: air, water, soil, vegetation and sediment, as well as chemical exposures through multiple pathways such as drinking water, food, indoor air and dust for human and ecological receptors.

- Dr. Kenneth Ramos is Distinguished University Professor of Biochemistry and Molecular Biology, as well as Director of the Center for Environmental Genomics and Integrated Biology at the University of Louisville. He is a leading expert in the study of gene-environment interactions and personalized and genomic medicine. His research program

integrates diverse approaches, ranging from molecular genetics to population-based public health studies. Dr. Ramos' published work has focused on genetic and epigenetic determinants of disease susceptibility, computational biology, molecular biology of adhesion and oxidative stress, and molecular signaling. Preclinical work in his laboratory focuses on the study of repetitive genetic elements in the mammalian genome and their role in genome plasticity and disease. His clinical studies aim to characterize diagnostic and prognostic biomarkers of chronic disease and cancer through advanced personalized and preventive medicine.

Dr. Paulson informed members that the Search Committee had evaluated applications to fill the critical position of EPA's Human Subjects Research Review Official (HSRRO). The Committee identified strong finalists for the position and recently sent an offer letter. The offer was accepted, and the formal announcement of the new HSRRO will be made in the near future.

Dr. Paulson stated that the previous week the Office of Inspector General had issued a report entitled "Improvements to EPA Policies and Guidance Could Enhance Protection of Human Study Subjects," which was prepared in response to a congressional request to determine whether EPA was following applicable laws, regulations, policies, procedures and guidance regarding exposure of human subjects to diesel exhaust emissions and small-diameter airborne particles at the air pollution test chambers at the U.S. EPA Human Studies Facility in Chapel Hill, North Carolina. The purpose of these studies is to better understand the health effects of pollutants on humans. The Inspector General's report found that EPA followed applicable regulations when it exposed human subjects to airborne particles or diesel exhaust in the five studies conducted in fiscal years (FY) 2010 and 2011. The Inspector identified some improvements, however, that should be made to EPA's policies, guidance and procedures to further enhance protection of human subjects. Among other recommendations, the Inspector General stated the following: (1) EPA should establish clearer procedures for obtaining approval from the HSRRO for modifications of study protocols during studies; (2) the Agency should ensure that consent forms used for human subjects consistently address pollutant risk; and (3) EPA should update its guidance to include the Agency's clinical follow-up responsibility. EPA has concurred with all recommendations and provided to the Inspector General a plan for corrective actions that meet the intent of the recommendations, as well as completion dates for those actions. All of the recommendations in the report have been resolved.

Dr. Paulson acknowledged that the HSRB's agenda for this meeting was full and included challenging topics. He stated that EPA looks forward to receiving the Board's reviews of these projects. The HSRB's recommendations and advice are used actively by EPA in fulfilling the Agency's mission to protect human health and the environment. He reiterated his welcome to new and returning members and wished the Board a successful and productive meeting.

Dr. Parkin thanked Dr. Paulson for his comments and introduced Mr. William Jordan (Deputy Director, Office of Pesticide Programs [OPP], Office of Chemical Safety and Pollution Prevention [OCSPP], EPA).

Welcoming Remarks

Mr. Jordan thanked Dr. Parkin and introduced his colleagues, Ms. Kelly Sherman (OPP) and Mr. Tim Leighton (OPP). He explained that as OPP's Deputy Director, he had assumed the role of formally welcoming the Board members because the Director of OPP recently had resigned to take a position in the Office of Research and Development (ORD). Mr. Jordan expressed his appreciation for the Board's efforts to help EPA move forward, as well as those of Mr. Downing and his colleagues to prepare for the Board meetings.

Mr. Jordan also welcomed members of the public. He stressed the importance to EPA of conducting its work in a manner that is transparent to members of the public, particularly in matters as crucial as the design and execution of research involving human participants, which is essential to meeting the Agency's high ethical standards and producing high-quality scientific information to inform decision making.

Mr. Jordan informed the Board about a recent amendment to the rule that governs the operations of EPA's HSRB. These changes were modeled on the Common Rule. Mr. Jordan provided background to the amendment. In 2006, EPA issued a regulation that applied to third-party intentional dosing with pesticides; this regulation governed the operations of the HSRB. As result of a lawsuit, EPA proposed amendments to the regulations. After considering public comments, EPA accepted these changes and issued a final rule. The new provisions in the rule obligate the Agency, when conducting science and ethics reviews, to consider and document certain aspects of research: the representativeness of the test population and the power of research to detect effects. These requirements were being met by EPA under the 2006 rule, and will continue to be met going forward.

Mr. Jordan indicated that to acclimate the new Board members, he would provide a basic introduction to the proposed research that they would be reviewing. He then offered a short presentation on the issues related to estimating pesticide handler exposure.

Estimating Pesticide Handler Exposure

Mr. Jordan explained the statutory framework for estimating pesticide handler exposure. OPP regulates pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which requires that all pesticides be approved by EPA (i.e., registered) before entering the U.S. marketplace. The registration process involves considering the composition of the product (i.e., the mixture of chemicals that will enter the environment through its use), the way in which it will be labeled, and the way in which it will be packaged. Labeling describes in detail how the pesticide product will be allowed to be used. Mr. Jordan noted that it is a violation of federal law to use a pesticide in a manner that is inconsistent with its labeling. Labeling requirements include the crops on which a product can be used, use sites (e.g., homes, crops, gardens, golf courses), application rates, and protective equipment that must be used. As required by law, EPA determines whether when this pesticide is used, it will cause "unreasonable adverse effects on the environment." Unreasonable adverse effects are defined in such a way that directs EPA to balance the risks and benefits of using a pesticide. It is the role of EPA, rather than the registrants or users, to assess risks and weigh them against benefits to decide if those risks are unreasonable.

Mr. Jordan explained that risk is the function of two different elements: toxicity and the amount of exposure. If there is no toxicity, there is no harm. Therefore, there is no reason to limit exposure. Conversely, if a product is toxic but there is no exposure, there is low risk.

As EPA reviews a product, it considers a wide variety of potential types of risk, including risks to human health and to the environment. For human health, EPA considers risks posed to workers handling or otherwise working with pesticides (i.e., mixing, loading and applying pesticides). There also is potential exposure for the consumer, such as that arising from use in the home or garden; dietary risk from consuming food and/or water containing pesticide residues; and potential exposures to "bystanders" who live near places where pesticides are being used, including risks from exposure in homes, schools or workplaces where they might encounter the pesticide.

In the area of occupational exposure, the Agency considers people who handle pesticides, as well as people who come in contact with pesticide-treated surfaces (e.g., a farmworker who picks apples in an orchard). In estimating handler exposure, EPA considers three factors. The first factor is the way in which a pesticide is mixed, loaded and applied. Pesticides in a variety of formulations are applied with different equipment (e.g., when spraying crops or fumigating medical equipment). All uses have distinct use patterns and scenarios. The second factor that influence handlers' exposure is how much pesticide is handled. The longer workers handle the product, the more their exposure. The third factor to consider in assessing exposure is the impact of using personal protective equipment (e.g., gloves, respirator, a Tyvek suit).

Mr. Jordan noted that the studies being reviewed in this meeting focus on the first element of the three factors. It generally can be assumed that with some exceptions (e.g., inhalation exposure), the type of active ingredient is not going to drive exposure when using a particular pesticide. Protocols for conducting studies with surrogate chemicals representing all active ingredients in different types of formulations are being developed. Dosimeters worn by participants over their whole bodies collect residues of pesticides. Studies aim to match how much active ingredient was handled under different scenarios with how much chemical was detected by the dosimeter, establishing a "unit exposure" relationship. A high-end estimate of handling quantities multiplied by unit exposure would be used calculate a high-end estimate of a handler's exposure.

The inherent assumption in using this method to estimate exposure is that the more an active ingredient is handled, the more likely a person is to get exposure. EPA has examined available data in the scientific literature to evaluate whether that assumption is supported by data. A 1985 study by Reinart and Severn compared exposures to application rates and a linear relationship with a positive slope and small confidence interval (CI). Other studies have not shown as clear a relationship, but in general, their results tend to support EPA's assumption, which is conservative and protective.

EPA's goal in estimating worker exposure is to use an approach that is not likely to underestimate the exposure of the more highly exposed worker population. From a policy perspective, this approach is protective of workers engaged in a particular scenario.

Board Questions

Dr. Maddalena observed that the focus in EPA's policy is on exposure rather than dose. The amount of pesticide that breaches the barrier between the worker and the environment is of concern as well. Mr. Leighton responded that in a risk assessment, dermal absorption factors are used to determine penetration from dermal exposure to determine an absorbed dose. Studies of surrogate compounds could be used, but a surrogate would need to be stable and nonvolatile.

Dr. Ramos asked how surrogate chemicals would be identified and validated. Mr. Leighton responded that surrogates must be relevant to the exposure scenario and labeled for the exposure being modeled, for example, paint. Surrogate samples are transported and analyzed with the corresponding field samples, and recoveries and reducibility are evaluated.

Dr. Ramos raised the issue of mixtures. Mr. Leighton replied that single active ingredients are measured within a matrix.

Dr. Ramos noted that the Reinart and Severn study showed a relationship with application rate rather than dose. He asked EPA to comment on the relationship between application rate and dose. Mr. Leighton responded that EPA is collecting data on exposure to skin over a range of amounts of active ingredient handled (AaiH) in various studies. For example, if an active ingredient in paint were being studied, the assumption would be that if the active ingredient were doubled in paint, painters would be exposed to the same amount of paint, but the amount of active ingredient and total residue would be more. Dr. Ramos asked whether EPA was using application rate as a proxy for dose. Mr. Leighton agreed that this was true for the applied dose, which is the amount on the skin, but not an internal dose.

Dr. Gbur wanted clarification about whether the figure from the Reinart and Severn study showed confidence or prediction intervals. Mr. Leighton stated that he believed that they represented 95 percent CIs. Dr. Cohen stated that the two cannot be distinguished *a priori*. Prediction intervals for a single measurement take into account variability of the error, whereas CIs apply to the mean. Mr. Leighton clarified that the graph was intended as an illustrative example.

Dr. Gbur inquired whether in the studies such as those the Board will be considering, confidence or prediction intervals generally are provided. In addition, he asked whether they are constructed point-wise or as a function. Dr. Cohen responded that the ranges given generally were CIs, and they represent the CI for the mean amount of exposure for a given amount of application in pounds of active ingredient.

Dr. Linda J. Young asked about the consequences of not having an intercept of zero, and the way in which this might affect the assumptions. Dr. Cohen responded that analyses are conducted in log-space. Regressions are performed on the logarithm of exposure data values. The mean exposure, therefore, is proportional to the mean amount of active ingredient. Proportionality is defined as the logarithm of exposure being a linear function of the logarithm of AaiH.

Dr. George Fernandez noted that the arithmetic mean is being estimated, but for toxicology or pollution-related exposure studies, a 95th percentile value and its CI might be more appropriate than reporting a mean or mean estimate. Methods are available to estimate percentiles. Mr. Leighton stated that depending on the hazard, EPA might decide to consider a measure other than the arithmetic mean.

Dr. Sidney Green, posed the question of whether in these types of studies, there might be instances in which ocular irritancy might have to be monitored in humans. This has not yet been done as an endpoint in a human study and is likely to be difficult to consider. Some toxicology studies in animals have shown a high level of ocular irritancy. He questioned why EPA is not considering ocular irritancy arising from exposure to these chemicals and is not considering the use of personal protective equipment (PPE) for chemicals with a high level of ocular irritancy. Mr. Leighton noted that for contaminants that are toxic to the eye, ocular irritancy might be mitigated through goggles. EPA has studied fumigants and measured rates of eye blink relative to exposure.

Session 1: A New Scenario Design and Associated Protocol from the Antimicrobial Exposure Assessment Task Force (AEATF-II) Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Manual Pouring of Solid Formulation Antimicrobial Products

Background

Dr. Parkin introduced the AEATF-II study and turned the floor to Mr. Leighton to provide the Agency's review of the scientific aspects of this study.

EPA Science Assessment

Mr. Leighton explained that the AEATF-II study was originally scheduled for review by the HSRB on October 1, 2013, but that meeting was cancelled as a result of the federal government shutdown that occurred October 1–16, 2013. He noted that all three of the exposure protocols being reviewed by the HSRB during this day of the meeting were for studies conducted by the AEATF-II. Mr. Leighton noted that Dr. Cohen would be joining them via teleconference to present the background and science assessment, and Ms. Sherman would follow with the ethics assessment.

Mr. Leighton remarked that the Joint Regulatory Committee (JRC) also had participated in the initial protocol design and had conducted a review before the final protocol was submitted for HSRB review.

Mr. Leighton described the regulatory context of the study design and rationale. He noted that the study is complex. Because the proposal involves scripted exposure, it is considered intentional exposure because otherwise the individual would not be exposed. The intent is to submit the resulting data to EPA for regulatory uses under FIFRA.

New exposure studies are needed because science moves forward and methods must be updated to standardize study design and methods, as well as to maximize the utility of generic data. Whereas prior studies only evaluated the mean exposure, this protocol intends to address the limitations of those data. Mr. Leighton noted that in January 2007, the FIFRA Science Advisory Panel (SAP) concurred with the need for new studies, the soundness of the "generic principle" of the research and the study design.

Mr. Leighton presented a matrix of the studies planned and conducted by the AEATF-II. He pointed out the studies that already have been reviewed by the HSRB, including both protocols and completed studies. All of the scripted, intentional studies are fairly similar with regard to experimental conduct; the primary difference is the exposures. Several observational studies also were planned by the AEATF-II, but challenges with the housing market reduced the source of occupational workers, and those opportunities now are limited. That study will be reviewed by the HSRB as a scripted study.

The solid-pour scenario definition includes manual pouring of solid formulation (e.g., powders and granulars) to represent an antimicrobial chemical poured into receiving containers. The scenario excludes application of the product because pouring usually is the application—for example, when consumers pour powder into a swimming pool. In an industrial context, such as a paint manufacturer, the workers pour the powder into the paint.

Mr. Leighton explained that the study objectives were to (1) develop more accurate information on exposures to antimicrobials to support exposure assessments for solid formulations that are manually poured; (2) satisfy a requirement for new data imposed by EPA's Reregistration Eligibility Decision (RED) documents; and (3) support OPP Registration Review, as well as pending and future registrations for various antimicrobial solid products and uses. The study also would support data call-in (DCI) requirements issued by EPA to pesticide registrants to obtain data or other information in support of an existing active ingredient or product registration.

Mr. Leighton presented the study design, which monitors two groups of test subjects (occupational workers and consumers) with two exposure formulations (powders and granules) for a total of four different exposure scenarios. The AaiH is divided into three groups that are randomly assigned to each individual. As an example, the individuals in Occupational Granules Group 1 apply 5 to 25 pounds of granules. Mr. Leighton referred to a prior HSRB conversation led by Dr. William J. Popendorf regarding the possibility of maintaining the same volumes of ingredient and stratifying by concentration.

The criteria for a surrogate solid product include adequate stability and low vapor pressure to ensure good field recoveries; robust data methods to eliminate nondetect issues; and exposure at the high end of the range for both powder and granule product types. Surrogate products must include a diversity of product packages, ranging in size from small to large containers, to build diversity in handling products. Also, the type of receiving container may influence exposure, so various container sizes and configurations are included. Scooping versus pouring might generate differences in exposure. EPA cannot modify a product's label for

scooping, so the studies build in variability to determine if exposure is affected. The study also ensures that an appropriate amount is poured to ensure detection of exposure.

The AEATF-II chose cyanuric acid (CYA) as a surrogate test material for its protocol. CYA is a pool chemical used as a stabilizer to maintain chlorine levels. Mr. Leighton remarked that FIFRA will apply to any substance and is not limited to pesticides; CYA is not an EPA-registered antimicrobial. Notably, CYA is only available as a 100-percent active ingredient. Thus, the protocol cannot vary the percent of active ingredient. CYA is available as both a granule and a powder; this reduces analytical complexity.

As CYA is not a registered pesticide, there are no toxicological data in the database. The rat developmental oral no-observed-adverse-effect level (NOAEL) for monosodium isocyanurate (used to represent CYA), however, is 200 milligrams per kilogram per day (mg/kg/day). The lowest observed-adverse-effect level (LOAEL) is 500 mg/kg/day based on increased hydrocephaly in rat offspring. Mr. Leighton asserted that pregnant women will not be included in the study. A 90-day oral study that investigated bladder effects of monosodium isocyanurate determined essentially the same NOAEL. Acute dermal and inhalation testing in rabbits and rats indicate minimal acute toxicity.

Mr. Leighton explained the potential dose estimates for powders to determine if any effects would be identified. Two approaches evaluate absorbed dermal dose: unit exposure (UE) and dermal absorption (DA) of 1 percent and maximum skin flux (Jmax units of milligrams per square centimeter per hour [mg/cm^2/hr]). Mr. Leighton reminded the participants that Dr. John Kissel had introduced the topic of Jmax at a previous HSRB meeting to use mg/cm^2/hr rather than a percentage to understand how much active ingredient can get through a barrier. The UE approach indicated a margin of exposure (MOE) of 7,600 for dermal exposure and 3,200 for inhalation exposure, while the maximum skin flux approach indicated an MOE of 800 for dermal absorption. Mr. Leighton noted that the maximum skin flux approach assumed that the product would be washed off the subjects' hands within an hour.

The AEATF-II study will be conducted at a single location in Concord, Ohio. Only one location was selected because pouring solids is not likely to vary geographically. The study will be completed indoors for the occupational scenarios. An outdoor scenario was considered, but exposure during the typical occupational exposure setting will be inside a facility or warehouse. The consumer scenario will be conducted outside using a simulated pool.

Mr. Leighton explained that many variables effect exposure from solid pouring, although he acknowledged that at times the protocol is overthought. Aside from the amount of active ingredient poured, variables include source container size (6-pound bags to 90-pound drums and pails); height of pouring (chest or knee height); receiving container types and contents (water or empty); number of pours (randomly assigned); use (or not) of scoop; predissolving the product or not (premix in water prior to dumping in pool); and intervariability of subjects (sloppiness of application). Variability within these elements was built into the design to introduce variability that might affect exposure. Mr. Leighton showed pictures of the proposed scoops to use in the study.

Mr. Leighton described the sample characteristics of the occupational and consumer scenarios. The occupational test subjects will be professional applicators who pour solids as part of their job; there will be no restriction to a specific industry or years of experience. The consumer test subjects will be drawn from the general public and will be restricted to individuals who have lived within the past 5 years in a house with a swimming pool. Test subjects will be asked to participate in both the powder and granule scenarios, resulting in 18 different subjects each for the occupational and consumer scenarios.

Mr. Leighton presented a chart depicting the study design. He noted that the occupational study design involves three sizes containers of containers (25, 50 and 90 pounds). Some groups will scoop and not pour from the 90-pound containers. Those in the larger AaiH groups will just pour. Mr. Leighton noted two illustrative examples: In one randomly selected consumer scenario, an individual in Group 1 will be selected to pour 6 pounds from one container. Another monitoring event (ME) will be to pour 15 pounds. The containers will be randomized.

The MEs will be stratified by AaiH. A constant concentration of test material (an inherent limitation of the available compound) will be handled. The exposure will vary with the amount handled, subject-specific behaviors (captured in observational notes) and characteristics of the sample design. The subjects will be instructed to pour as he or she would normally pour; no instructions will be provided. The minimum amount poured will be 5 pounds for the occupational scenario and 1 pound for consumer scenario, and the maximum amount poured will be 100 pounds for the occupational scenario and 50 pounds for the consumer scenario. The anticipated exposure duration is 6 to 40 minutes.

Mr. Leighton emphasized the random design elements incorporated into the study. The randomized elements include the selection of the study participants themselves, the source container assigned to each ME, assignment of consumers to predissolve the solid product, order of the granule versus powder MEs, and assignment to different size groups.

During the study, each subject will open the lid of the source container and pour the product into the receiving container. The source containers include bags, cans, pails and drums available in the marketplace. The product will be poured into containers with or without water to evaluate potential splash-back exposure. Four of the 18 MEs will include predissolving the powder formulation. Mr. Leighton relayed the new EPA recommendation: "Where scoops are applicable, scoop until you cannot scoop any more, and then pour the remainder." With regard to scooping, the JRC suggested indicating that the subject should scoop until he or she is finished. The participants will be offered multiple predetermined scoops from which to choose.

Field measurements will be collected to assess air temperature, relative humidity, wind speed, characteristics of the heating, ventilating and air conditioning (HVAC) system, and amount of material applied. Written and visual observations will be recorded to better understand high measurements (e.g., a subject might place his or her hand in the powder while scooping).

Whole-body dosimeters (WBD) will be used to measure dermal residues in the same manner as previous studies. Inner dosimeters will be worn against the skin to provide estimates of dermal exposure (DE) under a single layer of clothing. Outer dosimeters will include normal

work clothing and residues will be analyzed. Subjects will wash their hands and wipe their faces and necks at the end of the task to determine the amount of the chemical present.

Inhalation exposure will be measured using two personal air samplers, the Occupational Safety and Health Administration (OSHA) Versatile Sampler (OVS) and Institute of Medicine (IOM) Sampler that evaluates particle sizes of 100 microns (µm) and respirable particles of 4 µm or less. The flow rates are 2 liters per minute (L/min).

Mr. Leighton explained that the analytical phase will be the same as in other studies. An important consideration is to ensure that when a subject is exposed, the result is captured in the laboratory and nothing is lost in the field or during transportation.

EPA evaluated the fold relative accuracy to determine if the design of the study included enough samples. The arithmetic mean and 95th percentile are within the benchmark objective of threefold relative accuracy (K-factor is less than or equal to 3) based on the variance in existing data. When the study is completed, the K-factor will be recalculated based on the variance. If the results are not found to lie within the threefold limit, EPA will work with the AEATF-II to monitor more events in the future.

Mr. Leighton stated that the protocol has addressed the technical aspects of applicable exposure monitoring guidelines, including EPA Series 875 Group A–Applicator Monitoring Test Guidelines and the Organization for Economic Co-operation and Development's (OECD) own applicator guidelines. This study will be Good Laboratory Practices (GLP)-approved.

Mr. Leighton noted that previous comments by EPA and JRC all have been addressed satisfactorily by the AEATF-II, and EPA has provided several new recommendations.
Mr. Leighton presented the first recommendation that the study describe the orientation of the airflow in relationship to the pouring, as has been discussed during previous HSRB meetings. He recommended that the study be stopped if the wind speed is more than 30 miles per hour (mph). Mr. Leighton also recommended that the test subjects representing the consumer population also wear the same respiratory protection as the occupational test subjects (a dust mask). The AEATF-II can estimate the exposure for the entire face understanding that part of the face will be covered with the mask. Mr. Leighton suggested that the study allow consumers to scoop as they would and pour out the remainder of the container.

To account for hand-wash removal efficiencies, Mr. Leighton recommended that the 2007 SAP default factors be applied. He acknowledged that the forthcoming hand-wash removal efficiency study will provide updated correction factors. Two completed hand-wash studies have indicated getting 80 to 95 percent recovery from washing hands.

