EPA Human Studies Review Board (HSRB)

April 20 and 21, 2021 Meeting Minutes

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

Date and Time: Tuesday, April 20, 2021, and Wednesday, April 21, 2021, both 1:00 to 5:30 pm EST.

Locations: Via teleconference and webinar

Purpose: The HSRB provides advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research.

April 20, 2021 Meeting

Meeting was called to order at 1:00 p.m.by Tom O'Farrell, designated federal official (DFO) for the HSRB. Roll was taken and the following members and observers were present:

HSRB members Jennifer Cavallari, Sc.D. (Chair) Alesia Ferguson, Ph.D. (Vice-Chair) Philip Day, Ph.D. Thomas Lewandowski, Ph.D. Mark Aulisio, Ph.D. Janice Britt, Ph.D. AJ Allen, Ph.D., M.D. Ann Um, Ed.D. Lisa Corey, Ph.D. Lindsay McNair, M.D. George Milliken, Ph.D. Julia Sharp, Ph.D. Kendra Lawrence, Ph.D. (consultant)	EPA staff members Michelle Arling (EPA, OPP) Clara Fuentes, Ph.D. (EPA, OPP) Helen Hull-Sanders, Ph.D. (EPA, OPP) Shannon Borges (EPA, OPP) Sadaf Shaukat (EPA, OPP) Tom O'Farrell (EPA, OSAPE)
Members of the public, representatives of research sponsor and research team Cass Kaplinsky (Carrol-Loye Biological Research) Scott Carroll (CLBR) Shawn King (CLBR) Ralph Washington Jr. (CLBR) Lara Hall (Bergeson and Campbell, P.C.) Dana Lateulere (Bergeson and Campbell, P.C.) Stephanie Watson (Mimikai)	

Dr. Tom O'Farrell provided an introduction to the meeting and outlined the Federal Advisory Committee Act (FACA) procedures and took role of the meeting participants.

Ms. Michelle Arling said that EPA is expecting key study reports from the antimicrobial task force for the October meeting. One will be a scenario under the airless sprayer protocol. Also OPP is reviewing two published literature articles looking at exposure to a specific chemical that the Agency may use in risk assessments. The plan at this point is to bring that research to the HSRB at the meeting in July.

The Board reviewed the protocol "Field Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-based Repellent Spray Against Mosquitoes" by Mimikai.

The Agency's scientific review of this study was presented by Drs. Clara Fuentes and Helen Hull-Sanders of EPA's Office of Pesticide Programs (OPP). Dr. Hull-Sanders presented first. On behalf of Mimikai, Carroll-Loye had submitted a protocol dated February 17, 2020 to the EPA for review. The EPA identified deficiencies with the submission and Mimikai and Carroll-Loye revised the protocol and resubmitted to the EPA. However, EPA's current review is based on the revised protocol dated December 23, 2020. Two testing sites will be selected from potential locations, including California, Minnesota, Arizona, Florida, and Louisiana. The proposed product testing will be conducted with 13 treated subjects per field site. The product will be tested at a proposed application rate of 0.5 grams per 600 centimeters squared. The landing pressure should be measured before treatment and intermittently throughout the course of the test by treated control subjects. To estimate complete protection time (CPT), two untreated controls are sufficient. Controls should expose an untreated arm or leg briefly at regular intervals during the test to confirm acceptable landing pressure. CPT is the time from application of a repellent until efficacy failure as defined in each study. A confirmed event, also called the first confirmed landing, is one landing followed by another landing within 30 minutes. The EPA follows the repellency awareness guidance for skin-applied insect repellent producers in setting the CPT.

Dr. Fuentes continued the presentation. The objective of this study is to evaluate the CPT of the proposed repellent against mosquitoes. The active ingredient in OLE, or oil of lemon eucalyptus, is p-menthane-3,8-diol, which is abbreviated as PMD. The PMD is present at 65% concentration in OLE and the product proposed for registration and for testing contains 11% of OLE. From a 90-day dermal study in rats, the dermal no-adverse-effect level was 1000 mg/kg/day, and the lowest adverse effect level is 3000 mg/kg/day. The maternal and developmental, no adverse effects level is 3000 mg/kg/day in rabbits. PMD is non mutagenic and not genotoxic so the MOE, or margin of exposure, was not calculated because there are no end points of concern. The other active ingredient in the product is a methyl nonyl ketone, abbreviated MNK. The no adverse effect level for dermal irritation is 100 mg/kg/day, with no systemic effect from a rabbit study. MNK is not mutagenic, nor genotoxic. The product contains 7.75% by weight of MNK, and margin of exposure, or MOE, is calculated using a dermal loading rate from a 21-day dermal study in rabbits. The NOAEL is 100 mg/kg/day, based on moderate-to-severe dermal irritation at a dose of 300 mg/kg/day, with no systemic effect. The

