Meeting Minutes of the
U. S. Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
July 26, 2017 Public Meeting
HSRB Website: www2.epa.gov/osa/human-studies-review-board

Committee Members:	(See EPA HSRB Members List—Attachment A)	
Date and Time:	Wednesday, July 26, 2017, 1:00–5:00 p.m. EDT	
	(See *Federal Register* Notice—Attachment B)	
Location:	Via Teleconference and Webinar	
Purpose:	The EPA HSRB provides advice, information and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Liza Dawson, Ph.D.
	Vice Chair:	Edward Gbur, Jr., Ph.D.
Board Members:		Jennifer Cavallari, Sc.D., CIH Gary L. Chadwick, Pharm.D., M.P.H., CIP Alesia Ferguson, Ph.D. George C. J. Fernandez, Ph.D. Jewell H. Halanych, M.D., M.Sc. Walter T. Klimecki, D.V.M., Ph.D. Randy Maddalena, Ph.D.
Consultant to the Board:		Kendra L. Lawrence, Ph.D., BCE, PMP
Meeting Summary:	Meeting discussions generally followed the issues and timing as presented in the Meeting Agenda unless noted otherwise.	

Convening of the Public Meeting

Mr. Jim Downing, (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor, EPA [or Agency]), convened the meeting at 1:00 p.m. and welcomed Board members, EPA colleagues and the public. He explained that this meeting would include review of a new protocol for mosquito repellency testing for three topically applied insect repellent products containing IR3535. Mr. Downing expressed to the Board members the Agency's appreciation for their time and efforts preparing for the meeting.

As DFO under the Federal Advisory Committee Act (FACA), Mr. Downing serves as liaison between EPA and the HSRB and is responsible for ensuring that all FACA provisions are met regarding the operations of the HSRB. His responsibility is to work with Agency officials to guarantee that all appropriate ethics regulations are satisfied. HSRB members were briefed on provisions of the federal ethics and conflict-of-interest laws and have completed government financial disclosure reports, which have been reviewed to ensure that all ethics requirements are met.

In accordance with FACA requirements, meeting minutes that include 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 calendar days of this meeting. In addition to the minutes, a Final Report will be prepared by the Board as a response to the questions posed by the Agency and will include the Board's review of materials presented and recommendations to the Agency. The approved minutes and Final Report will be accessible through the HSRB website: www2.epa.gov/osa/human-studies-review-board.

Virtual Meeting Operations

Mr. Downing mentioned that the times on the agenda are approximate; time is dependent on public comments and Board deliberations. He also told the participants that the public would be allowed to comment at the appropriate time and that each public comment should be limited to five minutes. He indicated that no individuals had preregistered to provide public comments.

He thanked the Board members for their participation in the meeting and turned the meeting over to Dr. Liza Dawson (HSRB Chair) to introduce the Board members.

Introduction of Board Members

Dr. Dawson reminded the Board of the Adobe Connect website tools for making comments and voting on decisions regarding the research studies discussed during the meeting. Mr. Downing conducted the roll call of the Board members and asked them to introduce themselves, providing their names, affiliations and areas of expertise on the HSRB.

Opening Remarks

Dr. Thomas Sinks (Director, Office of the Science Advisor), thanked the HSRB and members of the public for their contributions and service. He acknowledged Mr. Downing and Ms. Michelle Arling (Office of Pesticide Programs [OPP], EPA) for their time spent supporting the Board. Dr. Sinks mentioned that during last winter and spring, EPA's Inspector General evaluated the performance of the Agency's scientific committees. Because the HSRB's performance received a high score, Dr. Sinks determined that no improvements to the HSRB are needed at this time. Dr. Sinks announced that two U.S. Senate appointees, Dr. Nancy Beck (Deputy Assistant Administrator, Office of Chemical Safety and Pollution Prevention, EPA) and Dr. Richard Yamada (Deputy Assistant Administrator for Research and Development, EPA), support the HSRB and serve to communicate the purposes of the Board's activities to the new Administration.

To highlight the importance of mosquito repellency as a component for the control of vector-borne diseases, Dr. Sinks described his professional experience at the Centers for Disease Control and Prevention (CDC). His interest in the discussion of mosquito repellency comes from more than 30 years of experience working on mosquito-borne illnesses at CDC. Dr. Sinks expanded on his comment by mentioning his efforts toward tracking the prevalence of Zika virus (ZIKV) in the Asia-Pacific.

Dr. Dawson thanked Dr. Sinks for his recognition and support of the Board's work. Dr. Dawson turned the meeting over to Ms. Arling.

Update on Research Reviewed at the Last HSRB Meeting

Ms. Arling thanked Drs. Sinks and Dawson for their remarks, then stated that there were no updates regarding the review of research studies that were deliberated during the April 27, 2017 HSRB meeting. However, Ms. Arling followed up on an issue discussed at this meeting related to the Federal Policy of the Protection of Human Subjects (Common Rule). This Common Rule was updated in January 2017 and governs research across the federal government. In response to this update, EPA recently

formed a workgroup that will update Agency-specific research regulations related to or derived from this Common Rule. An example regulation is section 40 CFR (Code of Federal Regulations) part 26, subpart K, which outlines the standards applying to research overseen by the OPP. Ms. Arling informed the participants that she will keep the Board abreast of this process.