In conclusion, Mr. Leighton stated that the protocol is likely to yield scientifically reliable information for EPA. The study will fulfill the DCI requirement for previous risk assessments, and the question cannot be addressed without the use of human subjects. The clear scientific objective is to provide more accurate information concerning the pouring of solid powders and granules. The study design should produce data adequate to meet the threefold relative accuracy goal, which will be confirmed after the assay is completed.

Board Questions of Clarification—Science

Dr. Parkin called for any questions of clarification regarding EPA's science assessment. Dr. Young requested an elaboration of the randomization procedures. She noted that the many variables might require a restricted randomization to balance the variables and ensure adequate coverage of all container sizes and pouring heights (kneeling and standing). Mr. Leighton replied that a randomizer program was used for several studies. He acknowledged the issue previously raised by Dr. Popendorf that it would be unacceptable if all subjects were assigned randomly to pour 50 pounds, for example.

In response to a question by Dr. Popendorf, Mr. Leighton clarified that only the occupational workers will wear gloves because there is no call for PPE on the label of the consumer products. All products for occupational use require gloves. Mr. Leighton noted that all JRC recommendations have been incorporated and this protocol represents the final version.

Dr. Popendorf asked about the particle diameter information, and Mr. Leighton noted that the data was provided within the definitions of the supporting documentation. Dr. Popendorf also asked whether the consumers assigned to predissolve the product also would pour the solution into the pool; Mr. Leighton answered affirmatively. Mr. Leighton added that doing the two steps will introduce more variability into the exposures, which will account for variation in methods.

Dr. Popendorf noted that an individual who pours a product occupationally also completes rudimentary cleanup of potential spillage. He asked whether there had been any consideration of having the occupational pourers clean up the work area following the pouring event. Mr. Leighton affirmed that it was a good recommendation.

In response to a question from Dr. Dawson, Mr. Leighton noted that if the variability in the data is too high, more samples will be run. Dr. Dawson noted that the purposeful introduction of variability (e.g., using different sizes of containers, scooping and pouring) might introduce too much variability, and she proposed an alternative to design the study to separate the pouring and scooping groups for comparison. Mr. Leighton remarked that collecting data points is expensive. Furthermore, the products are regulated by EPA based on the label, which does not discriminate between bags and pails or between methods of scooping and pouring. He emphasized the need to include the variability in exposure into the scenario.

Dr. Gbur commented on the possibility for additional data collection should the threefold rule fail to be met. He asked whether the analysis performed after collecting the second set of data would correct for the study being performed on two occasions. Mr. Leighton said that he and Dr. Cohen would consider the issue, and he encouraged the Board to include that point in its report.

Dr. Gbur asked whether a particularly poor randomization would be re-randomized. Mr. Leighton replied that the study investigators would address that question. Dr. Gbur also asked whether the time period between the first and second task was long enough to prevent a

carryover effect. Mr. Leighton noted that the pour area will be cleaned between MEs, hands will be washed and dosimeters will be replaced.

Dr. Fernandez asked whether the active ingredient selected represents commercially available numbers or low, medium or high level. Are they considered fixed or random effects? Mr. Leighton replied that to his understanding, the study design reflects the commercially available range of products. "Super sacks" holding 1,500 pounds exist, but those will be monitored in a separate study.

Dr. Fernandez commented that the MEs are not blinded, and he suggested doing so to ensure that subjects handling a higher dose are not overly cautious. Mr. Leighton remarked that in real life, individuals will always know the amount of product that they are pouring. Dr. Fernandez clarified that a person might not be aware of the amount of chemicals in paint, for example. Mr. Leighton noted that the point could be considered during the afternoon session addressing the painting study.

In response to a question from Dr. Maddalena, Mr. Leighton acknowledged that data from the laundering of handler's clothes was not part of the study. In reply to another question, Mr. Leighton stated that the standard definition of volatility limit is 10^{-4}. Dr. Maddalena asked if the subjects would wait for the product to dissolve before pouring. Mr. Leighton noted that the researchers will clarify that question.

Dr. Ramos asked how the decision was made to use CYA as a surrogate for antimicrobials. Mr. Leighton replied that the first criterion was for an active ingredient that could be formulated as a granule and a powder. AEATF-II also wanted a chemical with a low limit of quantification to reduce the possibility of nondetects, as EPA seeks to avoid basing risk assessments on nondetects and imputation. The surrogate also must be stable over time. In terms of physical properties, the percent field recovery is a consideration. Characteristics such as lipid solubility are not factored into the surrogate decision because exposure studies evaluate the amount of dermal and inhalation exposure. Subsequent risk assessments address such characteristics as chemical composition, dermal penetration, and physical properties of the product being evaluated. Dr. Ramos asserted the preference to perform studies to determine the extent of absorption of the surrogate molecule and then compare the profile to the actual products being assessed.

In response to a question from Dr. Leonard Ritter, Mr. Leighton clarified that EPA intends to recommend adding cleanup to both the occupational and consumer scenarios. Dr. Ritter commented on Mr. Jordan's profound statement that "the characteristics of a chemical turn out to be not terribly important in the exposure characteristics." Dr. Ritter also noted that typically, the only component for which there is a correction in a risk assessment is absorption, not other physical or chemical characteristics.

In response to a question about dust masks, Mr. Leighton responded that EPA is recommending the use of dust masks for both scenarios out of prudence. He elaborated that the inhalation exposure is collected by lapel monitors and will not be affected by the use of dust masks.

Dr. Maddalena asked if the subjects would be allowed to sprinkle product over the surface of the pool. Mr. Leighton responded that the receiving container is not large enough to sprinkle product. Dr. Elizabeth Heitman commented that many individuals scatter product, and Mr. Leighton said that a caveat to the "pour as you would usually pour" instructions would be added.

Dr. Maddalena noted that granules stick better to wet hands, and he asked if the dampness of a subject's hands would be assessed. Mr. Leighton acknowledged the good point and commented that the humidity conditions of the study would be recorded.

Mr. Leighton invited the study investigator, Ms. Leah Rosenheck (LR Risk Consulting, Inc.), to respond to several of the Board's questions, including: How long will the subject predissolve the product? What happens with the randomization if of the 18 MEs, everyone is the same for one variable? What is the length of time between the powder and granular MEs?

Ms. Rosenheck addressed the first question about predissolving the product in the bucket by explaining that four subjects will be randomly selected for the ME. The subjects will be given a bucket and stir stick and instructed to dissolve the product in the bucket first before adding the slurry to the pool. She acknowledged that the product will not be completely dissolved, which is normal in the real world. The purpose of the predissolving MEs is to introduce variability into the study, as some products instruct the user to dissolve the product in a bucket before adding to the pool.

Ms. Rosenheck estimated a 30-minute duration between the granule and powder MEs for the same individual. This includes the time needed to bring the individual to the changing room, remove the dosimeters, wash the hands, redress, and replace the air samplers. This also provides researchers with an opportunity to clean the area, remove empty containers, drain the occupational tank and refill it with water.

With regard to the avoidance of a poor randomization, Ms. Rosenheck remarked that randomization limitations could be included. For example, of the six individuals within each group, a limitation could indicate that a certain minimum percentage must be assigned to each variable. Similar output constraints could prevent the randomizer from always selecting the low end of the grouping (e.g., if all subjects in the 5- to 25-pound group get assigned 5–6 pounds). Mr. Leighton stated that the Board will consider the randomization during its deliberations.

Ms. Rosenheck made several minor clarifications. She clarified that the population recruited for the study must include individuals that live or have lived in a house with a swimming pool during the previous 5 years *and* have used granular or powder products to maintain the pool. One presentation slide mentioned that individuals will predissolve powders, but both granules and powders are predissolved in the scenario. In response to a question from Dr. Popendorf, Ms. Rosenheck clarified that a total of eight MEs will include predissolving the product (four consumers with granules and four with powder). Ms. Rosenheck reiterated the need for individuals to dispense the product as they normally would. An above-ground

swimming pool is included in this study, which will be large enough for individuals to pour, throw or walk around and dispense product in their typical manner.

Dr. Parkin thanked the participants for the discussion and invited Ms. Sherman to provide EPA's ethics review.

EPA Ethics Assessment

Ms. Sherman acknowledged that the Board has reviewed a number of previous studies and many of the ethics procedures have been refined and documented in standard operating procedures (SOPs) detailing informed consent, heat and other procedures.

Ms. Sherman remarked that the study provides value to society because many consumers and workers pour solid antimicrobial products, so reliable data on potential dermal and inhalation exposure are needed to support EPA exposure assessments. Existing data have limitations, and the improved data cannot be collected without human subjects.

Study subjects will be recruited through newspaper advertisements that target different demographics. Ms. Sherman noted that the advertisement was approved by the IRB. When potential subjects see the advertisement and call in, the researcher will use a script to determine if basic eligibility and experience criteria are met. The researcher also will explain what the subject will be asked to do in the study. Callers will be screened for age (over 18), pregnancy (must not be pregnant), and literacy (can speak and read English or Spanish). All consent materials are available in English and Spanish and recruitment will be conducted according to the subjects' preference. Ms. Sherman opined that the inclusion and exclusion criteria are complete and appropriate, with the addition of an exclusion criterion of skin conditions of the face and neck. After completing the screening process, interested subjects will be scheduled for a consent meeting. The use of newspapers to solicit participants minimizes the possibility of workplace coercion or undue process. No subjects will be from a vulnerable population.

Ms. Sherman remarked that the consent process is defined clearly in the materials. The principal investigator or bilingual researcher will meet individually with the subject to describe the study, review eligibility criteria, discuss risks, provide the product label and material safety data sheet (MSDS) information, and answer any questions. If the subject is still interested in participating and meets all the eligibility criteria, the study director will confirm understanding and then ask if the subject consents to participate .

Ms. Sherman identified four main categories of risk, which she noted were appropriately minimized in the protocol. The first risk is the irritant response to test material or to the soapy mixture used to wash the hands and face/neck, which is minimized by asking subjects about past sensitivity or reactions to CYA or soap products. Also, occupational subjects will wear gloves and all subjects will wear a mask to reduce the possibility of respiratory irritation. The second risk is for heat-related illness because subjects will be wearing a second layer of clothing as the dosimeter. The study documents procedures for managing heat stress, including monitoring the temperature and alerting researchers to symptoms of heat stress. Onsite medical attention will be provided. This risk is minimal because the MEs will be nonstrenuous and should not last longer

than 1 hour. The third risk is the loss of privacy in changing, which will be minimized by providing private changing areas and same-sex technicians to assist with changing. The final risk is unwanted disclosure of pregnancy test results. Each female will be asked to take a pregnancy test, which will be handled in a discreet manner. Results will be verified, but not recorded. Good procedures are in place to protect privacy.

Ms. Sherman commented that there are no direct benefits to subjects, but likely benefits to society from higher-quality risk assessments for antimicrobial products. She concluded that the risks have been effectively minimized, residual risks to subjects are low, and risks to subjects are reasonable in light of potential societal benefits.

Regarding respect for participants, Ms. Sherman remarked that the payments are reasonable. Subjects are paid $20 for the initial consent meeting and $100 to report to the study site. Subjects are told repeatedly that they are free to withdraw at any time. Procedures are in place to protect the identity of subjects by linking them to study numbers.

The study protocol was reviewed by the Shulman Associates IRB, who approved the protocol and supporting documents in English and Spanish. As this is a proposal for third-party research (not EPA) involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws, the primary ethical standards applicable to this research are 40 Code of Federal Regulations (CFR) 26, subparts K and L.

Ms. Sherman listed the revisions requested by EPA before the research proceeds. She noted that the AEATF-II already indicated that the changes will be made. Ms. Sherman asked the AEATF-II to add "skin conditions of the face/neck" and to clarify the exclusion criteria and medical-management triggers. She suggested that section 9D of the protocol be revised to specify that skin reaction or eye or respiratory irritation experienced by two or more subjects will trigger the study director to determine if further medical management is needed. Ms. Sherman requested that information about the dust mask be added to the consent form and that "skin reaction and respiratory irritation" be added to the research-related injuries section of the consent form. She recommended that the newspaper advertisement be revised to indicate the requirement for job experience for the occupational scenario. Lastly, Ms. Sherman recommended that the researchers incorporate the HSRB's forthcoming guidance about the return of results to study subjects.

Board Questions of Clarification—Ethics

In response to a question from Dr. Gbur, Ms. Sherman clarified that subjects with preferred languages other than English and Spanish are excluded from the study.

Dr. Galbraith noticed that a common risk in this protocol and the next one is the risk of embarrassment by changing, and both protocols indicate that a technician of the same gender will be present. He noted that some people might be more embarrassed with a technician of the same gender and suggested providing participants with the choice of gender. Ms. Sherman noted that the protocol could be revised to give the subject a choice of gender to assist with the

dosimeters. She noted that the general idea would be to lessen embarrassment, similar to a locker room.

Dr. Heitman noted that payments of any amount above $20 require reporting to the Internal Revenue Service (IRS) and collecting social security numbers. She questioned whether any additional information gathered is not mentioned. Ms. Sherman replied that the subjects are paid in cash and social security numbers are not collected. Ms. Rosenheck confirmed that social security numbers are not collected. Lawyers have indicated that it is the individual's responsibility to report the payment on tax returns.

Dr. Dawson requested that the protocol be revised to ensure that pregnant women are not allowed to participate. Ms. Sherman clarified that women take the test in the restroom, and if the test is positive, the woman can leave the study without discussing the results with the researchers. To participate in the study, the negative test results must be shown to the researcher for verification.

Dr. Sean Philpott-Jones (Consultant to the HSRB) asked whether the Sherman Associates IRB reviewed the consent form in both languages. Ms. Rosenheck noted that when a subject calls the toll-free number, an answering machine will require that the subject press 1 or 2 for information in English or Spanish. Subjects will leave their name and contact information, and the bilingual researcher will contact the individuals who prefer Spanish. Ms. Rosenheck agreed to check whether the IRB reviewed the consent form in both languages.

Dr. Parkin solicited any additional ethics questions and none were provided.

Public Comments

Dr. Parkin called for any public comments. Mr. Downing remarked that no public comments had been registered in advance. And no public comments were offered.

Charge Questions

Mr. Leighton read the charge questions into the record:

If the AEATF-II study proposal AEA07 is revised as suggested in EPA's science and ethics reviews and if the research is performed as described:

Charge to the Board—Science:

- Is this research likely to generate scientifically reliable data, useful for assessing the exposure of those who pour solid formulation antimicrobial pesticide products?

Charge to the Board—Ethics:

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

Board Science Assessment

Dr. Parkin asked Dr. Popendorf to address the first charge question. Dr. Popendorf made four points, in ascending order of importance, that addressed the effect of accumulation inside gloves in real-world occupational users; the narrow range of occupational conditions being evaluated, which poses limitations compared to the real world; the lack of usefulness for the residential scenario for pouring solids by consumers other than the swimming pool setting; and the weak justification for performing the occupational pouring scenario. Dr. Popendorf provided justification for each point as follows:

1. Regarding label issues, all occupational labels require gloves, so that is helpful. Dr. Popendorf noted that in the real world, however, workers might reuse gloves several times and there will be accumulation of product in the gloves. In the exposure scenario, each person gets new pair of gloves, which might underestimate exposure. He noted that this was a small limitation to the study design.

2. Dr. Popendorf noted the lack of science on the use conditions. One factor that affects dermal exposures is the products' distribution of particle diameters. That factor, along with the distance allowed for the product freefall within the pouring and receiving container, will influence the amount of aerosol or suspended material generated. He allowed that local airflow is being addressed. The geometry of the receiving container, including its width and shape, will influence the exposure. Dr. Popendorf noted that adding cleanup to the scenario will increase the realism of the scenario. He commented that it would be difficult to extrapolate beyond the fixed variables in the study. Dr. Popendorf also mentioned that the air exchange rate measurements are unnecessary.

3. Dr. Popendorf applauded the high variation in the consumer scenario. He noted, however, that the characterization of the pool, scoop, and predissolving will also increase the difficulty in extrapolating the data to other settings to generalize the data beyond individuals treating their pools.

4. Dr. Popendorf questioned the justification for conducting the solid-pour scenario. He noted that five justification factors were mentioned on page 21 of EPA's Science and Ethics Review that addressed key differences between agricultural and antimicrobial granules: (1) limited relevance for the data in the Pesticide Handler Exposure Database (PHED) and Chemical Manufacturers Association database to the pouring of antimicrobial products and poor quality from an analytical perspective; (2) application of dry agricultural granules compared to adding antimicrobial granules to water; (3) generation of outdoor-specific data that do not reflect the indoor environment where solid antimicrobial formulations are used; (4) low active ingredient concentration of agricultural granules; and (5) differences in solid formulations between the agricultural

and antimicrobial industries. Dr. Popendorf argued that each point of difference might not be significant enough to warrant duplicating the existing agricultural data with the proposed occupational scenarios. He acknowledged that current data are poor quality; however, the Agricultural Handlers Exposure Task Force (AHETF) is generating new data with reviewed protocols. He remarked that it was unclear if the occupational part of this antimicrobial study was justifiably unique from other studies based on the science.

Dr. Parkin asked if Dr. Green had any comments. Dr. Green agreed with the scope of Dr. Popendorf's discussion.

Dr. Parkin asked Dr. Young to provide her review of the science charge question. Dr. Young stated that her largest concern was in the design of the study. Randomization is important, but it might be used to the detriment of accomplishing the research goals. She noted the need for a representative range of AaiH and suggested that the researchers select discrete points of AaiH as part of the study design that can be used for regression analysis. Dr. Young continued, noting the importance of specifying different types of containers and scoops, rather than allowing the chance that one particular container is always selected. Randomization could be introduced through randomizing individuals to MEs.

Dr. Young noted that the assumption of proportionality is a large supposition that has not been proven by previous data. She elaborated that a subject who sticks his hand in the powder will disrupt any proportionality assumption. Dr. Young expressed another large concern about the lack of a 0 intercept when establishing proportionality, as well as a minor concern that a log-log transformation might not correct the skew of the data adequately. She suggested that the researchers consider using medians rather than means, to be more reflective of the middle distribution.

Dr. Gbur noted the need to ensure that any data from additional studies be combined appropriately to recalculate estimates. Dr. Young commented that additional data will provide more points for the regression line and will increase variation, which is a benefit. Dr. Gbur commented that at some point, variability becomes so large that it will be difficult to interpret the data. Dr. Young replied that the goal is to increase error as much as possible, and the regression line should be robust enough to accommodate the additional data points.

Dr. Parkin asked Dr. Popendorf to read the summary response to the charge question into the record. He stated that in general, with the modifications suggested, the research is likely to generate scientifically reliable data. The question of its unique usefulness to assess exposures is somewhat in doubt with regard to the difference between industrial and agricultural settings.

Dr. Parkin called for any additional discussion. Hearing none, she asked that Board members in agreement with Dr. Popendorf's summary response respond affirmatively. The statement was unanimously accepted by the HSRB.

Dr. Green commented that the toxicity studies did not support the conclusion that dermal and inhalation toxicity of the CYA were nonexistent. When he looked at the studies, particularly the dermal irritation studies, several questions related to the adequateness of the data were raised.

Dr. Green remarked that the study was completed in 1981 and was not performed according to GLP requirements that were enacted around the same time. Dr. Thomas Kuechler (Occidental Chemical) noted that although the 1981 dermal study laboratory was not instructed to conform to GLP, no deficiencies in the study were reported. Thirty subsequent years of industrial experience since then have raised no indication that CYA is an irritant. Dr. Kuechler acknowledged that systematic documentation is lacking, but no customers have reported toxicity effects or irritation. Dr. Ritter interpreted that data as anecdotal and remarked that the "absence of data" is not the same thing as "safe." Dr. Green opined that 30-year-old studies that do not meet GLP requirements should not be considered "quality data" for dermal toxicity testing.

In response to a question from Dr. Parkin, Dr. Green noted that his remark did not change the summary statement. He agreed to provide additional detail for the HSRB's report concerning the need to address the age and quality (e.g., compliance with GLP) of the studies being considered as supporting toxicity studies.

Ms. Rosenheck addressed Dr. Popendorf's comments about granular formulations. She noted that the majority of EPA's Health Effects Division work is performed with agricultural products. Granular products in antimicrobial industry, with very few exceptions, are added to water. In agriculture the products are applied dry or are dispersible when applied wet; thus, they are classified differently in the Agricultural Handler Exposure Database (AHED). Also in agriculture, an inert granule is added to the fertilizer. In the antimicrobial industry, antimicrobials are not a carrier, they are the active ingredient. Dr. Kuechler commented that the granular material for swimming pools contains 100 percent active ingredient. The products are designed to be dispersed directly in water and dissolved. No carrier is left behind.

Dr. Popendorf acknowledged the helpful discussion, but commented that not all agricultural chemicals are applied dry. From a science perspective, what affects exposure is the size of the granules and the pouring distance.

Mr. Leighton remarked that the AHETF studies might address larger sizes of commercial antimicrobials, including 1,500-pound super sacks that are not a part of this study.

Dr. Parkin summarized that the HSRB members believe that the study will provide scientifically reliable data, but questions about those data remain even when modifications are made.

Board Ethics Assessment

Dr. Parkin asked Dr. Philpott-Jones to address the charge question that asked whether the research was likely to meet the applicable requirements of 40 CFR part 26, subparts K and L. Dr. Philpott-Jones stated for the record that he is a consultant for the HSRB; thus, he will provide a review and recommendations but cannot vote. Dr. Philpott-Jones concluded that the technical requirements of the charge question are met with regard to the required technical documents submitted for review, and the protocol was reviewed and approved by an independent IRB human subjects review committee prior to submission. The HSRB members have access to the minutes of those meetings, a list of the IRB members, and a copy of the policies and procedures;

additionally, Shulman Associates IRB is a fully accredited IRB. Dr. Philpott-Jones addressed three broad questions: Are the risks to study participants commensurate with the anticipated benefits to the participants or to society? Is there voluntary informed consent for all subject participants? Is there equitable selection of study participants?

Dr. Philpott-Jones stated that he concurred with the conclusions of Ms. Sherman's ethics review. With regard to the risks being commensurate to the benefits to participants and society, Dr. Philpott-Jones raised a caveat. The concern is whether the study is unique. If the study is overly duplicative, this raises questions about the benefits of the study and calls into question whether it is ethical. If no benefits are provided by the study, it is inherently unethical regardless of the risk.

Dr. Philpott-Jones reiterated Dr. Young's concerns about whether the study would yield useful data. He put that concern aside, under the assumption that the science issues would be addressed adequately. Dr. Philpott-Jones next addressed whether the risks were commensurate to the benefits. He noted that the risks include sensitivity, heat-related illness, and psychological discomfort from undressing and pregnancy disclosure. Dr. Philpott-Jones asserted that the risks were minimized appropriately (e.g., by using only experienced handlers). CYA has low toxicity and is used widely as a pool maintenance chemical. The CYA label does not require the use of gloves, although the MSDS suggests chemical-resistant gloves for consumer use. The current industrial practices are overprotective to cover the handling of high amounts of product. Dr. Philpott-Jones noted that the study criteria exclude those with injuries to the hands, face and neck, as well as those with sensitivities. Subjects are reminded about safe practices and the use of PPE, and unintentional exposures are monitored. The protocol includes appropriate measures in the case of adverse outcomes by providing medical professionals on site. The protocol also excludes minors and pregnant women.

With regard to voluntary consent, Dr. Philpott-Jones disagreed with EPA's position that no study participants will be from a vulnerable population, which is always a possibility. The protocol does, however, include mechanisms to minimize coercion.

Dr. Philpott-Jones stated that if EPA's recommendations are incorporated in the consent materials, they will be adequate. The Spanish-language translations of the informed consent and recruitment materials do not interfere with the rights of non-English speakers to participate in the study. Dr. Philpott-Jones remarked that the monetary compensation is not so high as to affect participants unduly.

The study will recruit appropriately diverse participants from a city in Ohio, and the recruitment process will ensure that no subjects are coercively influenced. Dr. Philpott-Jones suggested several changes to the study protocol and informed consent documents. He noted that the Agency review suggested that a participant with a "skin or respiratory irritation" should inform the study director. Dr. Philpott-Jones remarked that the revision does not go far enough. He opined that any eye reaction, skin irritation or other injury should be reported and listed within the study protocol and informed consent documents. Any adverse event that occurs within the defined time period that results in seeking medical treatment should require a report to the study director.

Dr. Philpott-Jones remarked that it was not necessary or appropriate to state in the informed consent that use of CYA does not require gloves or PPE. This will be confusing because the participants are required to use gloves and will have access to the MSDS.

Study participants must report being in "good health," but Dr. Philpott-Jones commented on the ambiguity of that term. He suggested defining what "good health" means within the SOPs (e.g., must be able to move 25 pounds). Participants should be allowed to take a short break if needed. Dr. Philpott-Jones also mentioned that it is unclear if a hand wash is required if the subjects need a cold drink; he recommended that they do so to reduce ingestion.

Dr. Philpott-Jones recommended that all of the study researchers should have completed a course in human study protections within 3 years to ensure that their training is current.

Dr. Parkin asked associate discussant Dr. Dawson to provide her review. Dr. Dawson agreed with Dr. Philpott-Jones' recommendations. She affirmed that the term "good health" is so vague as to not be helpful. She suggested placing the exclusion criteria on the recruitment checklist to ensure that the questions are investigated at the beginning of the process. Dr. Dawson remarked that it was reasonable to include a criterion related to chronic respiratory conditions to eliminate potential confounding effects.

Dr. Dawson agreed that the risks posed by the study were acceptable in relation to the benefits, although language in EPA's review appeared overstated. Dr. Dawson suggested making a more general statement that the knowledge gained will be valuable for people who use the commercial products. She commented that the term "medical professional" should be clarified to indicate the type of medical training and qualifications of the professional. Dr. Dawson echoed Dr. Philpott-Jones' sentiments that if the study does not generate scientifically valid information, it is not ethical to proceed.

Dr. Parkin solicited additional questions and comments from the Board. Hearing none, she asked Dr. Philpot to read a summary statement for the Board's consideration.

Dr. Philpott-Jones recommended the following summary statement: Assuming that the answer to the scientific charge question is that the study will yield scientifically valid and useful information, the protocol is likely to meet applicable requirements of 40 CFR part 26, subparts K and L.

Dr. Parkin asked if all HSRB members accepted the summary statement, and there was no dissent.

Mr. Leighton introduced Mr. Jeff Dawson from EPA's Health Effects Division to provide a clarification for Dr. Young. Mr. Dawson commented that early in the HSRB's existence (2008–2009), the Board advocated for random selection of active ingredient stratification. The rationale for randomization protocols was based on the HSRB's earlier comments, as randomization of groups is helpful for comparing different levels of AaiH. If the purpose is to generate a line of regression, however, then randomization provides no benefit and it is better to

assign AaiH to ensure variability of exposure. Dr. Young agreed with Dr. Gbur that it was a challenge to incorporate so many sources of variation, and the potential for large errors to obscure the results is present. Dr. Gbur suggested determining the stratification of AaiH on a case-by-case basis.

Mr. Dawson clarified the question about range and pounds of active ingredient used for agricultural assessments raised by Dr. Popendorf. Of the three relevant mixing and loading scenarios conducted by the AHETF, 5–2,045 pounds of dry flow materials were monitored, indicating a large stratification. The liquids monitored ranged from 10 to 611 pounds. The granule protocol currently under review considers three strata: 5–15 pounds, 15–150 pounds and 150–400 pounds. The protocol is still under review and will be brought to the HSRB in the future.

Dr. Popendorf stated that during the HSRB review of an AHETF pour study in January 2011, the first three of five tiers matched the current antimicrobial scenario. The two additional tiers went up to 2,000 pounds. Mr. Dawson commented that he would collect more information and report back to the Board. Later in the meeting, Mr. Leighton clarified that 10 of the 28 agricultural studies performed to date include AaiH of less than 10 pounds. No scoops are included in those studies.

Session 2: A New Scenario Design and Associated Protocol from the AEATF-II Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Application of Latex Paint Containing an Antimicrobial Pesticide Product Using Brush and Roller Equipment

Background

Dr. Parkin introduced Session 2 and asked Mr. Leighton to provide EPA's science review for the study. Mr. Leighton introduced two protocols: The Session 2 protocol will generate data on the dermal and inhalation exposure during application of latex paint containing an antimicrobial pesticide product using brush and roller equipment, and the supporting study reviewed in Session 3 will generate data for hand-wash efficiency.

EPA Science Assessment

Mr. Leighton provided an overview of the regulatory context for the brush and roller protocol. He commented that the JRC also had participated in EPA's science review. The research involves scripted exposure, so it is intentional, and the same regulations apply as for the Session 1 protocol. New exposure data are needed based on the limitations of available data. Current data address only the use of paint brushes (no rollers) and evaluated only one concentration of active ingredient. Also, separate body-part dosimeters were used in the previous study, rather than WBDs.

The present study proposes to use both the brush and roller to examine exposure from the handheld application of indoor latex paint containing antimicrobials. Antimicrobials are used in paint and canned preservatives, and some possess fungicidal activity (e.g., fungicidal paint is

used to prevent mold in the bathroom). This study includes painting with brush and roller equipment, and the study will be performed on rooms with walls, ceilings and edging. This is representative of normal conditions under which consumers paint.

The objectives of the study are to (1) collect more accurate information on exposures to antimicrobials to support exposure assessments for antimicrobial treated paint; (2) satisfy a requirement for new data imposed by EPA's RED documents; and (3) support Registration Review, as well as pending and future registrations for antimicrobial products, such as in-can material preservatives. For the purposes of this study, Sherwin-Williams latex paint was used. The surrogate chemical used in this study was benzisothiazolinone (BIT), an EPA-registered pesticide and antimicrobial. The same amount of paint (2 gallons) will be used for every ME, but the concentration of BIT will be varied from 120 parts per million (ppm) to 600 ppm.

The toxicity of BIT was evaluated previously with a 90-day dermal rat study. The LOAEL was determined to be 100 mg/kg/day, and the primary effect was stomach irritation. Toxicologists examined the study and ensured that there were measures taken to avoid ingestion. Other effects on the kidney and liver were seen with a dose of 300 mg/kg/day. Based on these data, BIT was classified as category IV (slight irritant). There is no route-specific inhalation toxicity data. The vast majority of dermal exposure occurred through the hands. The highest AaiH was approximately 2.25 gallons at 600 ppm. The MOE was calculated as 3,000 for dermal exposure and 97,000 for inhalation exposure.

The study will be conducted at a single location in California. Mr. Leighton reasoned that painting indoor rooms should not vary geographically so there is no need to conduct the study in multiple locations. Two colors of paint will be applied to ensure a more realistic scenario (different color paint for ceiling and walls). The study participants will be given a roller, roller tray, edger and paint cup, all of which are typical equipment used by painters. Paint brushes and rollers were circulated around the room as a demonstration. Mr. Leighton noted EPA and JRC's discussion concerning the most representative brush to use for the study.

Test subjects will be selected from the general public with at least one painting experience in the last 5 years. Mr. Leighton noted that consumer test subjects have less experience than commercial painters. Different subjects will be used for each ME. Subjects will not be asked to clean their brushes at the end of the task, although they will be allowed to clean up spills. The study will test three groups who apply 2 gallons of paint at three different concentrations of active ingredient. The exposure time will be approximately 2–4 hours. Random design elements include the selection of study participants and the assignment of participants to three groups of different concentrations of BIT.

The painting procedures were designed to mimic "normal" painting conditions. Subjects will be given an extension pole for the roller, which adds variability but provides a more realistic simulation of real conditions. Field measurements will include air flow, frequency of rag use to clean hands, and any spills that might contribute to exposure. Mr. Leighton noted that the inclusion of air flow was in response to Dr. Popendorf's previous discussion concerning the utility of air flow measurements. Measurement of dermal residues will include the painters' cap, a separate assessment of hand-wash removal efficiency, face and neck wipes, and inner and outer

WBDs. Inhalation exposure will be assessed using the OVS tubes and RespiCon Particle Sampler.

Mr. Leighton noted the importance of accounting for losses in field recoveries and explained that the study will correct the field samples. Current studies approach 85-percent recovery. He noted that the data will be assessed to ensure a fold relative accuracy of less than 3 using the arithmetic mean and 95 percent parameters.

Mr. Leighton asserted that the protocol has met compliance with scientific standards, including the EPA Series 875 Group A—Applicator Monitoring Test Guidelines and OECD Applicator Guidelines. He noted that at one point, the study was intended to be observational.

Mr. Leighton presented EPA's recommendations, which suggested that the orientation of the air flow in relation to the painting and test subject be described; the participants be provided a paint edger device and paint cup, and the participants be provided with two different colored paints to foster realistic painting conditions. In summary, Mr. Leighton asserted that the study will provide scientifically reliable information to address DCI questions now and in the future. The roller and paint brush data generated will be more accurate for painting than current data, which address only the brush.

Board Questions of Clarification

Dr. Parkin asked for questions of clarification from the Board members.

Dr. Green asked if the data being collected in the study are being sought for reregistration purposes. Mr. Leighton said that current assessments use PHED data and might need to be reassessed based on the 2007 SAP review.

Dr. Green noted that for the inhalation study, exposure was extrapolated from oral toxicity. Mr. Leighton explained that inhalation rates were calculated based on exposure on the lapel and on the breathing rate, estimated at 29 mL/min.

Dr. Kissel noted that the brush and roller study, as well as the associated hand-wash study, made multiple references to a single PHED study, but he could not determine the active ingredient that was monitored in that study and at what concentration it was present. Mr. Leighton explained that the active ingredient was not provided due to waivers. Mr. Jeff Dawson, the principal investigator on the existing painting study, clarified that the active ingredient concentration was 0.5 or 1 percent, and the active ingredient was a commonly used bactericide. Dr. Kissel noted that 0.5–1 percent is considerably higher than the target in this study. If there is a concentration effect, the numbers will not be directly comparable. Mr. Dawson agreed.

Dr. Popendorf raised the question of using inexperienced test subjects and took issue with the justification that consumers would be "sloppier" than occupational workers. He asked whether there were any data comparing occupational painters to consumers doing the same work. Mr. Leighton answered that he was not aware of any such data.

Regarding the issue of cleanup, Dr. Popendorf suggested performing an extraction, allowing subjects to wash their hands, performing the cleanup and then determining if there is more residual active ingredient after the cleanup activities. Mr. Leighton suggested tabling this topic until the discussion period.

Dr. Popendorf raised the issue of exposure time. As subjects get tired, the likelihood of a large accidental spill increases. Mr. Leighton noted that if a subject accidentally kicks over a gallon of paint that will be included in the ME and recorded in the observational notes.

Dr. Ritter raised the issue of ventilation: EPA recommends that ventilation be turned off during the study, but the MSDS indicates that it should be turned on. Mr. Leighton said that the California review board had a similar question with the protocol, and the study sponsor will discuss this issue.

Dr. Ritter asked whether it would be a good idea to replicate this study in various locations across the United States because heating and air conditioning might affect exposures. Mr. Leighton asserted that rooms across the United States are similar, and that the results should not be affected by the geographical location. Monitoring in a room where the humidity and temperature are controlled should be replicable at any location. The anticipated temperature of the room will be a comfortable 68 to 80 degrees.

Dr. Maddalena noted that the conversation has focused on BIT, but paint also contains a number of co-pollutants. He asked whether there is information about the other compounds in the paint. Mr. Leighton will ask the Task Force to clarify the ingredients in the paint. He added that the paint satisfies California regulations.

Dr. Gbur asked about the statistical analysis on pages 13 to 14 of the EPA review. The CI of the slope is used to determine if the slope is significantly different from 0 or 1. Dr. Gbur asked how a CI that includes both 0 and 1 would be interpreted. Dr. Cohen replied that if the CI includes both 0 and 1, it is likely that more data are needed. According to an approximate power calculation that was performed, the chance of a CI including both 0 and 1 is very low. Dr. Gbur asked about the hypothesis being tested. Dr. Cohen answered that the null hypothesis was independence, which is equivalent to a log-log slope of zero. The alternative is that the slope is not zero.

Dr. Fernandez asked for clarification about the dosage, which mentioned 120, 400 or 600 ppm. He asked whether there would be a benefit of using a control of 0 ppm. Mr. Leighton said that if it were possible to get paint without BIT, zero exposure to BIT would be assumed.

A participant noted that this is a blinded study because the painter does not know the concentration of BIT.

With regard to a question about fold relative accuracy raised by Dr. Fernandez, Mr. Leighton explained that the sample size of 18 subjects allows a degree of accuracy when calculating an approximation. If the accuracy is not sufficient (e.g., a K-factor above 3)

following data analysis, it is possible to collect additional data. Dr. Fernandez expressed concern with the assumption that the log-log scale is the most appropriate. He suggested testing many different nonlinear dose-response models.

Dr. Galbraith asked whether the study had considered evaluating foam brushes in addition to the brushes with bristles. Mr. Leighton said that there is no information suggesting that foam is different from the bristle brush. The bristle brush is a best seller.

There being no further questions, Dr. Parkin transitioned the discussion to EPA's review of the ethical aspects of the study.

EPA Ethics Assessment

Ms. Sherman explained that the ethics procedures in place for this protocol are very similar to those from the study reviewed in Session 1. The subject selection was handled in the same way, using three newspapers targeting different groups. Ms. Sherman suggested adding "skin conditions of the face/neck" and "allergies or sensitivities to BIT" to the otherwise appropriate inclusion and exclusion criteria. She explained that subjects were not intentionally recruited from vulnerable populations. Ms. Sherman noted the IRB had decided to issue a conditional approval for the brush and roller study—conditioned on the California Department of Pesticide Regulation (DPR), HSRB and EPA review—that will be finalized after the protocol is amended. Ms. Sherman said that what is required is final approval from the IRB before moving forward with the research. The consent form and other relevant documents will be translated to Spanish after the final IRB approval.

The consent process was handled the same way as in the previous study, and the risks were similar. Ms. Sherman suggested that the sponsors add to the consent form the physical risk of using a ladder and injuries related to painting. She asserted that the risk-benefit balance is comparable to that of the previous study, and similar procedures are in place for payments. The applicable ethical standards also are the same as the previous study.

Ms. Sherman summarized EPA's recommended revisions, including the two additions to the exclusion criteria and a description of the test product as a pesticide rather than a chemical. The key point is that final IRB approval is required before moving forward with the research. Ms. Sherman suggested that the protocol incorporate forthcoming guidance from the HSRB on the return of research results.

Board Questions of Clarification

Dr. Heitman asked about the meaning of the novel phrase "chemical-based product." Ms. Sherman noted that the phrase was present in a consent form from which she borrowed the term. She agreed that many products are chemical-based. This study is not appropriate for people who know they have sensitivities to certain chemicals; although the term is not precise, it might be useful for subjects. Dr. Heitman acknowledged the need to use a consistent phrase across protocols. Within the documents, Dr. Dawson recommended using lay terms that individuals use to describe their sensitivity.

Dr. Philpott-Jones noted that the IRB approval is only conditional and questioned whether standard §26.1125 was met. He remarked that he cannot perform a complete review of the study because there are no Spanish-language documents. Dr. Philpott-Jones asked about the Agency's plan to ensure that §26.1125 requirements are met.

Mr. Jordan from EPA said that they were unprepared by the Shulman Associates IRB approach. EPA's preference is that the IRB complete the review and approve the protocol, which did not happen in this case. Mr. Jordan acknowledged that the conditional approval created an awkward situation. He said that it does not make sense to postpone the review of this protocol; EPA will proceed with the review, with the clear message that there needs to be final favorable review by the IRB before the research commences. The protocol reviewed by the IRB should reflect the changes recommended by the Agency. With regard to the Spanish-language aspect of the protocol, EPA is not equipped to perform the translation. Mr. Jordan solicited HSRB recommendations regarding that part of the protocol.

Dr. Galbraith asked why severe diabetes was listed as an exclusion criterion. Mr. Robert Testman (Coleman Pacific Laboratories), study director, agreed that including diabetes as part of the exclusion criteria does not make sense, and he recommended removing diabetes as an exclusion criterion. The generic question "can you conduct these activities?" is a sufficient inclusion criterion.

Dr. Popendorf noted that the review referred to a secondary painting container, and he asked for clarification. Mr. Testman explained that the paint is prepared in 5-gallon pails, but the subjects are provided the paint in 1-gallon secondary containers. The secondary containers have lids to open and close, which was a recommendation suggested by the JRC.

Dr. Popendorf asked how the hands were scrubbed and washed in this study, and whether the hands were extracted and analyzed separately or together. Mr. Testman clarified that in this study, the hands were extracted and analyzed together. The hands will be washed separately in the associated hand-wash study to generate more data points.

Dr. Maddalena asked for clarification about how subjects were monitored in the room. Mr. Testman explained that it was a good-sized room with two observers, one videotaping and one taking notes. Dr. Maddalena noted that the air change rate will vary in the room, and it is a critical value to measure. Mr. Testman explained that tracer gas will be used in several rooms to establish the exact air change for the room prior to using it in the study. The rooms will have a ventilation fan as well as an exhaust fan. He elaborated that the California DPR had indicated that the ventilation fan should be on because of the MSDS, but initial JRC comments suggested turning the fan off during the study to represent the worst-case scenario. Mr. Testman requested guidance from the HSRB on the issue. He professed the inclination to keep the fan on to err on the side of subject protection, but acknowledged that the worst case would not be modeled.

Dr. Gbur asked whether the subjects in the brush and roller study were the same or different than in the hand wash study. Mr. Testman explained that they were different groups of subjects, but there was no exclusion built in to exclude the same participants.

In response to a question from Dr. Heitman, Mr. Testman answered that the wall had wood trim simulating a window, not an actual hole that would affect ventilation. He also clarified that the painting equipment was chosen based on Home Depot's and Amazon's best-selling equipment.

Public Comments

Mr. Downing remarked that there were no pre-registered public comments and no comments were offered.

Charge Questions

Mr. Leighton read the following charge questions into the record:

If the AEATF-II study proposal AEA09 is revised as suggested in EPA's science and ethics reviews and if the research is performed as described:

Charge to the Board—Science:

- Is this research likely to generate scientifically reliable data, useful for assessing the exposure of those who apply latex paint containing an antimicrobial pesticide using a brush or roller?

Charge to the Board—Ethics:

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

Board Science Assessment

Dr. Parkin asked Dr. Green to provide his science review. Dr. Green said that his answer to the first question—is this research likely to generate scientifically reliable data—is yes. He did not identify any significant issues or questions to ask.

Dr. Popendorf agreed with Dr. Green that the study will generate useful and scientifically reliable data. He noted several suggestions for protocol modifications. Matching the hand-extraction protocol used in this study to that used in the supporting hand-wash validation study is one suggestion. He commented that there are no data to support the opinion that consumers might have higher exposure than occupational workers. Dr. Popendorf noted that the middle value of 400 ppm appeared arbitrary, and he suggested further discussion with the Board statisticians. He also had more questions and comments with respect to ventilation.

Dr. Fernandez agreed that the data from this study will be unique and valuable. He also offered several recommendations. The study has two components, one being data collection and the other being data analysis. Considering the data collection design, three doses were selected (120, 400 and 600 ppm). He asked for clarification regarding the selection of the doses. Mr. Leighton said that the study must include the 120-ppm and 600-ppm doses, but he is open to other suggestions for the middle dose. Dr. Fernandez commented that if the goal is to establish the lower limit and highest point, the intermediate dose should be determined by equally spaced intervals. Mr. Leighton agreed with the suggestion and said that the middle dose could be set to 360 ppm to facilitate the statistical analysis.

Dr. Fernandez raised a question about study blinding. If subjects are aware of the added chemicals in their paint, they may become overcautious to avoid exposure. Thus, blinding is necessary to ensure that there is no bias in the data. Mr. Leighton agreed that study participants should not know the concentration of the active ingredient in the paint that they are given.

Dr. Fernandez added that, in terms of analysis, the report will be based on log-log transformed data. A literature search about this type of study found instances using a logistic model with three parameters. Dr. Fernandez recommended that, rather than maintain the use of one model, the data should be analyzed using a variety of models to select the most appropriate simulation. The issue with log transformation is that log-transformed variances are underestimated. Mr. Leighton suggested scheduling a conversation with Drs. Fernandez and Cohen following the meeting to discuss statistical methods. Mr. Downing stated that an offline conversation is appropriate, providing that it is not related directly to the topic being reviewed by the Board.

Dr. Maddalena followed up on the ventilation question raised by Dr. Popendorf, which has ethical implications because it affects exposure not only to BIT, but also to physical paint spatter and other constituents in the paint. He recommended that the study comply with American Society of Heating, Refrigerating and Air Conditioning Engineers (ASHRAE) 62.2 minimal air exchange rates for a residential or work environment. Mr. Leighton said there have been many internal conversations about ventilation rates. He suggested that it would be helpful to include the ASHRAE regulations in the HSRB's report. Dr. Maddalena said he will provide the reference in the report. He noted the need for better characterization of the exposure environment. The report provides only sparse details about the room, including the 10 feet by 10 feet by 8 feet dimensions. Variance in paint spatter will depend on the combination of texture and density of the paint. There may also be carryover, if the same rooms are used for repeated trials in the experiment. Mr. Leighton agreed with Dr. Maddalena's comments and said that it would be helpful to have that information in the Board's report.

Dr. Kissel made several comments. First, there are two ways to do dermal exposure assessment: measuring flux and measuring percent absorbance. The different methods will generate different MOEs. In this example, toxicity was assessed by MOE using dermal information from a toxicity study that had significant flaws. In dose-toxicity studies in rats, additional active ingredient is applied to the same skin surface area, rather than expanding the surface area of exposure. The consequence is that this artificially reduces the apparent toxicity of the compound. Dr. Kissel suggested that EPA review all of the dermal toxicity studies ever

submitted and evaluate whether dermal studies were supply-limited or flux-limited. The calculated MOEs will be incorrect in the flux-limited studies. All of the dermal exposure work will need to be re-evaluated.

Dr. Kissel also raised the issue of hand washing. On the one hand, washing might reduce apparent exposure. Conversely, painters' rags may reduce exposures in some cases and increase exposures in others. If the rag is covered in paint, then using it would spread more paint. This raises the more general issue that there is a general assumption in the exposure arena that there is a linear accumulation of material over the workday. The rate of exposure is calculated as the daily accumulation divided by the number of hours. In fact, the material does not accumulate linearly. This is why washing should not be embedded in this study. Avoiding the washing, however, does not address the question of whether the subject's exposure is increasing or decreasing over the course of the day. Standard methods do not address this question. It is a difficult question in study design that must be addressed. Dr. Kissel emphasized that washing may not decrease exposures. It is not possible to determine how much of the dose has already entered the skin before the paint is washed off. Furthermore, if the paint is spread around because of the washing, this could increase exposure and toxicity.