Hearing no additional comments, Dr. Dawson invited Dr. Clara Fuentes (OPP) to present EPA's science review of the research protocol being discussed at this meeting.

Topic: Field Evaluation of Three Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida

EPA Science Review Highlights

Dr. Fuentes presented EPA's scientific review of the University of Florida's research protocol entitled "Protocol for Field Evaluation of Three Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida." This protocol is to determine the protection of three formulations of skin-applied insect repellent products containing increasing concentrations of an active ingredient, IR3535 (ethyl butylacetylaminopropionate), in the state of Florida. EPA's review evaluated the scientific aspects of this efficacy study to identify the complete protection time (CPT) of skin-applied repellents. Several aspects of the study including completeness of protocol submission and the compliance with ethical standards (as defined by 40 CFR subparts K and L) were evaluated. The study objectives are to (1) determine the CPT of the proposed products against wild adult mosquito populations using volunteer human subjects; (2) use the data from these studies to characterize product efficacy against mosquitoes; and (3) provide EPA with the reliable efficacy data required for product registration.

Dr. Fuentes explained the toxicity studies, dosage and application for the IR3535-containing products. Previous toxicity studies in laboratory rats revealed that IR3535 is not mutagenic or genotoxic. These toxicity studies determined that the dermal no-observed-adverse-effect level is equal to or greater than (≥) 3,000 milligrams per kilogram daily (mg/kg/day), the oral no observed effect level (NOEL) is ≥ 2,600 mg/kg/day, and the maternal and developmental NOEL is 600 mg/kg/day. The standard doses and methods intended for testing each product include a pump spray of 0.5 mg plus or minus (±) 10 percent per 600 centimeter square (cm^2) and lotions and wipes of 1 mg ± 10 percent per 600 cm^2. All three formulations are to be applied to the lower leg (ankle to knee); the concentration of formulation applied from wipes will be verified by weighing the wipe before and after application.

Field testing sites will be selected based on a high abundance ZIKA vectors (*Aedes albopictus*) mosquito species. Testing is planned for Alachua County, Florida (forest or wetland and an urban environment), and surveillance of the proposed test area(s) for mosquito-borne pathogens will be conducted for 1 month prior to study commencement. Quantitative reverse transcription polymerase chain reaction will be performed as a measure of positivity/negativity for pathogens.

Dr. Fuentes provided an overview of the important features of the experimental design and statistical analysis of the protocol. The protocol proposes to conduct dosimetry analysis for each formulation to determine the typical consumer dose rate for application. Under the protocol presented to EPA, study subjects will be evaluated for their "attractiveness" to mosquitoes using an "arm-in-cage" method prior to participating in the field testing. During both the attractiveness test and the field testing, aspirators will be used for collecting landing mosquitoes. At each test site and for each formulation to be tested, 10 subjects will be treated on a lower leg. Product efficacy will be determined by evaluating CPT, which is defined as the time from application of each test substance and the first confirmed mosquito landing on the treated subject. A median CPT (mCPT) will be determined for subjects treated with a test substance, not for control individuals. Exposure to mosquitoes will occur for 5 minutes every 30 minutes

for a total of up to 12 hours, or until product failure. mCPT will be calculated using the Kaplan-Meier survival analysis, which is a statistical method acceptable to EPA and the HSRB for mCPT calculation.

The study protocol is deemed by EPA to be in compliance with scientific standards. The experimental design, pre-training of subjects, and risk minimization were addressed. EPA recommends the following scientific-related changes to the protocol:

- Include the concentration of IR3535 in each formulation and a description of alternate field sites.
- Extend the testing for up to an additional 4 hours (or until seven treated subjects have their first confirmed landing) if fewer than seven people have first confirmed landing within 12 hours of the test initiation.
- Replace "protection from disease transmission" to "protection from disease vectors" in the study objective, section 1.
- Randomize treatment application sites to either the right or left leg.
- Increase the sample size to 13; and to include at least five male subjects and five female subjects.
- Add more description of who will apply the test product and how the standard dose will be calculated from diverse weight differences of applied wipe product.
- Revise the raw data sheets to classify which limb is treated.
- Define the statistical procedure for treated subjects' withdrawal. Data is "right-censored" if treated subject withdraws prior to experiencing product failure (first confirmed landing) or reaches the end of testing before experiencing product failure.
- Describe how first confirmed landings will be addressed if there is a missing exposure period between landings.
- In the event of weather-related delays, the testing may not continue if delay impacts more than three consecutive exposure periods. In addition, no more than 15 percent of all periods may be missed.
- Terminate the study if insufficient landing occurs for more than three consecutive exposure periods or at least 15 percent of all periods.
- Ensure that the Standard Operating Procedures for the study meet Good Laboratory Practice Standards.