Dr. Kissel added that there is confusion as to whether the study represents an average case or the worst-case scenario. The paint brush used represents the best seller. To study the worst-case scenario, it would be better to use cheaper brushes, which drip more paint and increase exposure. The current protocol is not specific enough. Dr. Kissel stated that the associated hand-wash protocol is problematic and poses a significant weakness for this study, as it is required for the data interpretation.

Dr. Popendorf said that it would be a good idea to perform an extraction without washing first, and that the study could consider adding a wash and measuring again after the wash. He also noted that, with respect to ventilation, he does not see the value in measuring local air flows because the ventilation will be the time-weighted average across the entire room as the painter moves around. For the purposes of this study, local air flows are not necessary.

Dr. Gbur asked a clarifying question about the statistical analysis, given that the groups are defined by the concentration in the paint, and the model is fitting the log of exposure as a function of the log of active ingredient. Dr. Cohen clarified that the AaiH will vary very little because the volume of paint is set at 2 gallons, plus or minus a quart (1.75–2.25 gallons). There are three concentrations of active ingredient to be tested (160, 400 and 600 ppm). The plan is to measure the AaiH that is actually used by the subject. There will not be much variability within each concentration group. Dr. Gbur confirmed that the data will be clustered in three narrow ranges. He asked whether the middle concentration should be chosen to prevent the low and high concentrations from having undue influence on the fit of the regression. He added that he is concerned that the assumption of fitting a straight line without looking at alternatives is dangerous. There is a need to discuss alternative models; this point applies to all of the studies being reviewed by the HSRB.

Dr. Young asked how the three values were chosen. Using only three points restricts the number of functions that can be fit to the data, such as quadratic functions and other complex lines. Mr. Leighton said that EPA would consider the point.

Dr. Green presented a summary statement to capture most of the concerns. He stated that the answer to the charge question is "yes" with the incorporation of several recommendations. He noted that Dr. Popendorf would like the hand extraction protocol to be reconsidered, he has concerns about the difference between exposure to consumers versus occupational workers, and he thinks that the ventilation protocol should be simplified. Dr. Fernandez recommended changes in data collection, and he is concerned about the three doses chosen, the blinding of the study, and the adequacy of the statistical model. Dr. Maddalena is concerned about the ventilation and the characterization of the diversity of exposure to the agent. Dr. Kissel is concerned about the use of dermal studies to predict toxicity.

Dr. Kissel elaborated that there are flaws in the way that dermal toxicity studies traditionally have been conducted. Typically, the absorption of the material was not adequately evaluated. In oral doses, most of the dose will be absorbed, but in dermal studies, the absorption efficiency varies greatly and must be evaluated adequately.

Dr. Parkin solicited any discussion concerning the summary statement. All committee members agreed to the summary statement and conclusion that the results of the study should be scientifically reliable and useful upon consideration of the recommendations by the HSRB.

Board Ethics Assessment

Dr. Parkin asked Dr. Heitman to present her ethics review. Dr. Heitman said that the protocol submitted for review, if modified in accordance with recommendations, is likely to meet the applicable requirements. The scientific discussion added a few more considerations to her original concern, which was that the technical questions regarding the availability of documents for IRB review were influenced by the conditional (not full) IRB approval. Dr. Heitman stated that the protocol will not need to undergo another full Board review pending the resolution of the scientific questions, as the ethical questions do not warrant an additional meeting. The Board is charged with addressing three specific ethical questions that evaluate risk and anticipated benefits, voluntary informed consent and ethical selection of participants.

Dr. Heitman addressed six risks identified in the study protocol. One risk is the reaction to latex paint or to the BIT active ingredient. Another concerns the discomfort from air flow that is modified by the question of ventilation in the room. Additional risks include possible irritation from the alcohol wash and wipes, heat stress (doing physical work while wearing two layers and a hat), embarrassment from changing clothes in the presence of a researcher, and the possible surprise from pregnancy test results and breach of privacy. Dr. Heitman stated that there are appropriate actions taken to reduce the low probability of harms from these risks, although the use of a ladder will introduce additional risk.

Regarding the question of ventilation, Dr. Heitman noted that heat stress could be worse if the room is enclosed. The Board is waiting for a resolution between California and EPA to

determine whether the rooms will be ventilated or not. On the question of voluntary and informed consent, this study is not actively recruiting from vulnerable populations, but some respondents might be vulnerable. There are mechanisms to minimize coercive recruitment. The advertisements will run in three local newspapers in Spanish and English. Dr. Heitman reiterated that the Board was not provided with the Spanish recruitment materials for review. If the English is modified as recommended by EPA, the Spanish version should adequately inform subjects of risks, discomforts and benefits, and rights to withdraw. The monetary compensation is appropriate and not so high as to unduly influence participants. Research participants will be drawn from a population likely to use latex paint, but the literacy requirement excludes many individuals who paint and are not necessarily literate. Because of this, the study may have a biased study population. It is not clear how to describe the potential risk of harm to people who have allergies or sensitivity to chemically-based products.

Dr. Heitman noted that there are several linguistic issues in the protocol. For example, the term "art applicator" used by EPA to refer to the person applying the paint could be confusing to lay readers, who might consider the applicator to be the device used to apply the paint. "Applier" or "user" might be better words.

Dr. Heitman raised the issue of privacy and confidentiality. One of the specified protections is that pictures will not show faces or tattoos in the final report. Dr. Heitman noted that a tattoo or jewelry on an ear is not part of the face, but could be identifiable. She also suggested that the consent form be modified. Currently, it states that if the subject accidentally gets some paint in the eye, it should be reported. "Some" should be replaced with "any" so that subjects do not minimize what could constitute an eye injury.

Dr. Parkin asked for Dr. Galbraith's assessment of the protocol. Dr. Galbraith commented that he largely agreed with the reviews. He wanted to emphasize points related to satisfying requirements of 40 CFR part 26, subparts K and L. The final page of the EPA review indicated that the HSRB did not receive minutes of the IRB meeting related to this protocol or any lists of attendance including relationships with the sponsor. He indicated that it is necessary for the Board to know who on the IRB roster voted on the protocol. Dr. Galbraith emphasized that, in his previous experience, conditional approval does not constitute approval. He asked that in the future, EPA work with the IRB to ensure that all materials are provided to the HSRB in advance of the meeting to avoid this type of situation.

Related to the translation of materials from English to Spanish, the IRB will often request certification or verification of the translation process. Dr. Galbraith recommended that some documentation be provided regarding how documents were translated and certified as accurate. He also noted that, in the consent form, there is mention of "we" or "research team," but it only listed the principal investigator's (PI) name as someone who could remove subjects from the study; there is no onsite registered nurse. He noted that an individual other than the PI should be able to remove subjects from the study if there is an adverse reaction. Dr. Galbraith recommended that "PI" should be changed to "PI or authorized member from research team." He also reemphasized that diabetes should be removed as an exclusion criterion, or it should be clarified that diabetes should be excluded only "if it interferes in ability to perform the duties."

Dr. Philpott-Jones offered several suggestions to the Board in his capacity as a consultant. In the past, he has warned that protocols should not say, "there is little incremental risk associated with the study." That statement was included in this protocol because the investigators decided that the test materials have low toxicity and that exposures are likely higher during normal residential/commercial activity. This is an intentional-scripted study, however, so any BIT exposure would not exist outside of the study; all of the risk is associated with the study, so no statement about incremental risk should be made.

Dr. Philpott-Jones also clarified the definition of "good health." This study has specific exclusion criteria, including immunologic suppression and severe diabetes, which requires investigators to ask invasive questions about medical history. The intention-to-participate script should mention the use of invasive questions because there might be a participant who comes to the enrollment research site and realizes only then that these questions about medical history will be asked. As it stands, the invitation to participate only states that subjects will be asked questions concerning general health. It is necessary to be explicit because it might affect potential research participants' willingness to undergo the enrollment process.

Dr. Dawson noted that a number of the exclusion criteria are not necessary, and she suggested that they be revisited. Dr. Galbraith agreed that the ability to do 3 hours of painting should be required, but wondered if exposure to painting would exacerbate medical conditions. Dr. Ramos said that it is not possible to exclude that possibility. Any chemical exposure could lead to an adverse response.

Dr. Philpott-Jones said that he does not yet believe that the requirements of §26.1125 are met. He reminded the Board that, after the study is completed, it comes back to the HSRB for review. If the Spanish-language translations are not submitted to the HSRB and the study proceeds, it is possible that significant ethical issues might arise when the completed study comes back to the Board, and the data might be unusable.

Dr. Heitman provided a summary statement. She remarked that the Board recommends that the protocol submitted for review be modified in accordance with Agency and HSRB recommendations on ventilation, final approval from the IRB, necessary modifications to language in the final consent document, and exclusion criteria changes to the protocol. With these changes, the protocol is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L.

The Board members approved the summary statement.

Session 3: A New Protocol from the AEATF-II Describing Proposed Research to Measure the Removal Efficiency of 1,2-Benzisothiazol-3(2H)-one (Known as BIT) from Hand Surfaces Using an Isopropyl Alcohol/Water Wipe-and-Wash Procedure

Background

Dr. Parkin asked Mr. Leighton to provide the Agency's review of the study protocol.

EPA Science Assessment

In starting his presentation, Mr. Leighton stated that the JRC had not examined the protocol for removing BIT from hand surfaces because it was the final of three submitted. It is the first hand-wash removal efficiency study submitted to the Board and to EPA. The study deals with intentional exposure to latex paint or to isopropyl alcohol (IPA) spiked with BIT applied to a subject's hands with the goal of assessing removal efficiency. The need for a hand wipe/wash removal efficiency study was identified through a SAP discussion and literature search, and the fact that the topic is not in EPA's guidelines.

Mr. Leighton reviewed the protocol details. The study will use a gauze sponge soaked with a 50/50 IPA and distilled water solution, and the hands will be rinsed with the same solution while the subjects rub their hands together. The study will involve 20 subjects placed into four groups of five per group, each group equaling 10 samples because the left and right hands are assessed separately. The volume will be 500 µL for paint per palm and 100 µL for IPA per palm. The treatment solution concentrations will be for paint 120 and 600 ppm BIT, and for IPA 1 to 4 mg BIT/mL. The palm surface area treated will be approximately 50 cm^2, and there will be two loading rates: 1.6 and 7.8 $\mu g/cm^2$. Subjects will prewash their hands with soap and dry them. The solutions applied to subjects using a glass capillary tube will be allowed to dry for 45 minutes before being wiped and washed off. As for the toxicity of the test materials, Mr. Leighton described the studies EPA has available, such as a 90-day dermal rat study, and noted that the subjects' maximum potential dose will be 0.0098 mg/kg/day.

EPA lacks a test guideline for the protocol, but to ensure compliance with scientific standards, this will be a GLP-approved study. Moreover, the recommendations of a 2000 study by Brouwer et al. were used as a guide to review the wipe/wash efficiency protocol. Mr. Leighton described specific protocol elements derived from Brouwer et al., such as the sample size of 10 palms per study group. He noted that there had been some thought that the brush study should precede the wipe/wash study to determine the loading amount, but EPA chose to conduct the wipe/wash study first. EPA is proposing 45 minutes as the residence time for the exposure, but that might not be long enough and perhaps should be 2 hours or longer. The method of contamination is different in the control study than it will be in the actual exposure study. The study will ensure good video recordings so that future researchers will be able to see the vigor with which a subject's hands are scrubbed.

In a summary of EPA's conclusions, Mr. Leighton stated that the protocol is likely to yield scientifically reliable information to fill an identified scientific and regulatory need that cannot be obtained except through a human study, pursuing a clear scientific objective with an adequate study design. The scientific objective is to obtain a removal efficiency correction factor.

Board Questions of Clarification—Science

Dr. Heitman asked Mr. Leighton to elaborate on the capillary tube used to spread the material. He responded that the paint will be pipetted onto the hand as a glob and will need to be spread over the skin. Dr. Heitman stated that she could envision a subject's hand being scratched

by the glass tube. Mr. Leighton said that he would make a note to ask the researchers about that issue.

Dr. Young stated that on page 23 of EPA's review document, there is a discussion of linear regressions used in generating calibration curves. She asked if EPA anticipates that proportionality will hold. Mr. Leighton responded that the section addressed only the mass spectrometer analysis. Dr. Young asked if it had been determined which statistical methods will be used. Dr. Cohen responded that EPA is proposing to calculate the CI for mean percentage removal efficiency for all four groups.

Dr. Maddalena asked why the protocol ruled out nitrile gloves with cotton over them as the receptor because the study focus is how much paint comes in contact with the skin, not absorption. Mr. Leighton responded that in 2007, the SAP had discussed the possibility that cotton gloves might act as sponge to hold paint. Dr. Maddalena asked if that would be a conservative approach. Mr. Leighton responded that the SAP discussion led to a decision that hand washing, not gloves, should be used.

Dr. Gbur asked if, when fitting the calibration curve for the covered percentage, EPA was assuming normality. Mr. Leighton responded that the question should be asked of the research chemists from the task force. Dr. Gbur asked if EPA was saying that the two measurements taken for each of a subject's hands will be treated as two independent measurements. Mr. Leighton responded affirmatively.

Dr. Maddalena asked about the decision to not include a blank; with IPA, a blank could be used. EPA cannot obtain paint without BIT. With IPA, what is removed cannot be seen, so variability in the technician's performance can occur. If some material is on each hand, that almost creates a double-blind situation. The study could be improved by including a blank. Mr. Leighton responded that this could be done with IPA, but not with paint.

Dr. Parkin asked that the study sponsors, Ms. Megan Boatwright and Mr. Testman, to come forward to answer Board members' questions.

Dr. Popendorf asked how much experience the sponsors had with the protocol in terms of loading people with paint or IPA. Ms. Boatwright responded that they had no experience with paint, but had conducted removal efficiency studies with didecyl dimethyl ammonium chloride (DDAC). Dr. Popendorf asked if subjects were expected to keep their hands flat, open and horizontal. Ms. Boatwright stated that they would sit holding their palms up. They will be seated at a conference table and will be provided cushioning for comfort, as well as television and other measures to enhance the subjects' comfort.

Dr. Gbur asked if, when fitting the calibration curve, the sponsors will assume that errors are normally distributed, as is typically done when fitting straight lines. Mr. Testman responded that the calibration curve in the protocol is referring to standards for analytical instrumentation, a linear response. Liquid chromatography-mass spectrometry (LCMS) instruments are linear. Dr. Gbur said that he had the impression that the sponsors were assuming the subjects' two hands were independent and asked why the data were not paired because data from one hand

likely are correlated with data from the other hand. Mr. Testman responded that it was a good point; the sponsors were treating the hands as independent.

Mr. Leighton asked the sponsors to clarify how the glass tubes would be used to spread paint on the subjects' palms. Mr. Testman explained that the entire capillary tube, not just the tip, would be used. Sealed capillary tubes with a smooth end are also being considered.

Dr. Maddalena noted that chunks of paint and material will be in the wash and asked if the ethanol extraction would be effective in removing compounds from the dried paint. Mr. Testman responded that removal was very efficient (more than 80 percent).

EPA Ethics Review

Ms. Sherman noted that the same comments applied to the protocol before the IRB issued a conditional review. OPP decided to ask the sponsors to ensure that EPA receives a final copy for approval before moving forward. The risks are less than in the previous study; there is no heat-related risk, just risk of skin reactions and risk related to the pregnancy testing.

Board Questions of Clarification—Ethics

Dr. Maddalena asked if the MSDS for the paints would not be provided to the subjects unless they ask for them. Ms. Sherman responded that part of the protocol is to provide both the label and the MSDS. Dr. Philpott-Jones commented that it is somewhat confusing because the protocol says two things: that both will be provided and that they will be provided upon request.

Public Comments

Mr. Downing announced that there were no requests for public comments. No public comments were given.

Charge Questions

Ms. Sherman read the charge questions:

If the proposed AEATF-II hand-wash removal efficiency study proposal is revised as suggested in EPA's review and the research is performed as described:

Charge to the Board—Science:

- Is this research likely to generate scientifically reliable data, useful for determining the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint and non-paint liquid solutions containing BIT?

Charge to the Board—Ethics:

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

Board Science Assessment

Dr. Parkin asked Dr. Ritter to provide his review. Dr. Ritter stated that the short answer is "yes"; the extent to which the information will be reliable will depend on a few discussion questions, which he reviewed briefly. He stated that EPA's review provides some justification with regard to BIT loading in IPA and paint of up to 600 ppm. The question is how relevant those concentrations will be for future studies. He noted that Dr. Kissel had raised a question about the effective concentration rate and the answer is unknown, so the relevance remains an open question. It is appropriate for this particular study, but the intent is to go further. BIT is already present in paint, so it does not require study at all.

Mr. Leighton responded that BIT is not added to all paint, but it is in the resins and other components mixed with the paint. The minimum is 120 ppm, with 600 ppm on the label as the maximum.

Dr. Ritter responded that those numbers are justified, but it is unknown if they are applicable in future studies. There are also questions with regard to whether the washing technique makes practical sense, such as having the two hands washed separately. The larger question pertains to the surface area. Dr. Maddalena's suggestion made an important point with regard to the applicability of the methodology of using cotton gloves as possibly more representative of the hand washing for a typical application. Although cotton might represent overexposure, the methodology might represent a worst-case scenario. Mr. Leighton noted that for the hands, the PHED study showed totals of 180, with 175 attributed to the hands. Dr. Ritter responded that the result is not atypical. The hands are always the majority of exposure, and if that were eliminated, exposure would be eliminated. The fact raises a question with regard to broken skin, which is almost impossible to avoid. He asked why broken skin would be excluded if it is typical for such exposures. Mr. Leighton responded that the MSDS instructs that gloves be worn with broken skin.

Ms. Sherman added that it comes down to ethics. With more absorption, a subject is more likely to have a skin reaction with cuts on the hands. The exclusion is meant to keep subjects comfortable. Dr. Ritter added that the situation depends on the exclusion criteria, and noted there are elaborate criteria pertaining to what broken skin means. He concluded that the wipe/wash study must be done and properly interpreted before being applied to other studies.

Dr. Kissel made several points. He stated that it was already conceded that the palm is not like the rest of the hand. The palm comes clean first, but the fingernails and folds of knuckles can take days to become clean, so testing only the palms is picking the part that is easiest to wash off and creates a high recovery result, which is not what researchers want to do in a recovery study. The active ingredient level in the PHED study was 1 percent, so with 10,000 ppm, that meant a skin loading of about 10 $\mu g/cm^2$. Now, EPA is assuming that if a material is used with an active

ingredient level that is 100-fold lower, there will still be 10 µg/cm^2 on the skin, which is extraordinarily unlikely. The design here is lower than the PHED number, but the PHED number is massively larger than the load that will end up on the skin as a result of the actual painting activity in the earlier protocol.

For two reasons—"cherry picking" the palm and the enormously higher wash load than the painting protocol—the wipe/wash protocol will lead to an overestimated recovery level. If nothing is seen on subjects' hands, it might lead to the conclusion that there is no exposure and total recovery has occurred, when in fact only 5 percent of what is on the skin has been recovered using the protocols. There is once again the percent-absorbed problem. The number is 40 percent at 72 hours, and a smaller number at 4 hours, but the larger total from which the percentage is drawn is unknown. Dr. Kissel noted that rat studies only recover a fraction of a test compound, ignoring what is absorbed in the skin and thereby underestimating the availability of a compound to the rat. Mr. Leighton responded that the rat study included what was in the skin, but Dr. Kissel pointed to page 8 of the EPA review document to make his point. The skin will act like a sponge.

Dr. Young noted that there are a number of design issues to be considered. The first is whether treating the hands separately produces observations that count as one observation or not. The reason the two hands are being treated separately is to double the observations. As Dr. Gbur pointed out, however, the hands are unlikely to be independent, which is an assumption. That assumption would have to be checked, and if it turned out they are not independent, EPA would have to decide what to do. Design study revisions could be made to address the question without making the assumption.

Dr. Young noted that although the document states that no hypothesis is explicitly stated, pages 20 and 21 of the EPA review provide a comparison of efficiencies with an implied hypothesis to be tested. EPA could place BIT on one hand and IPA on the other to test if the results are different. EPA would want the IPA-versus-BIT comparison to be made. Dr. Young said that she could not replicate the results of the sample size calculations found on page 21. As a general recommendation for studies, Dr. Young stated that it is very dangerous to propose a study when the statistical methods that will be used are unknown. It would be helpful to define the methods in advance because sometimes after data are generated it is unclear what to do with them. Unless the method is known, the study design is incomplete.

Dr. Gbur asked whether broken skin is determined by the subject or by inspection. It is a reason to exclude a subject, so he wanted to know when it would be done. Dr. Philpott-Jones commented that there is an inspection. Dr. Gbur asked what would happen when people are excluded, and in response Ms. Sherman noted that there are several alternates.

Dr. Popendorf concurred with Dr. Kissel on the loading issue. He was concerned that what stays on the skin is called adsorption, compared with what goes through the skin. He agreed that 88 percent in 72 hours is either through or on the skin. The circumstances of the loading of the paint are very important. The average hand is 6×8 cm, so if 2 cm are taken off, the result is approximately 6×4, 24 cm at the edge. If 500 µL of paint is put on a 25-cm^2 area, there will be a 2-mm layer of paint, which is far above what someone would even accidentally put or leave on

their hand. So there are some practical issues. Whatever level of loading occurs, the portion that is not capable of migrating through molecular diffusion to the skin will come off with whatever is used to remove it, not necessarily IPA. Dr. Popendorf noted that he had placed 500 µL of paint on his hand for 1 hour, and he found it uncomfortable to keep his hand open for that period of time. It is a huge level of loading that is unrealistic and the result is not applicable to painters in general, who will not leave 2 mm of paint on their skin for 45 minutes.

Looking at the dosing and retention data further, Dr. Popendorf said that it appears that if the data are plotted out, the skin retention is very linear in terms of percent per hour over a range from 4 to 72 hours, but the adsorption part is first-order kinetic. It is exponential, so the difference between 45 minutes and 4 hours is fourfold. That result needs to be first put into a thin layer. EPA should model the data to determine what they indicate about the results as a function of time, using a time-weighted average because not all of the dose will occur in the beginning. It will be spread out, so an integration can be done to assume consistent loading onto the skin. Concepts can be incorporated in the study design that will produce consistent results. EPA's test is scientifically reproducible, but it is not relevant to the question of how much BIT would be retained and therefore recovered from the skin.

Mr. Leighton offered some clarifications for issues the Board members should include in their report. He suggested a little more discussion on the residence time and how much exposure occurs over time, as discussed by Dr. Popendorf, versus the issue of ethically how long people can be kept sitting with the paint on their hand being uncomfortable. For the painting study, the task force will want to retain the double hand wash; that would turn the study into two hands, so half the samples would be lost. He suggested some discussion on how many samples would be needed; for example, instead of testing 20 people, would 40 be preferable? There is an ethical question of how many people should participate in the study compared with what level of data it will produce. The issue of whether the paint should be spread on the palm versus all over the hands needs further comment. Finally, until the study is complete, EPA will not know what the loading is for painters, but the Agency wants to conduct the study first, so any additional suggestions would be welcome.

Dr. Popendorf commented that if two hands are tested simultaneously, flexing will not be an issue; however, the person will be incapacitated for 45 minutes, which presents personal issues that need consideration. Dr. Kissel added that if thinner layers are applied the paint will dry faster than 45 minutes. Dr. Popendorf noted that some time will be needed to allow the paint to absorb.

Mr. Leighton responded that EPA had anticipated many of the discussion points. Because the Agency lacks guidance on the issue, EPA is looking for the Board's thoughts in the written discussion. The process must move forward.

Dr. Ritter summarized what he described as a broad discussion. Most of the concerns focused on what will be measured, how much paint to apply, how much is typical or a good model and other issues. He said that the Board must put the questions in its report. The Board's endorsement of the study is subject to the additions based on the recommendations and questions being asked, which are essential to achieve a scientifically valid study.

Dr. Parkin asked Dr. Ritter if the modified study would generate scientifically reliable and useful data, and he responded affirmatively, provided the questions and recommendations are addressed. Dr. Parkin asked if the Board was ready to agree. Dr. Ramos asked if Dr. Ritter's statement was that the Board has no solutions, only questions; if that was the case, the motion did not quite carry too clearly. Dr. Ritter responded that the Board does have solutions to offer. Dr. Ramos added that if EPA's decision is to use the paired approach, care should be taken because the palm of the hand's thickness will differ depending on the hand's dominance. If both sides of the hand are involved, absorption will differ on the sides, so it is not as simple as Dr. Young had implied, biologically speaking. Dr. Young responded that she had omitted mentioning that EPA would have to randomize which hands are exposed, for dominant versus nondominant hands.

Mr. Leighton stated that he hoped the Board's report will discuss comparing one hand to the other versus implementing two hand washes together, the approach taken in the actual study. What EPA really wants to know is the removal efficiency of paint. EPA would like to see the comparison with IPA, but for the IPA the Agency will not have to test additional subjects in the future if a researcher uses BIT for another exposure study. If the subjects are doubled to 40, however, that is a lot of people sitting for a long time. He urged the Board to comment on what would be gained from having that many people participate.

Dr. Young asked if the Board's role is to discuss the value of the test. Her main concern is with the issue of whether the test employs a good design, but the value of the test is a broader question. Dr. Parkin stated that the Board should stay focused on the charge question as its primary responsibility.

Dr. Popendorf added that he was trying to clearly understand the recommendation. The assumption is that based on what the Board concludes through its discussions, the members are trying to solve the problem through its limitations, committing to the fact that the study will be valuable if it is modified according to the Board's suggestions. Dr. Parkin commented that part of the concern is how much of the redesign the Board should provide as opposed to documenting the issues for EPA to resolve. Dr. Popendorf said that he would be comfortable if the Board statement was modified to state that EPA should address the issues the Board has raised. Dr. Ritter emphasized that it is important that the Board's recommendations in the report will indicate what should be addressed.

Mr. Jordan stated that he appreciated that collectively the HSRB was grappling with trying to answer some difficult scientific questions with regard to the best methodology to use for the study. He asked the Board to offer its best suggestions on all of the issues identified so that EPA can move ahead in working with the task force to create a protocol that is expected to generate reliable, useful data. There will be no guarantee how the data come out, and the Board will have an opportunity to review the results. If the Board leaves decisions up to the Agency, it is likely to do a poorer job of trying to interpret the Board's thinking. A less desirable alternative would be for EPA to work with the task force based on the Board's report and to bring the protocol back for discussion, but that approach would create extra work for the Board members and delay the research. He requested that using all of the Board's conversations the members

provide as much guidance as possible for what EPA should do regarding the amount applied, treating the hands independently or together, whether to apply materials to the palm or back of the hands and so forth.

Dr. Parkin responded that she appreciated Mr. Jordan's comments. Traditionally, the Board's final reports have been geared toward consensus statements, and in writing its report, that will be the aim; however, if there is a minority view, that will be documented. She noted her concerns that consensus will be difficult. She called for a vote on the statement: "If modified accordingly to address issues raised, the HSRB feels that the study will generate scientifically reliable and useful data." Dr. Maddalena suggested that the statement is acceptable if issues are addressed properly.

Dr. Parkin took the vote, which was all ayes. She moved the meeting forward to the ethics discussion.

Board Ethics Assessment

Dr. Philpott-Jones stated that his recommendation as a consultant to the Board was the following: There is a huge caveat about whether the study can be designed to address the question in a way that is both scientifically valid and actually answers the questions being asked. Assuming that is the case, he recommended that—while not currently in compliance with 40 CFR part 26, subparts K and L, and specifically §26.1125, because it lacks final approval from the IRB—if the protocol is modified in accordance with EPA's recommendations and those that he and his colleagues will likely make, the study would likely meet the applicable 40 CFR requirements. In the interest of time, Dr. Philpott-Jones reiterated that most of everything he stated previously applies in this case with respect to risk, informed consent documents, never saying that a study does not pose incremental risk and so forth. He cited characteristics of studies, such as whether the risks to the participants are commensurate with benefits to participants or society or whether there are no benefits to participants but benefits to society.

Dr. Philpott-Jones cited six risks associated with study participation: (1) allergic reaction or sensitivity to the test material, (2) allergic reaction or sensitivity to the latex paint, (3) allergic reaction or sensitivity to the IPA, (4) injury that could occur from application of the test material using a glass capillary tube, (5) irritation from rubbing the skin during the hand washing, and (6) the psychological stress from breach of confidentiality for pregnancy test results. The risks are largely minimized through the choice of test material, the exclusion and inclusion criteria, how the pregnancy test results are handled and other elements.

Regarding a point raised during the scientific discussion, there is likely to be discomfort to participants during the paint drying process; that is not a large concern, but it should be discussed. Because the study risks are minimal or only slightly above, he did not see a significant issue with raising the number of participants from 20 to 40, provided the study results are useful. It is a statistical not an ethical issue.

One surprising issue, which may be a carryover from the brush/roller study, is the exclusion of participants who have various conditions, such as severe respiratory disorders,

cardiovascular disease, severe diabetes and immunologic suppression. Dr. Philpott-Jones stated that those issues may not be applicable in this case given the burdens of the study. He suggested that EPA and the study sponsors consider why the exclusion criteria are necessary. In the script and enrollment, somewhat invasive questions will be asked about a person's health status and medical history. Standard concerns about vulnerable populations have been addressed. Monetary compensation is not a significant issue, but the lack of a Spanish-language version of the recruitment materials for the Board to review raises concerns. The materials do not have to be brought back to the HSRB, but EPA and the sponsors should consider how they will review the materials. If the HSRB does not review the materials, the Board will see them in the completed study and that might produce a conclusion that the study was conducted unethically. Good health is another question. He noted that investigators had not completed the human studies protection course within 3 years and strongly suggested a review and up-to-date training.

Dr. Heitman made two additional points. She had raised the question of injury from capillary tubes and the possibility of leg, shoulder and back cramps from sitting in a chair. The issues should be disclosed as part of the discussion of what the protocol will involve. People do become extremely impatient sitting. She suggested showing the participants a television show about painting safety. She echoed the comment that a study should not be done without a statistical plan in place, which is critical in figuring out how many participants should be in the study. It becomes unethical to conduct an underpowered study that puts people at risk for no purpose.

Dr. Parkin asked for a summary statement. Dr. Philpott-Jones recommended that the Board conclude the study be submitted for review if all of the appropriate documents are submitted to EPA and the IRB and approval is obtained; in addition, if the materials are modified according to the EPA and HSRB recommendations, then the study is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L.

Dr. Parkin asked if there was any discussion around the summary statement, and there was none, so she called for a vote. There were only ayes, so the statement was accepted.

Mr. Downing adjourned the meeting at 6:12 p.m.

Wednesday, April 9, 2014

Commencement of Public Meeting and Review of Administrative Procedures

Mr. Downing convened the meeting at 9:30 a.m. and welcomed Board members, EPA colleagues and members of the public. On behalf of the Agency, he thanked the Board members for their time and diligent work in preparing for the meeting deliberations. Mr. Downing also expressed appreciation to his EPA colleagues for their efforts in preparing for the meeting.

Mr. Downing noted that in his role as the DFO, he serves as a liaison between the Board and EPA and is responsible for ensuring that all FACA requirements are met regarding the operation of the HSRB. The DFO must work with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied regarding conflicts of interest. HSRB members have

been briefed on federal conflict of interest laws and have completed a standard government financial disclosure report. In consultation with the deputy ethics officer for OSA and OGC, Mr. Downing has reviewed the reports to ensure that all ethics requirements are met.

Mr. Downing informed the members that are several interesting and challenging topics on the agenda for the meeting. He advised them that the agenda times are approximate; although the discussion may not keep to the exact times on the agenda, he will strive to ensure adequate time for Agency presentations. Mr. Downing encouraged all speakers, including Board members and members of the public, to use their microphone and identify themselves before speaking, as the meeting is being recorded and broadcast on the Internet.

Copies of the meeting materials, supporting documents and public comments will be available at http://www.regulations.gov under docket number EPA–HQ–ORD–2014–0189 and are available on the HSRB website at http://www.epa.gov/osa/hsrb. Following the presentations, time has been scheduled for questions of clarification to EPA staff and the principal investigator and sponsors of the studies discussed. This time is to be used for points of clarification, rather than Board discussion. Clarifications on information presented could be requested during the meeting through the HSRB Chair or Mr. Downing. A public comment period will be offered, and remarks must be limited to 5 minutes. No members of the public had preregistered to make a public comment for the topics under consideration.

In accordance with FACA, 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 HSRB also will prepare a final report in response to questions posed by the Agency that will include the Board's review and analysis of materials presented. The final report will be available at http://www.regulations.gov and on the HSRB website at http://www.epa.gov/osa/hsrb. Mr. Downing turned the meeting over to the HSRB Chair, Dr. Parkin.

Introduction and Identification of Board Members

Dr. Parkin thanked Mr. Downing for the welcoming remarks and asked Board members to introduce themselves. The HSRB members completed their introductions. Mr. Downing asked for any conference line participants to introduce themselves. Dr. Parkin then asked Mr. Jordan to provide a follow-up to the previous day's Board activities.

Follow-up on the Previous Day's Discussion

Mr. Jordan introduced himself and his EPA colleagues. He noted that the EPA team held follow-up conversations following the previous day's meeting and earlier today to address several details. Mr. Jordan remarked that there were no follow-up issues to raise with the Board at this point. He commented that the previous day's session reminded him how much he enjoys listening to smart individuals closely examine EPA's work, and he appreciates the improvements that will come as a result of the useful advice. He said that he was looking forward to another helpful session. Mr. Jordan expressed appreciation to the Board members for their hard work preparing for these sessions.

Session 1: A New Protocol from the U.S. Department of Agriculture (USDA) Describing Proposed Research to Determine the Bite-Protection Level of Repellent-Treated Clothing for the United States Military

Background

Dr. Parkin introduced the USDA study and asked Ms. Sherman and Mr. Kevin Sweeney (OPP) to present the Agency's review of the scientific aspects of this study.

Ms. Sherman provided background on the protocol because it is very different than previous HSRB studies reviewed. She thanked Dr. Kendra Lawrence (General Dynamics) for joining the discussion and expressed appreciation to the Board members for their advice.

Ms. Sherman explained that the protocol is designed to test the repellent efficacy of fabric in military uniforms containing 1 percent etofenprox. Much information exists about the importance of protecting soldiers overseas against vector-borne diseases. Currently, uniforms are treated with permethrin and soldiers apply topical sprays to reduce mosquito bites. The current trend is to treat the materials with etofenprox. The regulatory situation is slightly different for this protocol because the research will be conducted by the USDA. USDA is a signatory to the Common Rule, and studies that are funded or conducted by an agency signed to the Common Rule do not require a protocol review before conducting the research. Before EPA can rely on the study in informing a registration decision, however, the completed study must be reviewed by the HSRB. In this case, USDA and other groups involved decided that it would be prudent to bring one protocol example to the HSRB for additional guidance before initiating the study to ensure that the Board's standards will be met when the study is completed. The protocol being reviewed represents a potentially large set of studies.

The study director, Dr. Ulrich Bernier (USDA), will be directing the research that ultimately will be used to satisfy EPA registration requirements. The goal is to use the protocol and subsequent study to standardize the experimental approach to evaluating the efficacy of repellent-treated textiles (e.g., tents, sleeping bags, clothes). The sponsor is testing the hypothesis that etofenprox treatment provides bite protection when mosquitoes are exposed to treated fabric compared to an untreated control. Etofenprox is an EPA-registered pesticide recommended by the World Health Organization (WHO) for use in public health vector-control programs, both directly by spraying infested areas and indirectly by treating fabrics, such as mosquito nets.

Ms. Sherman noted several key differences with previous studies reviewed by the HSRB. This is a laboratory study; previous studies were conducted in the field. The repellent effect of the pesticide is different. Skin-applied repellents provide an instantaneous, nontoxic repellent effect; in this situation, mosquitoes make contact and the effect is toxic. The efficacy measures are different. This study examines bite protection, and the measurement is blood-fed mosquitoes. Previous measures of efficacy included "landing with intent to bite" and the time of complete protection. One important difference is that subjects in this study will be receiving mosquito bites.

Mr. Sweeney showed a video that demonstrated the procedures used in study, which also are outlined on page 30 of the USDA Protocol. As described in the protocol, the first step involves harvesting 175 unfed mosquitoes from a cage by placing a hand over the edge of a cylinder to draw in mosquitoes that are likely to bite. After 175 mosquitoes are collected, they are transferred to a test cage. The sleeves treated with etofenprox are prepared. Gloves are placed on the hands so that the only exposed area is part of the forearm with a sleeve. The sleeve fits tightly to the arm, and both arms are used in the test.

All sleeves, including the treated and untreated samples, are stored in labeled plastic bags. During the test, the sleeves are fit to each arm and the area between the gloved hand and sleeve is taped. The subject then places his or her arms into the test cage for 15 minutes of exposure to mosquitoes. The hand is placed so that mosquitoes have access to bite the top and bottom of the sleeve. Research technicians are present to assist throughout the process. The untreated sleeves receive the most bites, and treated sleeves expect very few bites. At the end of 15 minutes, the subject removes his or her arms after knocking off the mosquitoes. The treated and untreated sleeves are removed and returned to the marked bags.

Data sheets are associated with each cage. The technician harvests all mosquitoes (those flying and knocked down) from the cage with an aspirator or similar device. Any active mosquitoes are then knocked down with carbon dioxide (CO_2), and the container is emptied. Mosquitoes are sorted and counted according to whether they are blood fed or not through a visual examination. That information is transferred to the data sheet associated with the sample. Mr. Sweeney explained that blood-fed mosquitoes are very obvious to identify visually. Mosquitoes identified as unfed will be aspirated out of the pan and a secondary check will be performed to determine if any blood had been taken. This procedure involves spreading and crushing the mosquitoes on a paper towel under a fume hood. Any fed mosquitoes will be identified through the presence of blood on the paper towels. All of the results are recorded.

EPA Science Assessment

Dr. Parkin asked Mr. Sweeney to present the Agency's review of the scientific aspects of this study. Mr. Sweeney reiterated that the video outlined the procedures described in the protocol. He commented that the protocol was well prepared; his recommendations include points of clarification for several details. When the final protocol is amended and the study conducted, the expectations are clear regarding the type of data collected and the purpose. EPA worked with the USDA on this protocol and has worked with the Department of Defense (DOD) in the past. The Agency is interested in seeing the protocol go forward to encourage a more standardized approach to these evaluations, especially for clothing treated with pesticides. The military needs to compare uniform types and vendors, and standardized procedures can be used for EPA registration decisions as well. Employing similar processes each time will ensure high-quality data.

Mr. Sweeney explained that the study is designed to determine the bite-protection level of etofenprox-treated U.S. Military Flame-Resistant Army Combat Uniforms (FRACUs), treated initially at an application rate of 1 percent, and to assess the bite-protection performance after 0, 20 and 50 washes. The results of this research will allow for determination of whether

etofenprox-treated FRACUs meet DOD specifications for minimum bite-protection level. The research has societal value because U.S. military personnel serving domestically and abroad are at risk of contracting insect-transmitted diseases. The data also will provide value through the improved ability to register products, such as military clothing, with EPA.

The bite-protection specifications are based on current military standards, which specify 85-percent bite protection for 0 washes, 80 percent for 20 washes and 70 percent for 50 washes. Etofenprox is minimally irritating to the skin and eyes and is not a skin sensitizer. Assuming a 70-kg subject, the equivalent dose rate is 9.08 mg/kg. The MOE is 231, which is higher than EPA's level of concern at 100.

Mr. Sweeney informed the HSRB members that the sleeves used by Dr. Bernier in the study fit tightly against the arm. The treated fabric has not been evaluated for skin irritation. A previously conducted 28-day dermal toxicity study in rabbits showed some skin irritation. The etofenprox registrant, Mitsui Chemicals, will soon be conducting a product-specific 28-day dermal toxicity study in rabbits with etofenprox-treated fabric. Mr. Sweeney stated that the toxicity study will be conducted before the efficacy study is initiated, and the Agency will review the toxicity study before it approves the efficacy study. Irritation from the fabric is not expected, but the rabbit study will ensure that no subjects are exposed to that risk.

Mr. Sweeney reviewed the experimental design testing paradigm for the protocol. There will be four test sets, and both arms of the subjects will be used to test coat and trouser material. Mr. Sweeney clarified that in DOD parlance, "coat" refers to shirts and blouses, and "trousers" refers to pants. The first test set will be the untreated and unwashed control; the second test set will be the treated and 50-times washed; the third test set will be the treated and 20-times washed; and the fourth set will be the treated and unwashed fabric. This design was purposefully precautionary to ensure that no residues on arms transfer between the test sets. The etofenprox, however, is tightly bound in material and no transfer is expected.

Mr. Sweeney continued, explaining that eight subjects will be included for each fabric and treatment condition. Two mosquito species will be tested, yielding a total of 16 replicates for each fabric type. The test cages contain 175–225 female mosquitoes (only females bite). As described in the video, female mosquitoes will be preselected from stock cages by using a specially designed draw box that uses odors from the hand of a laboratory staff member to attract mosquitoes upwind into a trap.

The unit of measure for determining the repellent effects is percent bite protection. The presence of blood in the mosquito's abdomen will confirm a bite. The bite-protection success will be based on differences in treatments and controls; each subject will serve as his or her own treatment and control. Mr. Sweeney noted that mosquito knockdown and mortality will not be assessed in the study. The percent blood-fed mosquitoes in the untreated control treatment after the test interval and the percent blood-fed in the etofenprox treatment after the test interval will be used to calculate the percent bite protection according to the formula

$$\frac{1 - (\text{treatment rate})}{(\text{control rate})} \times 100$$

The treatment and control rates refer to the calculations based on treated or untreated fabric, respectively.

Concerning the statistical analysis plan, the objective of the study is to estimate the mean level of bite protection and associated 95 percent CIs for different "treatments" (i.e., different combinations of fabric types [coats and trousers], number of washes and mosquito species). Previous HSRB meetings discussed the sample size, power and reliability of data, all of which affect the number of replications needed. Mr. Sweeney presented a table depicting the impact of the number of replications on the number of subjects to determine bite protection of treated fabric. The expected half-width of the 95 percent CI changes as the number of subjects increases, with a narrower interval and higher bite-through rates for the control fabric. The question is how many subjects are needed to run the test. Based on these data, eight subjects will provide a 1.6 percent half-width of the 95 percent CI for percent bite protection. The proposed sample size of 8 subjects represents a reasonable compromise between decreasing CI width and limiting unnecessary human experimentation.

Regarding data analysis, the numbers of blood-fed and total female mosquitoes found with treated and control fabric for each subject will be analyzed as binomial distributed data in a generalized linear model using a log link. Mr. Sweeney noted that a tremendous amount of details supporting the analysis of the study are included in USDA Volume 3–Statistical Methods prepared by Dr. Robert Sielken.

To ensure reliability, SOPs established under GLP requirements will be in place. The subjects' attractiveness to mosquitoes will be determined prior to testing. Laboratory technicians will assist subjects with placing the test sleeves on their arms and excluding all exposed skin from mosquito exposure. Laboratory technicians will assist subjects with insertion and removal of their arms in and from the cages.

Regarding compliance with scientific standards, Mr. Sweeney asserted that the study adequately addresses the available toxicity studies with etofenprox. The available toxicity studies adequately characterize the toxicological profile of the formulation, except for dermal irritation from intermediate exposures to treated fabric, which will be assessed in the supporting study. The available toxicity studies with etofenprox support the estimate of acceptable MOE. Several other elements of the experimental design and statistical analysis are generally acceptable but require refinement and clarification.

Mr. Sweeney presented EPA's science comments and recommendations. EPA recommends that a product-specific 28-day dermal-toxicity study in rabbits with etofenprox-treated fabric be conducted, and that the proposed efficacy study not be conducted until the results of the product-specific dermal-toxicity study have been submitted to and reviewed by the Agency. EPA also recommends that the study sponsor provide justification for testing two vector mosquito species instead of three and consider recruiting more than two alternate subjects. The statistical plan for analyzing the data will need to take into account how alternate subjects will be handled.

Mr. Sweeney recommended that the study sponsor add more details to the protocol about what will happen if a subject withdraws midway through the study and an alternate is brought into the study as a replacement. For example, will an alternate who replaces an original subject complete all eight pairs of sleeves, or only the pairs of sleeves that were not completed by the original subject? The subjects and alternates need to be randomly selected from a larger pool of qualified potential subjects, and screening should continue until at least 20 qualified potential subjects have been identified. Then, eight subjects and two or more alternates should be randomly selected from the pool of qualified potential subjects. EPA recommends that the study sponsor address the distribution of male and female subjects and discuss if this will impact the results due to differences, if any, in attractiveness to mosquitoes. Also, the protocol should be revised to specify exactly what will happen if there is unequal distribution or if only one gender is represented. The statistical analysis used to analyze the study data should be justified in the final report, which should include a description of how the data will be analyzed if the number of test subjects at the end of the test is less than eight.

Mr. Sweeney circulated the FRACU fabric that will be used in the study.

Board Questions of Clarification—Science

Dr. Parkin asked Board members if they required any clarifications. Dr. Young questioned why the MEs increased in concentration throughout the study. Mr. Sweeney explained that the scenario starts with the lowest dose of etofenprox to reduce the chance of any chemical transferring from the sleeve to the subject's arm and affecting the test results. He acknowledged that it is not a problem to increase the concentration of the MEs over time as long as etofenprox is determined to not be a skin irritant.

In response to another question from Dr. Young, Mr. Sweeney clarified that the investigators continue to pull mosquitoes from the same stock cage until the stock is exhausted.

Drs. Ritter and Gbur asked about the difference in fabric between the coats and trousers. Mr. Sweeney acknowledged that the fabric is not different, but military specifications require testing both coat and trouser material. Etofenprox will be added at 1 percent weight to weight, and the fabric weights are not substantially different.

Dr. Philpott-Jones expressed concern about the sequence of the testing paradigm. He accepted that the compound is tightly bound to the fabric, and not much compound is expected to transfer. He noted, however, that if the treatment was a failure, the subjects would be provided with no protection. By doing the reverse sequence, the individuals would be exposed to a high risk of bites without clear justification. He asked whether the concerns of carryover on the skin outweighed concern of reverse dose escalation. Mr. Sweeney acknowledged his point.