In conclusion, Dr. Fuentes indicated that if the protocol is amended based on the aforementioned recommendations, it likely will yield scientifically reliable information and satisfy scientific criteria that include (1) producing important information that cannot be obtained except from research using human subjects; (2) clearly defining scientific objectives; and (3) utilizing a study design that produces sufficient data to achieve the objectives.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. Dr. Edward Gbur noted an apparent discrepancy: the recommendation from the Science Ethics Review document (released June 29, 2017) states that the testing day can extend up to 16 hours, but this was not mentioned in Dr. Fuentes' presentation. Ms. Arling confirmed the increase of testing time to 16 hours; actual repellent testing will be delayed up to 2 hours after product application, followed by 14 hours of testing (28 periods of measurement). Dr. Fuentes reiterated that the 2-hour delay occurs between the time of application and the time of exposure in the field. Dr. Gbur asked how "15 percent of all exposure periods" is calculated. EPA responded that this refers to 15 percent of the number of exposure periods completed. For example, 15 percent of 20 exposure periods is three periods. The study would be discontinued if the exposure periods resulted in low landing rates. Dr. Gbur suggested that aspects of "15 percent of all exposure periods" be further defined in the protocol.

Dr. Maddalena recommended to focus on CPT in the charge to the Board that states, "Is the protocol for 'Field Evaluation of Three Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida' likely to generate scientifically reliable data, useful for estimating the amount of time each of the products tested repels mosquitoes?" Dr. Fuentes said that the description of "estimating the amount of time" in the charge question does, in fact, refer to CPT and clarified that the study is analyzing the action of mosquitoes landing before biting.

Dr. Ferguson asked for explanation regarding the various scenarios/parameters (e.g., withdrawal, point of failure, etc.) that are necessary for right-censoring. The member also wondered whether the current statistical approach can handle these parameters and whether this approach should also be applied to other types of censoring. Dr. David Miller (OPP) added that the Kaplan-Meier statistical approach can handle right-censoring irrespective of the conclusion of the study or if withdrawal occurs. A mCPT cannot be calculated if fewer than seven of the 13 participants experience product failure during the test period. Therefore, if no one experiences product failure in 12 hours, the mCPT would be worded as "greater than 12 hours." Dr. Gbur added that the withdrawal and right-censoring are not important factors for the Kaplan-Meier approach. Dr. Dawson conjectured that, in the case of several subjects withdrawing before the end of the study, the risk of right-censoring is underestimation of the product efficacy. Lastly, Dr. Miller reiterated that the statistical method takes into account this possibility.

In response to Dr. Dawson's question, Dr. Fuentes verified that the study sponsors already agreed to address all of the scientific recommendations.

Hearing no further comments, Dr. Dawson turned the meeting over to Ms. Arling.

EPA Ethics Review Highlights

Ms. Arling presented the ethics review of and recommendations for the protocol for "Field Evaluation of Three Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida." She highlighted the study's public health value by saying that the results from this study will establish efficacy in support of product registration. These IR3535 containing products can help consumers control the transmission of mosquito-borne illnesses. Regarding the recruitment and selection of subjects, Dr. Emma Weeks (Principal Investigator of the study) will recruit subjects from the Gainesville, Florida area via advertisements; there will be a follow-up with interested persons. The consent process involves an in-person meeting with potential subjects, followed by signing of the consent forms. Consenting individuals then will complete screening questionnaires and undergo mosquito collection training, followed by their evaluation for "attractiveness" prior to field testing. The inclusion or exclusion of subjects is based on several criteria that include, but are not limited to, between 18 and 55 years of age, those who have given consent, non-smokers and English speakers (inclusion) and nursing or pregnant women, those with allergies to mosquito bites, and those who have skin disorders (exclusion).

The protocol provides appropriate measures to minimize certain risks:

- Exposure to mosquito-borne diseases and mosquito biting.
- The physical discomfort of mosquito bites.
- Adverse reactions to test products.
- Exposure to a hot and humid climate.
- The loss of confidential information.

The protocol outlines steps to minimize the risks of exposure to mosquito-borne diseases by setting up mosquito traps and testing weekly for at least 1 month prior to testing dates; excluding subjects with bite allergies or phobia of bites, cuts, scrapes or sensitivity to skin-applied repellants; and testing in areas where mosquito-borne diseases have been identified. Additional steps to mitigate other risks of participation include providing subjects with training on the use of aspirators and head nets, water and food to prevent dehydration and maintain blood sugar levels, and instructions to wear lightly colored or loose-fitting clothing, as well as exercising discretion regarding subjects' identities and pregnancy test results. Ms. Arling noted that the University of Florida's institutional review board (IRB) reviewed and approved the protocol and informed consent materials. The IRB-review was performed in compliance with EPA's regulations.