Dr. Philpott-Jones asked about the existing data available for permethrin, and Mr. Sweeney explained that a large data set exists. Given that, Dr. Philpott-Jones asked if the justification for human subjects is met, because the researchers could use a membrane protocol to compare permethrin to etofenprox treated fabrics.

Dr. Heitman commented that the DOD lists 34 sizes of uniforms, and the size of recruited subjects will vary tremendously. She asked whether a variety of sleeve sizes will be provided or if obese participants will be excluded.

Dr. Kissel requested clarification on the testing protocol. Mr. Sweeney responded affirmatively that each of the eight subjects will perform the test with both mosquito species. The protocol is estimated to last for 4 hours. Dr. Kissel also expressed concern about the dose orientation.

In response to a question from Dr. Ramos, Mr. Sweeney clarified that his presentation referenced the current standards of bite protection for military uniforms. The study will determine the bite protection afforded by etofenprox. Dr. Ramos asked if the washing of the uniforms was standardized and reflected the way uniforms are washed in the military. Mr. Sweeney replied that the wash method is described in the appendices and is a standard method for washing fabrics according to textile manufacturers, which might be different than how the military washes fabric. Dr. Ramos noted that the spreading of mosquitoes across the paper towel was not standardized. Mr. Sweeney commented that it is clearly evident which mosquitoes have taken blood, and there is no risk of losing data.

In response to a question from Dr. Popendorf, Mr. Sweeney noted that the bite-protection specification represents the mean of the group and does not include the CI.

Dr. Fernandez asked how the optimal number of mosquitoes was determined for this study. Mr. Sweeney explained that the number is based on USDA experiments treating materials with permethrin. The number will ensure biting pressure throughout the test without exhausting the mosquitoes present. It is important to select aggressive mosquitoes that want to bite.

Dr. Young asked about the association between gender and the propensity to be bitten, including any genetic components. Mr. Sweeney said that Dr. Bernier will address the question.

Dr. Heitman expressed concern about diet restrictions for the subjects, as many people believe that garlic might prevent mosquito bites. Mr. Sweeney acknowledged the point and agreed that it might be worthwhile to explore the addition of diet restrictions to the tobacco restrictions already in place.

Dr. Parkin invited the study sponsor, Dr. Bernier, to respond to several of the HSRB members' questions. Regarding the justification for running the study from the highest amount of biting to the lowest, Dr. Bernier noted that dose escalation has been used historically to control for cross-contamination. Approximately 2,000 females are present in each stock cage, and typically 95–100 percent of mosquitoes respond each time they are drawn from the cage. Controls are used for each cage, and when 5 percent of males are drawn from the stock cage when it is nearing depletion, the stock cage is replaced.

Dr. Young reiterated her concern that the most aggressive mosquitoes will be drawn in the first pass and less aggressive mosquitoes will be drawn as the cage is depleted. Dr. Bernier

stated that the 15 minutes of time is enough to allow all active mosquitoes to bite, and he has identified no discernable differences in the level of response as the cage is depleted.

Regarding the reverse-dose escalation, Dr. Philpott-Jones accepted that the study is designed to standardize testing a variety of fabrics. He expressed remaining concerns about the possibility of etofenprox application to fabric failure, which inadvertently exposes subjects to the risk of bites. He suggested employing a series of controls to demonstrate that the unwashed fabric is effective at repelling bites. Dr. Bernier remarked that failure treatment would be determined early in the study. Experiments conducted on the treated fabric prior to the study will ensure that the treatment process worked. Dr. Bernier commented that air permeability determines the bite deterrent of the fabric. Most FRACUs provide close to 100-percent bite protection. The tests are performed to determine if chemical treatment is done at an optimized level to guide the fabric treaters and ensure an optimal surface concentration of etofenprox on the material.

In response to a question from Dr. Gbur, Dr. Sielken explained that the proposed method of analysis includes a generalized linear model using the same subject. He noted another point regarding assessing the controls first: If a subject does drop out of the study, the subject will have completed the control.

Dr. Gbur noted that washed fabric deteriorates, which might confound the results. Dr. Bernier acknowledged a small loss of fabric integrity from washing, but it provides a slight protective benefit from mechanical shrinkage up to 5 percent. Although there might be less active compound on the material, higher efficacy will result from the shrinkage. Dr. Gbur commented that wear and tear might offset some shrinkage.

Dr. Sielken noted that the advantage of Dr. Bernier's previous conduct of studies with permethrin is the opportunity to use bite-through analyses from earlier studies to help design this study. Earlier studies (2006–2007) showed a difference between coat and trouser fabric that reflected differences in the fabric weights. Uniforms have evolved, however; now there is no difference in the fabric weight, but the original military specifications still require testing of both. Dr. Bernier added that the coats and trousers are analyzed separately because the placement of seams and pockets can affect the treatment process.

Dr. Ramos requested clarification for how mosquito attractiveness is measured and controlled in the experiments. Dr. Bernier explained that research in the 1990s identified that compounds emitted from the skin of some individuals can attract mosquitoes, and the differences can be measured in the laboratory. He noted that 15 minutes of time is sufficient for even the least attractive subjects to interest mosquitoes and draw bites. The aggressive population of females provides added assurance of biting.

Dr. Bernier commented that using membrane-system socks as surrogates to human subjects provides a poor correlation between experiments and the real-world response. The best approximation is conducting experiments with disease-free mosquitoes in an optimization study using human subjects.

In response to a question from Dr. Ramos, Dr. Bernier clarified that if a subject must be withdrawn (e.g., because of bite sensitivity), another control will be run and the experimental conditions will be repeated. Eight subjects will complete all test sleeves.

Dr. Ramos requested a rationale for the selection of the vectors. Dr. Bernier explained that the species *Aedes aegypt* and *Anopheles albimanus* were selected because malaria (transmitted by *Anopheles*), yellow fever and dengue fever (both transmitted by *Aedes*) are the top diseases spread by mosquito vectors that affect military personnel. Dr. Ramos agreed that it was a solid rationale.

Dr. Philpott-Jones asked why the *Culex* mosquitoes were not included in the study. Dr. Bernier explained that *Culex* mosquitoes are not as responsive to humans as the other species and provide less useful information. He noted that results from the other two optimal species are expected to transfer easily to *Culex*. Dr. Sielken added that earlier permethrin data demonstrated very similar responses in the control rates and bite protection levels for both species.

In response to a question about the size of the sleeves, Dr. Bernier explained that single-ply sections are excised from treated uniforms. He clarified that the sleeves can be adjusted, but those with large forearms will be excluded from the study.

Dr. Popendorf questioned the low control rate indicated by the video and asked if there was a minimum bite rate allowed for the controls. Dr. Bernier acknowledged that a lower control bite-through rate will yield a higher error. The test is invalid with impermeable fabric. Dr. Sielken noted a 20–70 percent control bite-through rate in the permethrin data.

Dr. Philpott-Jones requested clarification regarding the attractiveness of a participant to mosquitoes and the sequence of events. Dr. Bernier remarked that a lack of bites is the first indication that a subject is unattractive. Three technicians operate in the 15-minute assessment time window to analyze the data from the test set prior to conducting the next test. This enables a determination of whether the number of blood-fed mosquitoes is adequate for the participant to continue the study. The time window is designed to catch all biological biting events. Dr. Bernier stated that he could add a delay to the control test to ensure attractiveness before initiating the next test phase.

Dr. Philpott-Jones asked about the determination of biting pressure that is too high and requires halting the test. Dr. Bernier clarified that the subject will be removed from the study if he or she is uncomfortable with the number of bites.

Dr. Lawrence addressed the issue of the membrane versus the human subject experimental models based on her extensive experience with membrane-feeding studies. Typically, membrane studies are used to screen compounds before products are developed. The membrane system involves blood-filled wells covered with a membrane and CO_2 to attract mosquitoes. It is an effective screening tool. In terms of evaluating bite-through of uniforms or topical repellents, however, it is important to recognize that the studies must address biters of humans; membrane-feeding systems are very artificial. From a public health perspective, it is not helpful to extrapolate from a membrane-bound to human model. Even animal models cannot

adequately mimic the 400 compounds that attract human-biting mosquitoes. Dr. Lawrence emphasized that when the Agency is interested in registering products used to protect public health, the goal is to reduce the transmission of disease, and the human model best addresses that need.

Dr. Philpott-Jones appreciated the point. He questioned whether the goal of the study was to compare etofenprox to permethrin. If that was the case, a model could be employed to compare existing human data on permethrin to determine if etofenprox was equivalent. Dr. Lawrence explained that permethrin is the only compound currently registered in the United States for treatment on clothing. A 2014 meta-analysis confirmed permethrin resistance in Africa and supported the need to develop permethrin alternatives to protect the U.S. military and civilians. It is important to evaluate new products against existing military standards, and the study will enable EPA to evaluate new chemistries in the future. An additional societal benefit is that other government employees—such as U.S. Forest Service staff—could wear treated uniforms.

Dr. Heitman questioned whether latex was an important component of protection or if nitrile gloves could be substituted. Dr. Bernier clarified that nitrile gloves could be used as a barrier, but latex sensitivity is an exclusion criteria.

Dr. Gbur asked Dr. Lawrence whether membrane studies could be performed with new compounds compared to permethrin to ensure success. Dr. Lawrence noted that etofenprox is an EPA-registered compound and has a lower toxicity profile than permethrin, which makes it a good candidate. Dr. Gbur relayed concern about the study ethics. Membrane studies might allay some fears.

Dr. Dawson asked whether past laboratory exposure scenarios could be used to predict how clothing will perform in a real setting (e.g., in reducing the incidence of malaria) to add value to future studies. Dr. Bernier reiterated that the intent of the study was to optimize the treatment of the fabric. Several unpublished studies address field-worn Army uniforms, but no rigorous study exists that correlates bite protection in the laboratory to a field setting. Future studies will be designed to test the relationship. Dr. Sielken added that current permethrin data indicate high amounts of subject-subject variability that would make the membrane studies hard to be predictive.

In response to a question from Dr. Kissel, Dr. Bernier clarified that etofenprox provides the same protection against both species of mosquito. The mosquitoes are at least 5 days old and, in the study director's experience, respond throughout the day. With regard to the randomization of species, the arms will be washed in between. Dr. Bernier said that he would clarify that point in the protocol.

EPA Ethics Assessment

Dr. Parkin asked Ms. Sherman to provide the Agency's review of the ethics.

Ms. Sherman explained that EPA's review concluded that the study would generate data of enough value to warrant human subject use. Subjects will be recruited from the general public through printed advertisements placed in a newspaper and posted on bulletin boards across the University of Florida campus. Ms. Sherman opined that the student population is likely to be comparable with soldiers because of the slightly younger university demographics. Callers will be informed about the study using an IRB-approved script to determine eligibility. An informed consent meeting with the study director will be scheduled to describe the purpose of the study, explain procedures, and show the video. Potential subjects will be told that they will receive mosquito bites and the number of bites expected. The study director will answer any questions and indicate the procedures in place to protect the subjects. A nurse will be available on site. The subjects will be told that they are free to withdraw at any time. If the participant is still interested, the study director will confirm his or her understanding and ask the subject to sign an informed consent.

Ms. Sherman remarked that the inclusion and exclusion criteria are complete and appropriate. Only subjects who can speak and read English will be recruited. Pregnant women are excluded, and the subjects must be ages 18–62 years. The study will recruit individuals in good health. Subjects who are afraid of or sensitive to mosquito bites—determined during the initial phone call—will be excluded, as will individuals with a latex sensitivity. Employees or any individuals with a relationship to the study director and sponsor will be excluded. Ms. Sherman noted that the protocol does not seek to recruit vulnerable subjects, but that is always a possibility.

Ms. Sherman identified four categories of risk, and she asserted that the protocol did provide appropriate measures to reduce the risk. The risks include exposure to biting mosquitoes and associated discomfort, potential for disease transmission, exposure to the test material, and breach of privacy through pregnancy testing. Subjects are told to inform the study director or nurse if they experience a skin reaction, and hydrocortisone cream will be available. The nurse is familiar with the protocol and will be available to help. Ms. Sherman referred to Mr. Sweeney's discussion of the dermal sensitization study that will be reviewed by EPA before the exposure study is approved. Subjects sensitive to pesticides or subjects with cuts/scrapes/skin conditions on their forearms will be excluded. All of these measures will reduce the risk of exposure to the test material. Good precautions are in place to protect privacy during the pregnancy test. Ms. Sherman commented on the need to clarify who will be responsible for confirming the negative pregnancy tests.

Ms. Sherman noted that the study will provide no direct benefit to subjects; the primary direct beneficiary is the sponsor, as well as military personnel who wear uniforms treated with etofenprox. The consent form indicates the lack of direct benefits to subjects. Ms. Sherman concluded that the risks have been minimized effectively and are reasonable in light of the expected societal benefits of the knowledge likely to be gained.

With regard to respect for subjects, effective methods will protect the subjects' privacy, including the provision of a study ID number. Pregnancy results will not be recorded. The proposed level of compensation is appropriate. Subjects will be free to withdraw at any time, and medical care for research-related injuries will be provided at no cost to the subjects.

Ms. Sherman confirmed that the independent Western Institutional Review Board (WIRB) had reviewed and approved the protocol and informed consent materials.

Ms. Sherman described several revisions requested by EPA before the proposed research proceeds. She requested minor revisions to the protocol and consent form, including an explanation of the process for inspection of the subjects' hands and arms, a resolution of the inconsistency about which member of the research team will verify the pregnancy test results, a clarification that there are no benefits to the subjects, an exclusion for people sensitive to pesticides or chemical products, and an exclusion for cuts, scrapes and skin conditions on the hands or forearms. She also mentioned the need for additional detail about what triggers an exclusion and who makes that decision.

Ms. Sherman concluded that the protocol is in compliance with all ethical standards, including the requirements of §26.1111, §26.1116, §26.1117, §26.1125 and §26.1203. She noted that if EPA's and HSRB's requested corrections are made, research conducted according to this protocol will likely meet the applicable requirements of 40 CFR part 26, subparts K and L. Ms. Sherman emphasized that this protocol review is not required by the regulations, which only require a review of the completed study. The protocol is being reviewed out of additional caution.

Board Questions of Clarification—Ethics

Dr. Parkin solicited questions for EPA and the study sponsor. Dr. Philpott-Jones requested clarification regarding the final version of the consent form. Ms. Sherman explained that the final version begins on page 195 in the review, and is stamped with an approval date of March 4, 2014.

Dr. Heitman commented that several exclusion criteria were not stated explicitly in the script or consent form. Ms. Sherman agreed that all of the materials should be consistent.

Dr. Ramos suggested specifying the length of time allowed for post-exposure medical attention at no cost. Ms. Sherman acknowledged that the language indicated that a subject should contact the study director or nurse if he or she becomes ill after participating in the study, but no time period is specified.

Dr. Lawrence requested clarification concerning how the subjects' confidentiality will be protected. The protocol does not specify how the records are kept (e.g., locked in a drawer) or how long they are retained after the conclusion of the study. Ms. Sherman agreed that it was a good suggestion.

Dr. Philpott-Jones noted that the financial compensation appeared to be $25 for each test set. He asked how much the subjects would be paid if they were excluded by the study director. Dr. Bernier clarified that the subjects would be paid up to the point that they were excluded. Dr. Philpott-Jones asked who determines the research-related injury: "If illness or injury is a direct result of being in the study." Dr. Bernier explained that the endpoint was inflammation resulting from mosquito bites, and he said that the team would consider how to address

Dr. Philpott-Jones' point. Dr. Philpott-Jones expressed appreciation for the vector test. He expressed concern over the lack of a notification plan if the test is positive. Dr. Bernier stated that a positive vector test is a virtual impossibility, but he will add a notification plan to the protocol.

In response to Dr. Heitman's question about the availability of the nurse, Dr. Bernier clarified that the nurse will be on call 0.5 miles away and not physically present.

Dr. Lawrence noted that the protocol specifies showing the video upon consenting individuals' request. She suggested that the video should be shown automatically as part of the consenting process to improve retention.

Public Comments

Dr. Parkin called for public comments. Mr. Downing noted that there were no preregistered public commenters; however, the HSRB had received a written comment from Captain Dr. Gregory Beavers in advance of the meeting that professed general support for this type of research. The letter had been shared with all HSRB members prior to the meeting.

Charge Questions

Ms. Sherman read the charge questions into the record:

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

- Is the protocol "Laboratory Evaluation of Bite Protection from Repellent-Impregnated Clothing for the United States Military" likely to generate scientifically reliable data, useful for estimating the level of mosquito bite protection provided by two different textiles treated with etofenprox?

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

Board Science Assessment

Dr. Parkin asked Dr. Kissel to address the first charge question. Dr. Kissel commented that the study generally seems to address a significant public health issue (i.e., risk of disease from mosquito bites) in a logical way to determine if treated uniforms are effective against mosquito bites. He expressed concern over several protocol, dermal toxicity and statistical design issues. Dr. Kissel noted that some individuals could experience 500 or more mosquito bites during the testing day, which seems unpleasant. This might increase the dropout rate. Given that the ideal outcome is for eight or more people to complete the whole scenario, he suggested recruiting many more than eight subjects.

Regarding the issues of potential carryover between test sleeves, Dr. Kissel agreed that it made sense to go from low to high doses. One issue is the high dose of the first species will precede the low dose of the second species, but washing in between was suggested. He commented that implicit in the design is that clothing can be washed without removing the etofenprox; thus, the need for washing arms is not apparent. Dr. Kissel noted that the ramifications of the presence of urine metabolites of etofenprox, similar to the urine metabolites of permethrin, are unclear as this might indicate the presence of the compound in the skin.

Dr. Kissel continued, indicating that if the trouser and coat material is the same, performing both sets of studies might not be justified on the basis of "that's the way the military does it," which is not the best scientific rationale. He commented that regarding toxicity issues, the MOE presented in the oral review was different than that contained in the document that was received and reviewed in advance. Dr. Kissel allowed, however, that the MOE is protective because it is based on 100 percent of the chemical in the fabric being absorbed, which is very conservative. Dr. Kissel expressed skepticism of traditional dermal-toxicity protocols and commented that the dermal toxicity of etofenprox is not known.

Dr. Kissel referred to a sentence in the EPA review document that indicated a low dermal availability of 7 percent but did not specify a unit to lend context. He requested additional details in the review. Dr. Kissel agreed with EPA's insistence on conducting the fabric-irritancy study prior to the exposure study.

Dr. Ritter added several points. He emphasized the concern about the similar coat and trouser fabric and the possibility for a smaller sample size. He asked whether the fabric was selected consistently from the same or variable locations in the uniform. Ms. Melynda Perry (U.S. Army) explained that typically uniforms for percent bite-protection testing are sampled from the side and back panels of the garment. She commented that seams are avoided when possible. Dr. Ritter noted that the variable site selection might impact the outcome of the study. Ms. Perry replied that typically USDA can cut the sleeves in a single layer to avoid seams.

In response to a question from Dr. Young, Ms. Perry indicated that the sleeves are labeled according to their origin from one of three test garments. Dr. Bernier added that the eight individuals test identical sleeves generated from the same treatment process.

Dr. Ritter asked about the size of the sleeve. Ms. Perry explained that the Army uses a specific size template to excise the material from the uniform, and USDA further trims the sleeve. Dr. Ritter expressed concern about the tight-fitting sleeves. He also mentioned that more robust individuals might have a different attraction to mosquitoes. Dr. Bernier acknowledged the possibility of a sleeve that is too tight for a particular subject. He said that it would be possible to re-sew the sleeve if needed. Dr. Bernier shared that he has not yet experienced a situation where a subject could not fit into the sleeve.

Dr. Ritter noted that washing the fabric is an important aspect for determining the efficiency criteria. He asked Ms. Perry if the washing protocol is relevant to the way that Army uniforms typically are washed. He said that he was satisfied that the fabric will be washed uniformly. Ms. Perry explained that the fabric will be washed using home laundry procedure.

The detergent and temperature will be controlled, and the soap is a standardized detergent similar to what can be bought in a grocery store. Ms. Perry said that worst-case conditions (e.g., hot water) will be used to wash the fabric. Dr. Bernier added that other studies are evaluating factors related to the standardized washing procedure, but the current washing standard is the best available.

Dr. Ritter referred to Dr. Kissel's concern with the dermal-toxicity studies. He acknowledged that the 28-day dermal-toxicity study will be completed before the exposure study begins. Given that uniforms are worn over a long period of time, however, Dr. Ritter asked whether 28 days was a relevant length of time. Mr. Sweeney commented that there had been much discussion about the length of the toxicity study. At this point, based on past studies of animal models with dermal application, any irritation is seen by 28 days. Twenty-eight days is a standard time.

Dr. Young expressed concerns about the protocol design. She agreed that both coat and trousers might not be necessary. Another concern was the repeated drawing from the stock cage, because the most aggressive mosquitoes will be drawn first and exposed to the unwashed control fabric, which will generate the highest bite rate. The results could be interpreted as a function of the aggressiveness of the mosquitoes, not the protection of the material. Dr. Young indicated that this is a strong argument that supports the need for an early control in case a subject is excluded from the study.

Dr. Young said that she was less worried about the excision of samples from various locations on the same garment than between garments. She noted that using the same garment on all subjects will not capture garment-garment variability, and she encouraged further consideration about the garment assignments.

Dr. Young acknowledged the challenging study design, and she commended those involved in developing a robust document to facilitate discussion and lead to a strong study. She applauded EPA for trying to incorporate randomness into the studies and expressed a preference for randomizing the treatments for each arm. Dr. Young advocated for performing a restricted randomization to ensure inclusion of subjects of each gender in each test group. Regarding the carryover effect between treatments, she opined that allowing randomization of the treatment sequence without impairing a subject's attractiveness to mosquitoes would be very beneficial. If the subjects drop out of the study, it would be alright to treat the data as random. Overall, Dr. Young concluded that it was a nicely done protocol.

Dr. Parkin solicited comments from the HSRB members.

Dr. Popendorf noted that page 13 of USDA Volume 1—Protocol indicates that fabric items *can* be identical composition and weight, which might mean that the items are not *always* identical. The fabric flaps and pockets affect the treatment process. With regard to the seaming issue, Dr. Popendorf suggested using fabric from the bolt before it is made into uniforms. Ms. Perry replied that in the factory setting, coats and trousers are treated separately and there are differences in the application method. The military treats uniforms, not bolts of fabric.

In response to a question from Dr. Ramos, Ms. Perry indicated that three garments are validated post-treatment using the bite protection assay.

To address Dr. Young's concern about selecting more aggressive mosquitoes first, Dr. Lawson suggested an alternative design to incorporate untreated controls for each test sleeve. This would double the amount of sleeves and increase the burden on participants. Another alternative is to have each subject tested with just one mosquito species. A proper control for each subject is imperative, recognizing the variability between humans. Dr. Lawson said that it was not unreasonable to perform a human subjects study of this type, but less burden on the participants would make it more appealing.