EPA recommends the following ethics-related changes to the protocol:

- To ensure the scientific integrity of the study, increase the number of test subjects from 10 to 13 and increase the number of alternate subjects to five per test day to ensure that subjects are available to replace individuals who withdraw.
- Randomly assign test and control subjects each test day.
- Add more information about the IRB review and ethical conduct policy, including a statement that protocol amendments may not be initiated without IRB approval unless it is necessary to eliminate apparent immediate hazards to subjects.
- Eliminate the dose determination phase of the study (dosimetry) to minimize exposure of human subjects; use EPA standard doses for skin-applied repellents.
- Require subjects to stay at the study site after the product is applied.
- Describe how withdrawing during the testing will be handled and when subjects will return to the laboratory after field testing.
- Revise the inclusion/exclusion criteria to address EPA's recommendations.
- Clarify whether subjects will be provided with unscented products to use for the 24 hours prior to each test day.
- Provide more details about the training of subjects (e.g., who will conduct the training and consent meetings).
- Include questions regarding the understandability of the consent form following the initial consent meeting training.
- Expand the recruitment section to provide more details about the recruitment process.
- Ensure that recruitment reaches a broad segment of the population.
- Incorporate EPA's comments into the telephone screening script.
- Provide a shaded, screened area with seating for subjects to use between 5-minute test periods, as well as drinks and snacks.
- Offer subjects gloves and head nets to protect exposed skin from bites during field testing.
- Require at least 72 hours between test days for subjects enrolled in more than 1 test day.
- Update the consent form to address diverse topics, such as IR3535 uses and compensation.
- Provide trained first-aid staff or an on-call nurse onsite during test days.
- Offer the first-aid staff or on-call nurse a copy of the final approved protocol, and brief them on the study process and test substances.
- For evaluating adverse events, clarify who will exercise "medical judgment" and how they are qualified.
- Explain how any adverse events that occur during field testing will be handled.
- Define the response if a subject does not reply to the 72-hour follow-up contact.
- Indicate that if and when subjects request first-aid supplies, over-the-counter antiseptics and hydrocortisone cream will be provided at no cost to the subjects.

- Describe in the compensation section the appropriate level of compensation; clarify how subjects will obtain payment.

Ms. Arling reviewed the study's adherence to the established ethical standards. She noted that the proposal is for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. She said that Attachment 1 to EPA's review contains a detailed evaluation of how this protocol addresses the requirements of 40 CFR 26, subparts K and L. Ms. Arling noted that with EPA's recommended changes accepted, the ethics standards requirements have been met. The risks have been effectively minimized and are reasonable in light of the expected societal benefits of the knowledge likely to be gained. There are no study deficiencies relative to 40 CFR 26, subparts K and L, or to the Federal Insecticide, Fungicide, and Rodenticide Act, section 12(a)(2)(P). EPA concluded that the protocol meets the applicable requirements of 40 CFR Part 26, subparts K and L.

Ms. Arling then read the charge question to the Board: "Is the research likely to meet the applicable requirements of 40 CFR Part 26, subparts K and L?"

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. Dr. Halanych asked for an explanation regarding the screening questionnaire for a history of present illness (HPI); she did not see this in the review document. Ms. Arling replied that this is in the protocol, but she would send it separately to the HSRB members as well. Dr. Halanych wondered about the rationale behind the statement on page 4 of the document that describes a criterion for exclusion: a subject participates in an intervention study other than an insect repellency study within the last 3 months. Dr. Halanych said that if the statement read "participated in another interventional study in the previous three months" it should be adequate. Dr. Halanych said if a person is taking part in repellent studies all the time, you would not want that person in this study, but under the conditions of this study (3 days, 72 hours apart) it would be OK. Dr. Weeks explained that the time-based exclusion criterion is 72 hours for this particular study, not 3 months.

Dr. Halanych asked if local monitoring organizations normally screen for dengue and Chikungunya when they monitor for disease vectors. In response to Dr. Halanych's's question, Dr. Kendra Lawrence (Consultant to the HSRB) said that it is unlikely that local monitoring stations are screening actively for dengue and Chikungunya viruses because these pathogens are atypical of regions outside of southern Florida (such as, Alachua County).

Regarding a statement on pages 12 and 13 of the Informed Consent, Dr. Halanych cautioned against non-study-related health professionals' being allowed access to subjects' personal health information from past, current and future medical visits. She recommended that access be granted only in the case of an adverse events. Dr. Weeks replied that the protocol can be adjusted to specify this restriction.

Dr. Klimecki said in the EPA's report it states that the data for currently registered IR3535 containing products does not contain the rationale for dose exposure levels. Dr. Klimecki said it was unclear whether the currently registered IR3535 containing products were not required to provide dosing information in their registration, or if we cannot use dosing information from the currently registered products to derive the equivalent values for the products in this study. In response to Dr. Klimecki's question, Ms. Arling cautioned against extrapolating the mCPT of the three IR3535-containing products based on existing registered products. Dr. Dawson clarified Dr. Klimecki's's point that there should be more clarity in the protocol about why the data are needed for these products. Dr. Klimecki said that one

could interpret the protocol as saying the currently registered products are not required to produce human exposure data and that would be incorrect. The point is that new data are needed for these products because existing product data cannot necessarily be extrapolated to these newer products. Dr. Dawson said it begs the question as to what were the data used for product registration and there must have been some human exposure data so it was good Dr. Klikmecki brought up that point.