Dr. Bernier agreed that half of the participants could be exposed to *Aedes* and half to *Anopheles.* He clarified that the mosquitoes should be viewed as binary: are they responding appropriately at this time, or not? The first mosquitoes pulled are not always the most aggressive. The assumption is that if they come through the trap, they will be aggressive; this has not been a problem in Dr. Bernier's 15 years of experience. Dr. Bernier also mentioned the assumption that the treated fabric has passed the Army's quality-control processes to ensure the bite-protection standards are met. The FRACUs are the most permeable uniform, which makes them difficult to test. Dr. Bernier clarified that if a subject drops out, the replacement participant will complete all of the tests.

Dr. Kissel provided a summary statement. The protocol is likely to generate reliable and efficacious data, but some improvements in design related to sequencing and the numbers of participants in each sleeve should be considered.

Dr. Parkin solicited any discussion concerning the summary statement. Hearing none, she asked all those in agreement to say "aye." The statement was accepted unanimously by the Board.

Board Ethics Assessment

Dr. Parkin asked Dr. Heitman to address the second charge question. Dr. Heitman began by asserting that the protocol submitted for review is likely to meet applicable requirements of 40 CFR part 26, subparts K and L. She commented that several questions based on scientific questions need to be resolved. The protocol, especially with regard to the IRB review of the documents, was appropriate. Dr. Heitman asserted that Ms. Sherman's presentation was appropriate, and she concurred with EPA's recommendations with regard to the acceptable risk-benefit ratio and equitable inclusion criteria. There are no benefits to the participants, but the risks will change on the basis of the answers to the scientific charge question. Dr. Heitman remarked that the range of sleeve sizes available might affect exposure and introduce the risk of embarrassment or psychological discomfort if a subject cannot fit into the sleeve. She suggested excluding individuals by asking what size shirt they wear during the screening procedures. Dr. Heitman noted that the range of potential subjects who respond to the advertisements might be broad, and the sleeve must fit equally well for men and women.

Dr. Heitman remarked that the question of latex gloves needs to be addressed. The question is in the survey, but not stated in the script or consent documents. She suggested offering nitrile gloves to those with latex allergies. Also, the fact that the nurse will not be physically present needs to be made clear. It is not a problem that the nurse is 0.5 miles away. Regarding individual reactions to mosquito bites, Dr. Heitman referred to the "minor discomfort" mentioned in the survey. She suggested that the need to sit still for 15 minutes might be a discomfort for some individuals and that should be added to the materials.

With regard to informed voluntary consent, Dr. Heitman acknowledged that all recruited participants must be able to read and write. She asserted that showing the video as part of the consent process will clarify the procedure. The monetary compensation is not high enough to induce people to participate, but one question arose during the previous day's meeting regarding the potential tax liabilities and confidentiality concerns if social security numbers are recorded.

Dr. Heitman remarked that the study selection appeared equitable, but she questioned whether the Gainesville, Florida population was representative. The protocol does not seek to recruit members of vulnerable populations, but there might be some there. Dr. Heitman suggested clarifying that it is not a benefit of the study to receive compensation for one's time.

Dr. Philpott-Jones remarked that as a consultant, all of his opinions are suggestions to the Board. He agreed with all of Dr. Heitman's comments and added a few points. Related to the compensation issue, he expressed concern when subjects are excluded after partially completing the study due to a factor beyond their control, such as attractiveness to mosquitoes. Dr. Philpott-Jones suggested that subjects deserve full compensation in those cases. He also strongly encouraged the informed consent to be revised from "compensation for injury" to "research-related risk" and to clarify the vague language determining whether injury or illness is a direct result of the study.

Dr. Philpott-Jones applauded the study director and sponsor for ensuring protections from arthropod-borne illnesses. He noted that the possibility of a positive result requires a plan for notifying the subjects that must be included in the protocol. Dr. Philpott-Jones also raised the need for an objective measurement to determine when the biting pressure becomes too high for a subject's safety or comfort. A subject's complaints are subjective, and many individuals do not feel bites. A strict objective rule should be included, and the protocol design should allow sufficient time between each phase to ensure that the biting pressure is not exceeded.

Dr. Philpott-Jones raised concerns about the sequence of sleeve use. He reiterated that treatment failure of uniforms might expose subjects to high levels of risk in testing a material that does not work. He suggested including one or two additional subjects to test the repellency effectiveness of the unwashed uniforms.

Dr. Philpott-Jones commented that studies like this protocol are needed to evaluate novel ways to protect military and civilian populations from mosquitoes. He was convinced of the need for human subjects by what was said during the conversation. Dr. Philpott-Jones suggested that the sponsors provide additional justification to the Agency by elaborating on the need for human

subjects. Also, the sponsors should consider that the availability of more data and sufficient models might preclude the need for human testing.

Dr. Parkin solicited additional discussion points.

Dr. Ramos reiterated the suggestion to define the length of time for medical follow-up to protect the subjects as well as the study sponsors.

Dr. Dawson supported Dr. Philpott-Jones' request to better justify the need for human subjects in the protocol. These studies are necessary to establish appropriate procedures to treat clothing, and there is a public health justification because the military needs to protect its personnel.

Dr. Galbraith noted that the sponsors might want to recommend that subjects bring music or videos to keep their minds occupied during the exposure testing, especially if an objective measurement for biting pressure is included.

Dr. Lawrence opined that the risk from vector-borne diseases was overstated in the materials. Laboratory colonies of mosquitoes possess a negligible risk. She suggested that the vector test is not necessary. Ms. Sherman asked if that part of the consent form should be removed. Dr. Dawson agreed that if there is no evidence of risk, that information should not be included in the consent form. In human-subjects research, it is important to identify all risks; at the same time, the risks should be based on a solid scientific foundation. Dr. Heitman commented that it might be useful to include a description of the fact that laboratory-raised mosquitoes pose negligible risk. Dr. Galbraith supported leaving the language in the consent form because the risk of exposure and the mitigation steps are identified to indicate that subjects will not be at risk of vector-borne diseases. Dr. Popendorf countered that if the risk does not exist, it should not be included. Dr. Philpott-Jones noted that diseases such as West Nile are well known and it would be acceptable to indicate that there is no risk of acquiring a mosquito-borne illness in this case because of the reasons described. Dr. Dawson agreed with Dr. Philpott-Jones' suggestion to leave the language in the consent form to reassure subjects that there is no risk. She suggested removing several sentences related to testing and indicate that the mosquitoes have been raised in a laboratory without a chance to acquire disease.

Dr. Heitman read the summary statement into the record: Considering the recommended scientific modifications, if the protocol is modified with EPA's and the HSRB's ethical recommendations, it is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L.

Dr. Parkin asked if the HSRB members were in agreement with the summary statement, and there was no dissent.

Session 2: Background Presentation on the Repellency Awareness Graphic and Possible Implications for the HSRB

Dr. Parkin asked Ms. Rose Kyprianou and Ms. Sherman to introduce themselves and begin the presentation to the Board.

Presentation

Ms. Sherman set the stage for the presentation, explaining why the session topic was of interest to OPP. The program has reviewed quite a few insect repellent studies for both mosquitoes and ticks. During those reviews, questions have arisen about how EPA uses the data and what information is conveyed on the labels. As part of a side project examining repellent labels, EPA worked with consumer focus groups to understand their views about the product labels—asking, for example, if the labels were understandable and sufficiently informative and what might be done to improve the labels. A key point the focus groups made was that the labels were not conveying information about the duration of a repellent's effectiveness. Such information is important for knowing when to reapply a product and could lead consumers to select different products based on the expected effectiveness duration.

Ms. Kyprianou presented PowerPoint slides providing an overview of the Repellency Awareness Graphic, noting that OPP welcomed recommendations that the HSRB members might offer to help make the project a success. The project is a voluntary effort EPA initiated to encourage the use of a standardized graphic for skin-applied repellents. The graphic will indicate the hours of repellency for mosquitoes and/or ticks and is similar in concept to the SPF (Sun Protection Factor) for sunscreens. EPA has spent years developing the necessary background information. Over the last few years, the Agency has refined the Repellency Awareness Graphic and developed guidance to accompany it, explaining how to apply for the graphic, how to use it and so forth. During the years developing the project, EPA spoke with stakeholders and the general public to solicit feedback. Although not yet in use, the graphic will be available in three versions communicating the repellency hours for ticks, mosquitoes and both combined.

At this point, the Repellency Awareness Graphic will be for skin-applied products only. It will be part of the approved registration and labeling for products, requiring companies to use a new or amended registration application. Before registering, preferably companies would review the guidance to help determine if they possess the appropriate data or need additional studies for their products. Data will need to satisfy certain quality requirements, either following the current test guidelines or an equivalent standard. OPP would like to see multiple studies informing a product's label claims. For ticks, OPP is asking for studies of three representative test species; for mosquitoes, two field studies. As in the past, OPP's data analyses will use the median to calculate a product's protection time. OPP also has developed other criteria to determine the number shown on the graphic, including, for example, how to handle rounding the number and the minimal complete protection time (CPT) required to use the graphic.

Ms. Kyprianou stated that OPP regards the Repellency Awareness Graphic as important. The program wants to promote the graphic's usage to help public health protection by improving consumers' knowledge about how to protect themselves against vector-borne diseases such as

West Nile virus and Lyme disease. The graph provides rigor and consistency for both the data generation and analysis. OPP hopes the graphic increases both EPA's and consumers' confidence in labelling claims and enhances public health information and pesticide product labeling.

Ms. Sherman explained why OPP is talking to the HSRB about the Repellency Awareness Graphic. As noted by Ms. Kyprianou, companies that have products currently registered already have studies they are relying on for product efficacy determinations. Some might qualify for using the graphic based on their current data; others, however, might have data that is very old and does not meet current testing requirements. OPP anticipates that some companies will want to test a large number of products to qualify for the graphic. Because companies will find it desirable to have the graphic on their labels, it will provide a carrot to encourage updated product testing. If that occurs, OPP foresees a large number of human studies requiring review.

EPA has heard comments from product registrants and laboratories interested in streamlining the review approach through EPA developing a standardized protocol that the HSRB would approve. Generally, EPA is open to exploring ways to streamline the process. A company could, for example, have eight products to test. In the past, when reviewing products, each study was reviewed separately. A protocol could, however, lay out procedures for testing multiple products that could be reviewed simultaneously in a manner similar to task force studies for agricultural handlers involving various surrogate products from which selections could be made for testing. If criteria were met, research could be done under standardized protocols from laboratories, with a review of product safety for subjects. OPP wanted to bring the issue to the board for any input Board members might want EPA to consider as the Agency moves forward. At future meetings, examples of protocols could be put forward, so OPP is seeking input now.

Board Questions of Clarification

Dr. Parkin noted that the public comment period for the Repellency Awareness Graphic had ended on March 6, 2014. Ms. Sherman responded affirmatively, adding that Ms. Kyprianou and others were reviewing the comments and OPP expects to start receiving protocols shortly. OPP is actively encouraging interested companies to talk to EPA about next steps and measures to make the graphic a reality.

Dr. Parkin asked if OPP anticipated trying to have the labeling in place by next summer or 2016. Ms. Kyprianou responded that, based on discussions with people close to the industry, it would be possible to move quickly and label products by 2015. It is more likely, however, that more labeling will occur in 2016.

Dr. Parkin asked if OPP already has set criteria for judging whether data are sufficient. Ms. Kyprianou responded affirmatively, noting that the criteria were published in November 2013 for public comment. Dr. Parkin stated that the HSRB had not yet seen the criteria. The Board could review the criteria in time for 2015, but reviewing a standard protocol for multiple products would take longer. She added that she was attempting to get an understanding of the timing of the workload that the HSRB would face in reviewing new or existing data.

Ms. Sherman responded that it is uncertain; OPP is waiting to hear about the research plans from companies.

Dr. Dawson asked how much incentive companies have to adopt the graphic, especially if doing so involves new studies. She wondered if incentives might be bolstered if a number of companies participated with existing data to create pressure in the marketplace. She asked how many products would meet the criteria based on existing data and whether that might jump-start the process. Ms. Kyprianou responded that not a large number of products meet all of the criteria, although there are some. Some companies might be waiting to "lay out their cards" because the comment period ended a month ago. The vast majority of products have some data missing. Newer products might have some but not all of the tick species required. It is likely companies would want the combined graphic with both the tick and mosquito numbers.

Dr. Philpott-Jones noted that he had served on the HSRB since 2006 and reviewed many insect-repellent labeling studies. The studies have improved, but many concerns are brought to the Board for prospective review of study design, sample size and other issues. He expressed concern that the graphic might lock EPA into accepting a set of studies that might not be that good; that would remove the incentive for companies to improve the type of data they collect because OPP is giving its stamp of approval for studies that it deems good enough to say a repellent protects for up to 4 hours.

Dr. Green asked for clarification of Ms. Kyprianou's slide stating that the Agency may have to deal with multiple datasets. Ms. Kyprianou explained that more than one study site or test species dataset will inform the ultimate message on a label. For example, for ticks, OPP is asking for three tick species, each with its own dataset producing a CPT median number. OPP has made a determination for how to generate the number that will appear on a repellent label.

Dr. Gbur commented that OPP had not revealed to the Board its thinking on how it would deal with those issues. He asked what the status was of that discussion. Given some of the statistics questions that had been asked, he found it interesting that OPP wants to combine multiple studies. Ms. Kyprianou clarified that OPP is not combining different studies and averaging across them, but instead is taking the individual study with the lowest median CPT as the worst-case scenario to add conservatism to the number. OPP's guidance issued for public comment in November 2013 was the result of 2 years of public engagements with stakeholder groups and EPA's SAP. Criteria adopted in the guidance received SAP review and are available for anyone to see. For the HSRB, OPP intended an overview rather than a highly detailed presentation.

Dr. Gbur responded that Ms. Kyprianou's explanation satisfied his interest in knowing that the graphic had gone through an advisory panel, so at least some people outside of the HSRB had reviewed the project from an advisory perspective.

Dr. Fernandez asked about the presentation of information on a product's shelf life or expiration dates. Ms. Kyprianou responded that she was not sure how companies deal with that aspect of the labeling. She does not work directly with the registration of repellents.

Dr. Parkin suggested that EPA consider the sequence of bringing work to the Board. For example, if OPP wants the Board to focus first on the use of existing datasets, those questions would presumably be brought to the HSRB fairly soon; however, if EPA has questions about a generic protocol for different types of products, that would take more effort to package materials and bring them to the Board. Ms. Sherman responded that OPP was more interested in teeing up the possibility of standardized protocols to test a large number of products in the future. Decisions about whether a dataset meets qualifications to construct a graphic will be made within EPA. The Board's approval for specific studies may allow a company to qualify for the graphic, with a focus on research. OPP's goal was to introduce the protocol in the event that many studies are submitted to the Agency. It would be too much for the HSRB to review, for example, 20 different repellent studies at a single meeting. EPA is striving for lean processes to achieve the same benefits more efficiently.

Dr. Parkin commented that the Board has approved protocols in the past, but whether it would do so for the graphics project remains uncertain. The issue would have to come forward generically, and the Board would have to discuss the science and ethical issues before deciding whether the HSRB is the appropriate domain for approval. She said that she looked forward to seeing what OPP presents. There were no additional comments from the Board.

Session 3: Report from the HSRB Work Group on the Return of Individual Research Results

Dr. Parkin initiated the session by noting that the issue of the return of individual research results emerged over a period of years. Board members made up the work group that developed the report now being presented to the full Board for discussion and decisions about next steps.

HSRB Work Group on the Return of Individual Research Results Report

Dr. Philpott-Jones stated that the issue surfaced in approximately 2009–2010 when he was the HSRB chair and Dr. Parkin was the vice-chair. The study sponsor contacted him regarding the question of returning individual research results and then brought forth the study protocol with a letter to participants to inform them of their individual exposure results. At that meeting, a number of concerns were raised about the letter and its format. Broader questions were also raised concerning when it would be appropriate for study sponsors to return individual results to study participants. EPA charged the HSRB with looking at the question.

The issue is particularly timely and unresolved, even within the research ethics and bioethics community. Most of the discussion in the scientific literature about the return of individual results, as opposed to aggregate findings, relates to clinical research that falls into the categories of either genetic testing studies, especially genome-wide association studies (GWAS), or other studies that might include clinically relevant incidental findings. For example, if research involved functional magnetic resonance imaging (MRIs) of the brain and a participant had an abnormality but no symptoms, the question arises: What is the responsibility of the investigator to release the results to the participant?

Within the clinical context, there are both ethical and legal obligations for physicians and other providers to inform their patients about the results of individual diagnostic tests. Such results have a direct benefit to the patient and an effect on their clinical treatment. In the research realm, the issue becomes more complicated because the researcher is not always a physician, so there is not the same patient-physician relationship. A question arises, however, whether researchers have a patient-physician relationship and therefore have the same ethical obligations in the research context. There are legal obligations as well. For example, if a laboratory test is conducted, the researcher under law cannot release test results to the individual unless the laboratory is certified under CLIA (Certified Laboratory Improvement Amendments) or GLP (Good Laboratory Practices), but most are not. He noted that examples abound, including a study that Dr. Heitman shared in which a colleague of hers who identified an individual with a gene associated with pulmonary hypertension could not inform the participant because the laboratory was not CLIA or GLP certified.

A review of the literature on the issue showed that some consensus is emerging in the context of clinical research. Outside of the legal questions, there is a general consensus that researchers have an obligation to inform individuals of findings that have serious, clear and unequivocal clinical implications and when the tests are done in a CLIA or GLP laboratory and treatment is available.

In areas where those conditions are not met, there is still debate. For example, some people argue that an allele that makes a person 40 percent more likely to be obese, according to population studies, is clinically actionable and relevant because an individual could make decisions to reduce their likelihood of developing the disease. Others say providing the results is a direct benefit because it respects the individual's autonomy and honors his or her right to know, and also creates a sense of trust between investigators and participants as part of the research endeavor. The debate has moved into a realm with some consensus about the duty to disclose test results of clinical research, a duty that increases with the certainty of the information and whether it will impact the treatment and prognosis for individuals.

Some argue that in some cases there is an obligation to withhold results if informing a participant leads to psychological harm—for example, in cases where a researcher discovered the gene associated with Huntington's disease. There is still some agreement about when there is an absolute obligation to provide the information. In general, however, there is an idea that there should be an offer and the obligation is related to clinical relevance and actionability.

Dr. Philpott-Jones raised the question of what the debate means for the HSRB. The challenge is that the issue is applicable to the clinical realm. For intentional exposure studies, researchers may not be in a situation in which providing individual exposure results would be clinically relevant or actionable. Most exposures fall well below EPA regulatory thresholds for safety. There are questions about the relevance of the information to the individuals for making decisions about professions and future behaviors.

The question for the Board was focused on when there is an obligation to provide individual results. The Board formed a work group that met in January 2013 to answer three specific charge questions: (1) In research studies that do involve intentional exposure of

participants to EPA-regulated compounds, do researchers have a moral obligation to offer individual research results to participants? Why or why not? (2) What would be the circumstances under which there is a moral obligation? (3) What is the ethical basis for any obligation to provide results to individuals, and are there ethical arguments supporting not disclosing information?

The work group consisted of HSRB members, former members, consultants representing outside interests, including those who represented communities involved in exposure studies, organizations that provide low-cost healthcare to farmworkers, and community advocacy groups. The members were asked to address the charge questions. The work group created three scenarios drawn from the types of studies reviewed by the HSRB in the past and applied the charge questions to the scenarios. The three scenarios involved a protocol similar to the antimicrobial task force protocols. In one case, the scenario was exposure to a liquid pesticide applied using a bucket and mop. The question was whether the participants who mopped should be told their individual exposure. The second scenario was more akin to a protocol from the agricultural handlers' task force, dealing with people who work for utility companies applying liquid pesticides to vegetation in rights of way. The third scenario involved a dosimetry and effectiveness study for insect repellents under field conditions, approaching exposure to average consumers and involving a laboratory phase and a field phase.

The work group offered three specific recommendations that Dr. Philpott-Jones read into the record.

1. For many intentional exposure studies, individual results are unlikely to be clinically relevant, but despite that, study sponsors or investigators have an obligation to offer individual results to participants.

2. There is an absolute moral obligation to return aggregate results to all participants, for example, via a letter written in lay language, unless a participant declines notification.

3. There is a strong presumptive moral obligation to return individual results to people that requested them, an opt-in choice. Researchers should provide individual results in a way that is contextualized, meaningful, understandable, relevant and useful. Although not tasked with addressing the way results are retuned, the work group felt that there was a natural connection between the obligation to return results and the way it was done.

There are situations in which a researcher may not have the moral obligation to return individual results if they cannot be presented in a comprehensible, relevant or useful way to the participants. For example, in a repellent-efficacy field study, everyone receives the same dose. In that case, the question arose as to whether it would it be relevant to report to someone after the study was completed that they had received 100 milligrams of an active ingredient. More importantly, there is a question of how relevant such information would be to the average participant when the formulation available years later might contain a very different concentration and application instructions.

In the first scenario, researchers were recruiting janitorial workers because the mop and bucket application of pesticides was directly relevant and useful to them as part of their professional activity. The same was true for the second scenario because utility workers were exposed based on the way they apply pesticides in rights of way and the information was directly relevant in making decisions to protect themselves. For the third scenario, it was harder to find a direct correlation between the data being provided to the individuals and the relevance to them later in their lives. The majority of the work group concluded that in this scenario there was a presumptive but not an absolute moral obligation to provide information. One work group member, however, disagreed with the majority's recommendation because of concerns outlined in the memo attached to the report. The concerns relate to questions about who determines the relevance and utility of information. If a study sponsor decides it is not relevant, that creates an easy loophole to sidestep a moral obligation. The dissenting members stated that the only situation in which a researcher should not return individual results was when the information could prove harmful to the recipient. For example, an individual who learned that they had a low level of exposure and had indicated that he or she was overly cautious could use the information to adopt more lax practices and thereby increase exposures. That standard, however, would be hard to meet, essentially creating an absolute obligation to inform.

The majority found support for their position throughout the *Belmont Report* framework, which provides support for opt-out aggregate and opt-in individual return choices. Reciprocal justice requires that those who assume the risks of a study should receive additional benefits; participatory justice stipulates that the mere act of participating in a study means there are certain justice obligations.

Dr. Parkin stated that if the Board agrees with all three recommendations, there would need to be discussion about how the recommendations would change the work of the Board in terms of reviewing protocols and studies. Dr. Philpott-Jones responded that approval would change the work of the Board, EPA and study sponsors because ethics members of the Board would have to examine the procedures in place for informed consent, for the study itself and for the post-trial obligations of researchers. In particular, the Board's ethics members would have to examine whether sponsors included consideration of that issue in their protocols, and EPA would be obligated to consider the issues in its review and discussions with sponsors. Study sponsors would have to consider how to operationalize the Board's recommendations, such as how to logistically handle the return of aggregate and individual results. Researchers would have procedural obligations that continue beyond the conduct of a study.

Dr. Parkin asked if Board members had any questions of clarification before the broader discussion. Dr. Ramos asked for clarification of how "clinically relevant" is defined.
Dr. Philpott-Jones explained that a level of exposure was clinically relevant if it meant that the individual should either inform a clinician about the exposure if it had acute or chronic effects, or if the exposure required seeking treatment. He explained the thinking behind that definition, such as the fact that all of the studies the Board had reviewed contained careful medical monitoring and stopping rules. Dr. Ramos inquired about Dr. Philpott-Jones' interchangeable use of the terms result and outcome. The dose of a study—100 milligrams of an active ingredient—would not be its result. Dr. Philpott-Jones apologized if his presentation was unclear and added that the work group was tasked with looking at the issue of informing participants about how much of an

EPA-regulated compound they were exposed to as part of a study. When the variable is not an exposure level, there is still an exposure value, a distinction that Dr. Ramos accepted as clear. Dr. Ramos stated that for the work group's third recommendation, which led to dissension, he would require a restatement of the majority versus minority opinions because, at a glance, the minority opinion contained many compelling arguments.

Dr. Dawson noted that the return of results recommendations were not addressed in regulations. She asked what status they possessed if they are not part of regulations and not official policy. Are they an enforceable standard or a recommendation for consideration? Dr. Parkin responded that the HSRB's discussion will be in its final report and will be in the public domain, with public dialogue about it. The report will become an appendix to the Board's report for this meeting, and all materials will be available publically. Any advice and recommendations to EPA would not be regulation, standards or policy unless the Agency takes them forward as such.

Dr. Philpott-Jones added that the work group's charge questions were not provided in accordance with applicable 40 CFR requirements, which means that the recommendations will not be an enforceable standard but will simply make recommendations to study sponsors. Dr. Parkin added that they likely will have impacts on the recruitment, enrollment, informed consent and other elements embedded in many protocols.

Dr. Dawson commented that on the scope of CLIA, she was unclear about how CLIA applied to laboratory testing that is not supposed to be about clinical tests, such as testing pesticide residues. Dr. Philpott-Jones responded that CLIA and GLP do not apply to pesticide testing, but he had discussed them to provide context regarding the debate occurring in the research arena. Dr. Dawson added that the report was well written, with good information about what is obligatory or not obligatory and good reasons provided to communicate with participants about research. She would not frame them in terms of rights and obligations for specific research but as broader issues about how to communicate about science and to respect communities related to social justice issues. Dr. Philpott-Jones responded that the work group did attempt to take that approach, but because of the specific charge questions, members tried to focus on answering those questions.

Dr. Popendorf asked if there was an implied exemption if someone cannot decide how to be comprehensible about the results. Dr. Philpott-Jones responded that there was not. There is a very strong obligation on the researcher to provide individual results to those who request them, and to do so in a way that is comprehensible, contextualized so that the person knows what the results mean to their life, relevant to what they do and useful or actionable. Research related to the formulation of a pesticide is not relevant because the results might not be relevant or useful. A strong argument and justification are needed for that point, but one work group member disagreed vehemently with that position.

Dr. Popendorf noted that the first two scenarios were occupational and asked if consumers were purposefully not chosen. Dr. Philpott-Jones responded that the aim was to choose protocols reviewed by the Board. The third scenario involving consumers was introduced to determine whether occupational or consumer differences mattered.

Dr. Dawson, drawing from her experience in the AIDS field, noted that often there is a sense among patients and the advocacy community that they want to know what is going on simply because they want to know, not because it is "useful." For example, women in a cohort study were asked for consent to conduct genome-sequencing studies, and all wanted a copy of their genome on a CD. The issue for participants is not necessarily about the utility of results, but about such questions as: Can I trust you? Do I have a right to information because I gave you my information? In Dr. Dawson's view, the concept is to create a social process that moves in the direction of better education. A hard-and-fast moral obligation is too stringent a requirement.

Dr. Philpott-Jones stated that Dr. Dawson captured what the majority of the work group felt, which is why it was written as a strong presumptive obligation, not an absolute one. One of the differences here is that these studies are so discrete, so there is less sense of a community obligation than in the AIDS arena.

Dr. Ramos commented that it was interesting how Dr. Philpott-Jones placed a spin on what Dr. Dawson said to validate his position when Dr. Ramos heard the opposite. He asked if the work group had practitioners who provided input. Dr. Philpott-Jones said that there were healthcare practitioners who worked directly with farmworkers and the migrant farmworkers network.

Dr. Young stated that whether for opt-in or opt-out, it would be helpful to have some standards expected for "relevant" and "useful." Dr. Philpott-Jones commented that the work group concluded those details went outside the scope of its charge; instead, it gave some parameters on what should be considered, leaving it to the Board to determine how to apply those standards.

Dr. Parkin added that the work group recognized that if it went more deeply into defining characteristics, doing so might require individuals with different backgrounds. A decision was made to bring the report to the Board at this point to either accept recommendations or indicate that the report needs revision. The Board could ask EPA to convene a separate work group. Those are the options.

Dr. Young said that her inclination was for the Board to decide on the report and then provide the details regarding what likely would meet the guidelines. A lot of information that is not helpful could be communicated to individuals. Dr. Dawson recommended taking a step back and asking whether the study is the right place for the recommended communication to take place. If researchers cannot communicate the aggregate results, they would be unlikely to communicate individual results. She wondered if it was more appropriately an EPA responsibility to provide education. It requires expertise in communication, psychology, risk perception and other fields that the Board lacks and that a study sponsor would not be expected to have. The Board should think about why communication is needed; the individual findings should be placed in the context of a broader communication initiative. Dr. Philpott-Jones added a caveat that if the communication is moved out of the sponsors' realm and broadened to EPA, that would raise regulatory and jurisdictional issues, as well as privacy and confidentiality issues. A breach in confidentiality could occur.

Board Discussion

Dr. Parkin broadened the discussion beyond clarifying questions. Dr. Galbraith stated that Dr. Philpott-Jones touched on a concern that he, as a member of a community hospital that conducts biomedical research, shared regarding confidentiality. In that setting, clinicians and researchers often know several of the people enrolled in a study, even at a social level. In the protocols that are presented to his hospital's IRB or others, after consent is registered, identifiers are stripped from the data; only one member of the research team has access to the identifiers. This is to ensure that when the analysis is done, researchers will not know that results are for a specific person. He stated that the potential social harm must be considered of having the requirement that a link be maintained between data and individuals. Typically, links can be stored separately in case the information is needed. Introducing more people into the process, especially in small rural areas, runs a greater risk of social harm.

Dr. Philpott-Jones responded that the work group discussed the issue, as is shown in the detailed transcript. Members supported an opt-in for individuals to explicitly say that keeping the links would be acceptable and would not be a violation of privacy rights if the researchers agreed to share information with the individuals.

Dr. Heitman offered several observations. She is part of other clinical projects that are trying to understand what it really means to return results or, if not results, then something else of value to research subjects. This issue will catch everyone, whether or not there are legal standards, and most organizations that do research are now trying to think about the matter. At the same time, the Board heard the previous day that an advance notice of proposed rulemaking was about to become a notice of proposed rulemaking. She has scoured the advance notice of proposed rulemaking to see if it had statements about return of results, but she found nothing concrete. The Board may want to wait before stating what it wants to do or making recommendations about implementation until after more is known about the notice of proposed rulemaking. The notice may catch up with other areas where the Common Rule stipulates what "must" be done.

In addition, Dr. Heitman stated that she was very aware from her work with hospital IRBs that the IRBs who work with sponsors will need to change their logistical practices. Most IRBs now say that a researcher may not re-contact study participants. That will have to change so that participants can make a decision about whether they want to be re-contacted, creating another logistical layer of oversight and tracking. Researchers will not be able to shred data any longer because they will need to know where to find participants 2 years after a study. There will be associated costs and many practical implications to consider.

Dr. Philpott-Jones stated that he did not disagree, especially because all Board members are all tracking the advanced notice or formal rulemaking expectations. The Board cannot punt on the issue and must make a declarative statement to EPA and study sponsors about expectations. Right now the study sponsors are highly inconsistent on the issue. The Board could say, "Let's wait, but our recommendation to the Agency and sponsors right now is X."

Dr. Parkin noted that the Board's final report could make a statement that differs from this one. If the Board's mood is to not fully adopt the language of recommendations, there may be some other recommendation it wants to make at this time. For example, members could say that the Board acknowledges receipt of the report and discussed the efforts made to date, and then recommend steps. EPA and study sponsors can refer to the report as an example of "thinking through the issue" and can identify key elements of the debate.

Dr. Green asked if it was envisioned that, for example, a sponsor could determine that the release of information is not relevant or useful, but the Board would retain its ability to review the information and could disagree with the sponsor's decision. He asked what would happen in that case.

In response, Dr. Philpott-Jones stated that such a scenario is exactly what is going to happen. The historical precedent is that EPA and the sponsors almost uniformly listened carefully to what the Board said and made the changes recommended. The Board is advisory, and they do not have to do anything the Board requests, but they always do everything suggested. He said that he believes that if the Board raised questions about their justification, they would come back with a stronger justification or a better explanation, or could ask for help in figuring out a better approach. Oddly, the sponsors themselves are eager to do this; they agree with Dr. Dawson that this is part of their obligations, and they want to meet the obligations to build a sense of community and trust. They are moving down the path of sharing information and are looking for guidance from the Board on how to do it. The Board can make a variety of recommendations, such as slowing down to await the notice of proposed rulemaking for the Common Rule's statements about the release of individual results.

Dr. Ramos stated that he was pacified by the approach Dr. Parkin discussed for moving forward. He stated that the work group's document was very well done, but needed to capture many of the sentiments expressed during the Board's discussion. Dr. Parkin clarified that the report is the product of the work group and the Board did not need to modify it, but if Dr. Ramos wanted to make a different statement based on the report that could be done.

Dr. Ramos described what drove the majority of his concerns about the report. Despite the disclaimer that the document is not a clinical document but describes a certain type of research, he was concerned about the clinical-centric process for contextualizing the document and for driving the document's underlying thinking. That discrepancy is at the root of the problem with the document. He recognized fully that the reason the work group struggled with separating the issues is that the work group was navigating in both the clinical and research worlds. He strongly urged maintaining clarity that the research is not clinical.

Dr. Philpott-Jones responded that the concern was valid. The work group tried very hard to remove itself from the clinical context. In discussions about how much background information to provide, the report erred on the side of providing information on the current thinking, and it is all within the clinical realm. The detailed rationale refers to "non-clinical research such as this."

Dr. Dawson stated that the advance notice of proposed rulemaking for the Common Rule does not address the issue. The President's Bioethics Commission on Incidental Findings was based on clinical incidental findings, which took the discussion into the clinical realm. The Board's work started with the research relationship model, but the environmental exposure studies that examine community impact processes is a better model.

Dr. Philpott-Jones commented that the work group looked for other resources. He agreed that the environmental studies model talks a lot about communication, but it says very little about communicating individual research results. The Board is moving into unchartered territory. The report of the President's Bioethics Commission was clinical but also was highly theoretical, so it provides some considerations on researchers' obligations that are worth examining.

Dr. Parkin noted that the discussion was nearing completion, and it seemed that the Board was not ready to adopt verbatim the recommendations in the report; however, the Board had discussed the report at length and recognized the need for additional discussions about what the Board will recommend to EPA. Enough issues remained on the table that further discussion was warranted. She asked if that suited everyone. The Board members agreed with her suggestion.

Topics for the Next HSRB Meeting (June 10–12, 2014)

Ms. Sherman covered logistics for the next meeting on June 10–12, 2014. There was no final agreement on agenda topics, but it is likely that they will include three older iodine-toxicity studies conducted in the 1980s or 1990s before the human studies rule went into effect in 2006. EPA would like to reevaluate some products that contain iodine. There is not a lot of information on those studies. There is also a possibility of another topic pertaining to an already-conducted study that a company would like to rely on.

Closing Remarks

Mr. Downing stated that a notice will be posted in the *Federal Register* on the exact times of the Board's June 10–12, 2014 meeting. Depending on the agenda, the meeting will use 1 or 2 days. He asked Board members to report any conflicts that they might have with any of the 3 days. The Return of Research Results topic could be on the agenda in June as well. He thanked the Board members for attending and adjourned the HSRB meeting at 3:18 p.m.

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

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Attachment B

FEDERAL REGISTER NOTICE ANNOUNCING MEETING

[*Federal Register* Volume 79, Number 53 (Wednesday, March 19, 2014)]
[Notices]
[Pages 15332–15334]
From the *Federal Register* Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2014–05908]

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ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2014–0189; FRL–9908–30–ORD]

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

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

ACTION: Notice.

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

DATES: This public meeting will be held on April 8–9, 2014, from approximately 9:30 a.m. to approximately 5:30 p.m. Eastern Time. Comments may be submitted on or before noon (Eastern Time) on Tuesday, April 1, 2014.

ADDRESSES: The meeting will be held at the Environmental Protection Agency, Conference Center, Lobby Level, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA 22202.
Comments: Submit your written comments, identified by Docket ID No. EPA–HQ–ORD–2014–0189, by one of the following methods:
Internet: http://www.regulations.gov: Follow the website instructions for submitting comments.
Email: ord.docket@epa.gov.
Mail: The EPA Docket Center EPA/DC, ORD Docket, Mail code28221T, 1200 Pennsylvania Avenue NW, Washington, DC 20460.
Hand delivery: The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Avenue NW, Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding federal holidays. Please call (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available online at http://www.epa.gov/epahome/dockets.htm.
Instructions: Direct your comments to Docket ID No. EPA–HQ–ORD–2014–0189. The Agency's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the

comments includes information claimed to be Confidential Business Information (CBI) or other information the disclosure of which is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or email. The http://www.regulations.gov website is an "anonymous access" system, which means the EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an email comment directly to the EPA without going through http://www.regulations.gov, your email address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, the EPA recommends that you include your name and other contact information in the body of your comments and with any disk or CD-ROM you submit. If the EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, the EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact Jim Downing at telephone number (202) 564–2468; fax: (202) 564–2070; email address: downing.jim@epa.gov; mailing address Environmental Protection Agency, Office of the Science Advisor, Mail code 8105R, 1200 Pennsylvania Avenue NW., Washington, DC 20460. General information concerning the EPA HSRB can be found on the EPA Web site at http://www.epa.gov/hsrb.

SUPPLEMENTARY INFORMATION:

Meeting access: Seating at the meeting will be on a first-come basis. To request accommodation of a disability, please contact the persons listed under **FOR FURTHER INFORMATION CONTACT** at least ten business days prior to the meeting using the information under **FOR FURTHER INFORMATION CONTACT,** so that appropriate arrangements can be made.

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

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

I. Public Meeting

A. Does this action apply to me?

This action is directed to the public in general. This Notice may, however, be of particular interest to persons who conduct or assess human studies, especially studies on substances regulated by the EPA, or to persons who are, or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act or the Federal Insecticide, Fungicide, and Rodenticide Act. This notice might also be of special interest to participants of studies involving human subjects, or representatives of study participants or

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experts on community engagement. Since many entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.**

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

In addition to using regulations.gov, you may access this **Federal Register** document electronically through the EPA Internet under the ''**Federal Register**'' listings at http://www.epa.gov/fedrgstr/. *Docket:* All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA/DC, Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue NW., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding federal holidays. Please call (202) 566– 1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm). The Agency's position paper(s), charge/ questions to the HSRB, and the meeting agenda will be available by the last week of March 2014. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov Web site and the EPA HSRB Web site at http://www.epa.gov/hsrb/. For questions on document availability, or if you do not have access to the Internet, consult Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.**

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

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

D. How may I participate in this meeting?

You may participate by providing comments in this meeting by following the instructions in this section. To ensure proper receipt by the EPA, it is imperative that you identify Docket ID No. EPA–HQ–ORD–2014–0189 in the subject line on the first page of your request.
1. *Oral comments*. Requests to present oral comments will be accepted up to Tuesday, April 1, 2014. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via email) to Jim Downing, under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern Time, Tuesday, April 1, 2014, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Official to review the meeting agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation and the organization (if any) the individual will represent. Oral comments before the HSRB are generally limited to five minutes per individual or organization. Please note that this includes all individuals appearing either as part of, or on behalf of, an organization. While it is our intent to hear a full range of oral comments focused on the ethical and scientific issues of the topics being considered by the

Board, we do not intend to permit organizations to expand the time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, further public comments may be possible.

2. *Written comments*. Submit your written comments prior to the meeting. For the Board to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of this meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the HSRB members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the agency strongly encourages you to submit such comments no later than noon, Eastern Time, Tuesday, April 1, 2014. You should submit your comments using the instructions in Section I., under subsection C., ''What Should I Consider as I Prepare My Comments for the EPA?'' In addition, the agency also requests that persons submitting comments directly to the docket also provide a copy of their comments to Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.** There is no limit on the length of written comments for consideration by the HSRB.

E. Background

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

1. *Topics for discussion*. At its meeting on April 8–9, 2014, EPA's Human Studies Review Board will consider ethical and scientific issues surrounding the following topics:

a. AEATF–II Protocol: A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial

b. AEATF–II Protocol: A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of Latex Paint Containing

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an Antimicrobial Pesticide Product Using a Brush and Roller for Indoor Surface Painting

c. AEATF Protocol: Determination of Removal Efficiency of 1,2- Benzisothiazol-3(2H)-one (BIT) from Hand Surfaces Using an Isopropyl Alcohol/Water Wipe and Wash Procedure

d. Laboratory Evaluation of Bite Protection from Repellent Impregnated Clothing for the United States Military

e. Background presentation on the Repellency Awareness Graphic and possible implications for the HSRB

f. Report from the HSRB Work Group of the Return of Individual Research Results

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

Dated: March 10, 2014.

Glenn Paulson,

Science Advisor.
[FR Doc. 2014–05908 Filed 3–18–14; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
APRIL 2014 PUBLIC MEETING AGENDA

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

Tuesday, April 8, 2014

HSRB WEBSITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA–HQ–ORD–2014–0189

10:00 a.m. **Convene Public Meeting—**Jim Downing, Designated Federal Officer, Human Studies Review Board (HSRB), Office of the Science Advisor, EPA
Introduction of Board Members—Rebecca Parkin, Ph.D., MPH, HSRB Chair
Opening Remarks—Glenn Paulson, Ph.D., Science Advisor, EPA

Welcome—Mr. William Jordan, Deputy Director, Office of Pesticide Programs (OPP), Office of Chemical Safety and Pollution Prevention, EPA
Estimating Pesticide Handler Exposure—Mr. William Jordan, Deputy Director, OPP, Office of Chemical Safety and Pollution Prevention, EPA

Session 1: **A New Scenario Design and Associated Protocol from the Antimicrobial Exposure Assessment Task Force II (AEATF-II) Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Manual Pouring of Solid Formulation Antimicrobial Products**
(This topic was originally scheduled for review by the HSRB on October 1, 2013, but that meeting was cancelled as a result of the federal government shutdown that occurred from October 1-16, 2013.)

10:20 a.m. **EPA Science Review—**Mr. Tim Leighton (OPP, EPA)
10:50 a.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA, Principal Investigator/Sponsor
11:00 a.m. **EPA Ethics Review—**Ms. Kelly Sherman (OPP, EPA)
11:20 a.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA, Principal Investigator/Sponsor
11:30 a.m. **Public Comments**
11:40 a.m. **Board Discussion**

If the AEATF-II study proposal AEA07 is revised as suggested in EPA's science and ethics reviews and if the research is performed as described:

Charge to the Board—Science:

- Is this research likely to generate scientifically reliable data, useful for assessing the exposure of those who pour solid formulation antimicrobial pesticide products?

Charge to the Board—Ethics:

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

12:30 p.m. Lunch

Session 2: A New Scenario Design and Associated Protocol from the AEATF-II Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Application of Latex Paint Containing an Antimicrobial Pesticide Product Using Brush and Roller Equipment

1:30 p.m. **EPA Science Review—**Mr. Tim Leighton (OPP, EPA)
2:00 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA, Principal Investigator/Sponsor
2:10 p.m. **EPA Ethics Review—**Ms. Kelly Sherman (OPP, EPA)
2:30 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA, Principal Investigator/Sponsor
2:40 p.m. **Public Comments**
2:50 p.m. **Board Discussion**

If the AEATF-II study proposal AEA09 is revised as suggested in EPA's science and ethics reviews and if the research is performed as described:
Charge to the Board—Science:

- Is this research likely to generate scientifically reliable data, useful for assessing the exposure of those who apply latex paint containing an antimicrobial pesticide using a brush or roller?

Charge to the Board—Ethics:

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

3:35 p.m. Break

Session 3: **A New Protocol from the AEATF-II Describing Proposed Research to Measure the Removal Efficiency of 1,2-Benzisothiazol-3(2H)-one (Known as BIT) from Hand Surfaces Using an Isopropyl Alcohol/Water Wipe and Wash Procedure**

3:45 p.m. **EPA Science Review—**Mr. Tim Leighton (OPP, EPA)
4:10 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA, Principal Investigator/Sponsor
4:20 p.m. **EPA Ethics Review—**Ms. Kelly Sherman (OPP, EPA)
4:40 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA, Principal Investigator/Sponsor
4:30 p.m. **Public Comments**
4:40 p.m. **Board Discussion**

If the AEATF-II study proposal AEA08 is revised as suggested in EPA's science and ethics reviews and if the research is performed as described:
Charge to the Board—Science:

- Is this research likely to generate scientifically reliable data, useful for determining the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint and non-paint liquid solutions containing BIT?

Charge to the Board—Ethics:

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

5:30 p.m. **Adjourn**

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
APRIL 2014 PUBLIC MEETING AGENDA

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

Wednesday, April 9, 2014

HSRB WEBSITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566–1752
Docket Number: EPA–HQ–ORD–2014–0189

9:30 a.m. **Convene Public Meeting—**Jim Downing, Designated Federal Officer, Human Studies Review Board, Office of the Science Advisor, EPA
Introduction of Board Members—Rebecca Parkin, Ph.D., MPH, HSRB Chair
Follow-up on Previous Day's Discussion—Mr. William Jordan, Deputy Director, OPP, Office of Chemical Safety and Pollution Prevention, EPA

Session 1: **A New Protocol from the U.S. Department of Agriculture Describing Proposed Research to Determine the Bite Protection Level of Repellent Treated Clothing for the United States Military**

9:40 a.m. **EPA Science Review—**Mr. Kevin Sweeney (OPP, EPA)
10:25 a.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA, Principal Investigator/Sponsor
10:40 a.m. **EPA Ethics Review—**Ms. Kelly Sherman (OPP, EPA)
11:00 a.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA, Principal Investigator/Sponsor
11:10 a.m. **Public Comments**
11:20 a.m. **Board Discussion**

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

Charge to the Board—Science:

- Is the protocol **"Laboratory Evaluation of Bite Protection From Repellent Impregnated Clothing for the United States Military"** likely to generate scientifically reliable data, useful for estimating the level of mosquito bite protection provided by two different textiles treated with etofenprox?

Charge to the Board—Ethics:

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

12:15 p.m. **Lunch**

Session 2: **Background presentation on the Repellency Awareness Graphic and possible implications for the HSRB**

1:15 p.m. **Presentation—**Ms. Rose Kyprianou and Ms. Kelly Sherman (OPP, EPA)
1:35 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., MPH (HSRB Chair)

Session 3: **Report from the HSRB Work Group of the Return of Individual Research Results**

2:00 p.m. **HSRB Work Group on Return of Individual Research Results Report Presentation—**Sean Philpott, Ph.D., Work Group Chair
2:20 p.m. **Board Discussion—**Rebecca Parkin, Ph.D., MPH (HSRB Chair)
2:50 p.m. **Topics for next HSRB Meeting (June 10-12, 2014)—**Ms. Kelly Sherman (OPP, EPA)

3:00 p.m. **Adjourn**