Dr. Chadwick asked about EPA's comment on slide 63 of Ms. Arling's presentation regarding the use of gloves and head nets. Ms. Arling said that these materials are required only during the exposure period. Dr. Chadwick also asked how an investigator would achieve EPA's recommendation that theymust "ensure that recruitment reaches a broad segment of the population." Ms. Arling replied that in the protocol, the use of social media is suggested as an advertisement method to recruit from among the general population, not just within the university population.

Hearing no further remarks, Dr. Dawson called for public comments.

Public Comments

Hearing no public comments, Dr. Dawson introduced a discussion on the review of the protocol.

Board Discussion

Board Discussion—Science

Dr. Dawson asked discussants Drs. Walter Klimecki and Alesia Ferguson to provide their comments.

Dr. Klimecki commented that his scientific review of the study is from a toxicology-based viewpoint. He deemed EPA's ethics and science reviews and safety testing appropriate and affirmed that the proposed risk of exposure to the compound is consistent with good scientific practice within the boundaries of the charge to the Board. Dr. Klimecki expressed his approval of EPA's plan to coordinate with local surveillance programs regarding vector-borne disease transmission. He recommended that the mosquito surveillance period be extended to sometime after the study commences, which will address any potential data skewing. He wondered if collecting pre- and post-serum samples from subjects will reveal immune responses to the vector-borne pathogens to be tested in the study.

Dr. Ferguson outlined several points from her scientific review. She commented that EPA's review of the protocol was thorough and mentioned that EPA's presentation provided more comments and direction for the study sponsors than the documents provided to the Board. Regarding specific recommended changes to the study, she suggested that more description of the targeted demographics is needed in the protocol. She recommended that the protocol describe the method of determining the dose of applied product in the wipes, clarify whether the consent form includes five or six alternatives, and include additional language clarifying the "confirmation of the mosquito landing within the next test period (e.g., 5 minutes)."

Dr. Ferguson asked for clarification concerning the times that subjects will be contacted. She referred to page 3 of the protocol, which outlines a "48-hour contact period for an adverse event," but noted that other locations within the protocol state that the subject will be contacted within 72 hours to determine if they wish to participate again in the study. EPA confirmed that subjects will be contacted within 72 hours to ask if they have experienced adverse events. EPA agreed with Dr. Ferguson's recommendation that the 48-hour time be corrected on page 3.

Related to the exclusion criteria for individuals unable to perform aspiration, Dr. Ferguson asked if potential subjects can be made aware of this criteria early (e.g., in the initial interview) and recommended that clearly defined exclusion/inclusion criteria be stated in the protocol. EPA replied that it does not have a strong position regarding this matter. Dr. Ferguson suggested that more information be added to the protocol regarding the aspiration process.

Dr. Ferguson asked if lunch will be provided for the subjects and whether the types of food they consume within the 16-hour test period should be monitored. EPA offered to inform the study sponsor of this recommendation. Dr. Dawson wondered if there is scientific evidence that different types of food affect human attractiveness to mosquitos. Dr. Lawrence responded that alcohol consumption is an exclusion criteria and may affect attractiveness; food exclusion is unnecessary. Dr. Gbur cautioned against the sponsor's providing food for the subjects because of the likely complicated facets of their diets (e.g., allergies, vegetarianism, etc.). Dr. Dawson reaffirmed her earlier point that unless scientific evidence is present, restricting foods is unwarranted. Dr. Klimecki recommended that the sponsor provide food refrigeration. Dr. Ferguson said that consistency is needed regarding exclusion criteria (e.g., avoidance of spicy foods, alcohol, etc.).

Dr. Ferguson continued her earlier comments related to censorship. She alluded to what she deemed an inaccurate statement on page 13 of the protocol noting that withdrawal prior to a bite is to be right-censored. She said that sponsors should replace this statement with a description that designates right-censoring as a procedure for those who do not fail. Results from those who fail are censored, but right-censoring refers to the time (hours) to failure (no bite) when the study would end, which is considered a long period of protection against a bite.

Regarding ethical guidelines, Dr. Lawrence mentioned that the protocol indicates that subjects who undergo pregnancy testing are asked to show their negative test results, which are not recorded. EPA added that it made provisions to allow for discreet disposal of test results for subjects.

Dr. Ferguson recommended that a description of the products' active ingredient, ethyl butylacetylaminopropionate, be included in the protocol. EPA verified that the protocol includes monitoring of vector-borne diseases 4 weeks prior to study initiation; however, the study will not continue if these tests are positive after 2 weeks. In response to Dr. Ferguson's question about the use of ethanol after washing the tested area with unscented soap, several meeting participants agreed that ethanol is not required for the study and may be used to remove other products, such as diethyltoluamide, known as DEET, or lotions.

Dr. Gbur provided his statistical review. He requested clarification regarding the distinction between times to failure and CPT as the study's endpoint. Dr. Gbur said that the proposed method of statistical analysis is standard. He pointed out an apparent wording discrepancy related to the duration of the study each day. EPA's slides describe extending the study to a 16-hour day, whereas the written EPA review mentions an extended timeframe from 12 hours minimum to 16 hours. It is unclear if the minimum timeframe is 12 or 16 hours. Dr. Gbur also recommended that the protocol provide a numerical example of how many non-consecutive periods could be missed before reaching the 15-percent limit.

Related to the study procedure, Dr. Ferguson suggested that subjects be instructed not to rub or scratch their legs during the 30-minute rest periods between testing times. In response to Dr. Gbur's question, EPA clarified that the rest period is 25 minutes. Dr. Dawson reiterated that all Board comments in the margins of the review will be addressed by the study team. EPA verified that it will work with the sponsor to incorporate all edits, recommendations and clarifications; the revised protocol and consent document changes will be approved by the IRB before study commencement.

Concerning the intended use of the product, Dr. Dawson commented that although the protocol specifies that the product be applied to the lower leg, the subject may apply the product to other areas, which may alter the dose and also reach EPA's level of concern (a Margin of Exposure [MOE] less than or equal to a ratio of 100). EPA replied that it has discussed this issue with toxicologists and believes that this is not a concern because the study will not approach an MOE. Because the dermal NOEL is greater than 3,000 mg/kg, which is non-toxic, EPA has no toxicological concern for the proposed study.

Regarding study site selection, Dr. Dawson suggested that the protocol recommend contacting public health programs that are actively surveying for locally acquired human cases of vector-borne diseases that are likely to appear in humans in a certain area prior to detection in mosquitoes in that area. For example, ZIKV is more readily detected in humans earlier than in mosquitoes in the same geographical area. Regarding the sufficiency of previous research findings required for product registration, Dr. Dawson recommended adding usage of the active ingredient from prior similar studies to the protocol's background section.

Hearing no further comments, Dr. Dawson asked Drs. Klimecki and Ferguson for a response to the charge question: "Is the protocol for 'Field Evaluation of Three Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida' likely to generate scientifically reliable data, useful for estimating the amount of time each of the products tested repels mosquitoes?"

Dr. Klimecki proposed rephrasing the charge question to an affirmative statement: "The study is likely to generate scientifically reliable data to estimate the amount of time that the product repels mosquitoes."

Dr. Ferguson raised a concern about the method of dose calculation, or dosimetry, and the dose consistency for wipes. EPA replied that dosage studies in wipes have been performed previously; a protocol approved in 2015 outlines the dosimetry methodology that can be applied to the current proposed study. Dr. Lawrence asked what additional aspects of the method of using wipes are not specified already in the study's guidelines. EPA replied that the previous protocol differed from the guidance document regarding the usage of wipes; in the previous studies, the repellency formulation was extracted from the wipes and applied to the skin, which was therefore an application of the correct dose. Dr. Klimecki asked if material will be extracted from the wipes for the current protocol. EPA said that dose precision can be achieved only via extraction; the formulation administered to subjects will be from the wipes. The subjects will receive the same formulation at the dose rate expected. Dr. Ferguson asked if the wipes' manufacturer calculated the amount of released formulation and active ingredient.

Regarding EPA's recommendations for dose selection in the protocol, the Agency relied on previous dosimetry studies. The results from these studies provided the benchmark for standardizing the dose for the proposed study. Dosimetry studies are pre-studies to assess consumer behavior and identify the typically applied consumer dose. The results from these studies are used as a dose approximation for a particular study. Therefore, wipe products will possess a consistent dose based on consumer behavior. Dr. Lawrence asked if formulation must be extracted from the wipe or provided in bulk to ensure that the correct dose is administered during each application. EPA replied that the formulation can be provided in bulk, but is dependent on the sponsor's preferences. The formulation will be obtained either from bulk or extracted material from the wipe. Dr. Ferguson recommended creating a consistent method of application based on knowing the dose that is released from the wipes. EPA does not have data for the wipes that will be used for the proposed study. Dr. Dawson mentioned that section 8.5 of the protocol describes weighing the wipes before and after use. Dr. Dawson asked why the wipes are not used in the study if their use produces a standard amount of product applied to the skin. Dr. Lawrence explained that applying the formulation from the wipe, rather than using the wipe itself, ensures consistent dosing across individuals.

Dr. Scott P. Carroll (University of California, Davis) commented that as an entomologist, his research team presented protocols in which they designed dosimetry studies in response to a prior EPA request. His approach included abstracting mean values from consumer dosing behavior studies to provide the standard of dosing for end-users of the product. He said that based on his experience, the exact dose applied to the skin is difficult to calculate when using pump sprays and aerosols and cautioned EPA against generalizing doses of spray and aerosol-based delivery methods. Dr. Dawson thanked Dr. Carroll for his remarks and reminded him that his comments should have been raised during the meeting's timeslot for public comments.

In response to Dr. Dawson's question regarding the Board's consensus statement, Dr. Ferguson requested rewording the protocol to specify that the wipes will not be weighed, but the extracted or bulk-derived standard dose will be applied to subjects via a pipette.

Dr. Klimecki wondered what data support the assumption that the sponsors can use the product using the dosimetry studies. Dr. Lawrence mentioned that public comments were solicited when the Agency and the HSRB had the opportunity to review the previous data that are being used to set the standard dose in the proposed study. Dr. Dawson pointed out that the HSRB's role is to decipher an individual study within a larger process; the review of previous data does not equate to the HSRB's understanding and endorsement of a study portfolio. HSRB members must be allowed to ask questions to understand the overall study process.

In lieu of taking time from future HSRB meetings, Dr. Dawson suggested that to better understand EPA's viewpoint, the Agency can provide more scientific background to the Board regarding a proposed study. Dr. Klimecki expressed his approval of Dr. Dawson's assertion and deemed Dr. Caroll's comment important and worthy of discussion. Dr. Ferguson agreed that providing more background data is relevant.

Dr. Dawson recommended adding to the proposed study a fourth product testing group that will receive the same purported dose as the group using the wipes. Dr. Lawrence cautioned against this idea, commenting that the way the protocol is written is sufficient and the dosing for the formulation that is "impregnated" into the wipe is appropriate. Adding wipes as a test group will require the addition of the pump spray and lotion methods of application, which will present a difficulty when calculating the CPT of the product. Dr. Weeks asked whether approval will be required if the sponsor decides to change the material of the wipes (e.g., cotton matrix). EPA replied that as long as the percentage of active ingredient remains unchanged, approval is unnecessary.

Dr. Dawson mentioned the usefulness of the discussion to better understand the Agency's perspective. She recommended that the rationale for using the standard dose be described more fully in the protocol and that background information be provided in the memo to better understand the sequence of events for future proposed studies. These comments will be incorporated into the Report to develop a succinct response to the charge question. Different aspects of and questions related to the study design will be addressed.

Dr. Dawson reiterated the response to the charge question: "The study is likely to generate scientifically reliable data to estimate the amount of time that the product repels mosquitoes, with the suggestions for changes from EPA and additional changes from the HSRB."

The Board reached consensus and agreed to the response to the charge question.

Board Discussion—Ethics

Dr. Dawson asked discussant Dr. Jewell Halanych to provide her comments. Dr. Halanych began by reading her response to the charge question: "When the changes suggested by EPA and HSRB are incorporated, the proposed research will likely meet the applicable requirements of subparts K and L of 40 CFR 26."

Dr. Halanych commented that EPA did a wonderful job with its review and she approves of its ethics-related comments. Regarding adherence to subpart K, she noted that the study is compliant with the University of Florida's IRB requirement of addressing adequately the recommendation to minimize risk to subjects by coordinating with local health officials. Despite her agreement with the Agency's comments, she recommended written changes to certain portions of the protocol. Concerning the eligibility criteria, the guideline that participants should have a generally good health status should be consistent throughout the protocol. For scientific soundness, she suggested removing "except repellency trials" in the exclusion requirement for subjects who have been enrolled in other intervention trials within 3 months, except repellency trials. Dr. Halanych raised the following suggestion for section 17 (page 12) of the Informed Consent: remove the word "create" from the first paragraph, because the study will not create HPI. In the second paragraph (page 10), the sentence should read "Your protected health information may be collected, used for and shared with others to determine if you can participate in the study." Dr. Halanych suggested removing the middle section of this paragraph and adding "This information will be gathered from you via a health questionnaire."

In response to Dr. Halanych's question, EPA verified that a health screening questionnaire, rather than hospital testing (e.g., blood screening, X-rays, etc.), will identify any potential HPI in subjects. Dr. Halanych reiterated her earlier recommendation that the second and third bullets in section 19 of the Informed Consent be switched. She also recommended that the third bullet read "In the case of an emergency, medical professionals at the University of Florida, Shands Hospital..." Dr. Halanych suggested replacing the word "should" with "will" in section 6.2 on page 14 of the protocol, which states "The description of adverse events should be reported to the IRB." Regarding section 6.6.2, she recommended that all serious adverse events be reported to the IRB, not merely those considered "related and expected by the Principal Investigator." Lastly, Dr. Halanych indicated that completion of the proposed aforementioned changes will be in compliance with the regulations.

Dr. Weeks asked for clarification regarding the suggestion of removing the following text: "other than a biting study (except repellency studies)." Dr. Dawson commented that repeated enrollment in various clinical trials increases the risk of exposures to multiple products, which may cause deleterious effects on the proposed study. An HSRB member clarified the perceived concern: There should be a time delay between enrollments in different studies, allowing for sufficient clearance of product treatment. Dr. Weeks explained that in the proposed study, subjects wishing to take all three products at both sites are permitted to do so because these individuals would not likely be involved in other insect biting trials. Dr. Weeks agreed to Dr. Halanych's suggestion to remove "except repellency trials" from the exclusion criteria statement of the protocol; subjects will be allowed to use different products (e.g., wipe or lotion), applied at 72-hour intervals, rather than waiting 3 months between testing.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Halanych's ethics review statement, "These (changes) will be in compliance with subparts K and L of 40 CFR 26 once the proposed revisions have been made."

The Board reached consensus and agreed to the review statement.

Mr. Downing announced that Drs. Halanych, Gary Chadwick and George Fernandez will be leaving (terms expiring) the HSRB on August 31, 2017, after serving on the Board for several years. He thanked them for their service and commented that their contributions to the HSRB have been extremely helpful. Dr. Dawson thanked Drs. Chadwick, Fernandez and Halanych for their service and expressed her pleasure in having them as her colleagues. Mr. Downing noted that the next HSRB meeting is scheduled for October 24 through October 26, 2017.

Adjournment

Mr. Downing thanked all the attendees for their contributions and adjourned the meeting at 5:00 p.m. EDT.

Respectfully submitted:

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

Certified to be true by:

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

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

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

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

Vice Chair

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

Members

Jennifer Cavallari, Sc.D., CIH
Assistant Professor
Division of Occupational and Environmental Medicine
University of Connecticut
Storrs, CT

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

Alesia Ferguson, Ph.D.
Associate Professor
Department of Environmental and Occupational Health
University of Arkansas
Little Rock, AR

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

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

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

Walter T. Klimecki, D.V.M., Ph.D.
Associate Professor
Departments of Pharmacology and Toxicology
The University of Arizona Health Sciences
Tucson, AZ

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

Members (continued)

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

Consultant to the Board

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

Attachment B

***FEDERAL REGISTER* NOTICE ANNOUNCING MEETING**

ENVIRONMENTAL PROTECTION AGENCY

[FRL-9960-98-ORD]

Human Studies Review Board; Notification of a Public Meeting

AGENCY: U.S. Environmental Protection Agency.

ACTION: Notice.

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

DATES: A virtual public meeting will be held on Wednesday, July 26, 2017, from 1:00 p.m. to approximately 5:00 p.m. Eastern Time. A separate, subsequent teleconference meeting is planned for Friday, September 15, 2017, from 2:00 p.m. to approximately 3:30 p.m. Eastern Time for the HSRB to finalize its Final Report of the July 26, 2017, meeting and review of other possible topics.

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

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact the HSRB Designated Federal Official (DFO), Jim Downing on telephone number (202) 564–2468; fax number: (202) 564–2070; email address: downing.jim@epa.gov; or mailing address Environmental Protection Agency, Office of the Science Advisor, Mail code 8105R, 1200 Pennsylvania Avenue NW., Washington, DC 20460.

SUPPLEMENTARY INFORMATION:

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

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

How May I Participate in This Meeting?

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

1. Oral comments. Requests to present oral comments during either conference call will be accepted up to Noon Eastern Time on Wednesday, July 19, 2017, for the July 26, 2017, meeting and up to Noon Eastern Time on Friday, September 8, 2017, for the September 15, 2017, teleconference. To the extent that time permits, interested persons who have not pre-registered may be permitted by the HSRB Chair to present oral comments during either call at the designated time on the agenda. Oral comments before the HSRB are generally limited to five minutes per individual or organization. If additional time is available, further public comments may be possible.

2. Written comments. Submit your written comments prior to the meetings. For the Board to have the best opportunity to review and consider your comments as it deliberates, you should submit your comments by Noon Eastern Time on Wednesday, July 19, 2017, for the July 26, 2017, meeting and up to Noon Eastern Time on Friday, September 8, 2017, for the September 15, 2017, teleconference. If you submit comments after these dates, those comments will be provided to the HSRB members, but you should recognize that the HSRB members may not have adequate time to consider your comments prior to their discussion. You should submit your comments to Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.** There is no limit on the length of written comments for consideration by the HSRB.

Background

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

Topics for discussion. On Wednesday, July 26, 2017, EPA's Human Studies Review Board will consider one topic: Field evaluation of three topically applied insect repellent products containing IR3535 against mosquitoes in Florida. The Agenda and meeting materials for this topic will be available in advance of the meeting at *http://www2.epa.gov/osa/human-studies-review-board*. On September 15, 2017, the Human Studies Review Board will review and finalize their draft Final Report from the July 26, 2017, meeting, in addition to other topics that may come before the Board. The HSRB may also discuss planning for future HSRB meetings. The agenda and the draft report will be available prior to the teleconference at *http://www2.epa.gov/*. Meeting materials for these topics will be available in advance of the meeting at *http://www2.epa.gov/osa/human-studies-review-board*.

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

Dated: June 14, 2017.
Robert J. Kavlock,
Acting EPA Science Advisor.

[FR Doc. 2017–07134 Filed 4–11–17; 8:45 am]
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