only effect is dermal irritation with lack of systemic toxicity. The results indicate there are no unacceptable risks to human. The toxicity profile of the repellent, Lilly Pilly, is toxicity category IV for all routes of exposure and it is not a skin sensitizer. The rate of application will be 0.5 grams per 600 cm^2 of skin surface area. The study will be conducted at two ecologically different sites, representing different habitats where predominant mosquito species differ. The sites will be selected based on mosquito abundance, activity and diversity, as well as absence of mosquito-borne pathogens. Samples of 1000 trapped mosquitoes will be screened for detection of pathogens using reverse transcription and quantitative PCR. There will be 20 subjects, 10 males and females. Two subjects, one male and one female, will be asked to participate as untreated controls, and 13, six of one sex and seven of another, will be randomly assigned to either of the two test sites. Prior to testing, all participants will be evaluated for their attractiveness to mosquitoes in the laboratory, and only participants who are attractive to mosquitoes will be eligible to take part in the study. All subjects will be trained in the use of an aspirator for collecting landing mosquitoes in the lab prior to the studies. To monitor landing pressure throughout the study, the controls will expose untreated skin for five minutes every 30 minutes, or until five landings occur, whichever happens sooner. Following exposure by controls, the test subjects will proceed to expose their treated skin for five minutes every 30 minutes. Data from control subjects will not be used for statistical analysis in the calculation of median CPT. The Kaplan-Meier survival analysis will be employed to estimate the median CPT across 13 subjects, with a 95% confidence interval. The test will be stopped when consented duration time is reached, when the subject experiences a CPT, for safety reasons, medical reasons, if the subject withdraws, or landing pressure is above or below the threshold, or because of bad weather. The test will be stopped when 15% of all projected exposure periods have inadequate landing pressure or are skipped due to bad weather, or when three consecutive exposure periods have been skipped for any combination of low landing pressure or bad weather. If the first landing occurred at an exposure period that is preceded by either a missed period due to bad weather or with inadequate landing pressure, the first landing will be considered confirmed at the preceding missed period, or the preceding period with the low landing pressure. The following elements are adequately addressed: the experimental design, the pre-training of subjects, and the risk minimization.

Dr. Hull-Sanders continued the presentation. EPA gave the following recommendations for the study:

1) EPA recommends a revised informed consent form. Subjects should not be instructed to cover treated skin between exposure periods, since this practice is likely to disturb the applied repellent. The informed consent forms should further be revised to inform subjects that they may be randomly assigned as controls, and the controls should be randomly chosen. Applications to lower legs should be randomly applied, and randomization process should be described.
2) EPA recommends that the protocol delete, "Has participated in another field repellency test day of the study in the previous 72 hours." Each subject will not participate in more

than one field test. EPA recommends that “landing with intent to bite” (LIB) be replaced with landings on the heading of the raw data collection sheets for controls.

3) EPA recommends that exposures of the second treated limb be removed from 4.8.4 on page 31. It does not apply to the experimental design. EPA recommends that the approximate period of exposure delay be indicated from the time of production application to the first field exposure.
4) EPA recommends that the protocol specify what and how data from treated and control subjects will be summarized and reported, and to add to the exclusion site criteria that subjects who are considered unattractive to mosquitoes will be excluded from further participation in repellency testing.
5) EPA recommends removal of the statement, "attempted to bite" on line 1,584, and 4.8.4, page 32, and replace it with "landings". The EPA recommends amending 4.7.2 on page 29 to propose that only mosquitoes that land on exposed skin of control and treated subjects will be collected.
6) EPA recommends that the last paragraph on page 2,021 be replaced with, "A sample size of 13 subjects is based on EPA simulation of our analysis provided in appendix eight. A sample size of 13 subjects should be enough for generating reliable results without including more subjects than necessary."
7) EPA recommends that the criterion for subjects' attractiveness be repeated to five landings per minute, according to the EPA 810.3700 guidelines to add to the protocol that if first landing occurs at exposure period followed by low landing or a skipped period, and it is not confirmed by a second landing within 30 minutes, the CPT will be recorded at the time of the first landing.
8) EPA would like clarification and more detail on the criteria for when to replace withdrawn subjects, and when to use their data. It would also like for the protocol to clarify in more detail the length of testing time, that data from withdrawn subjects will be right censored or the data not used, and when a subject is replaced.
9) That the protocol specify that data from withdrawn subjects who are not replaced should be counted as right-censored data for statistical analysis, that the data sheets be revised to identify which limb is treated at each trial, and to consider stopping tests when more than half the subjects have reached CPT.
10) EPA recommends testing of treated subjects continue during periods of low landing pressure and amend the language on stopping test item seven and 4.7.7 on page 29 to say that testing will be stopped if more than four non-consecutive exposure periods or more than three consecutive exposure periods occur under low landing pressure or missed due to bad weather.

In conclusion, if amended to address the concerns raised in the EPA review, the field efficacy test of an oil of lemon eucalyptus, a methyl nonyl ketone-based repellent spray against mosquitoes is likely to yield scientifically reliable information satisfying the following criteria. It would produce important information that cannot be obtained except from research using human subjects. It has clear scientific objectives and the study design should produce adequate data to achieve those objectives.

The Board asked questions about the science presentation. Dr. Lisa Corey asked how the rate of application is going to apply to end user rate, because it just will be dispensed from the syringe vs. another mechanism. Dr. Corey wanted to get some additional information on how that will differ in the rate of application, the coverage over area, and then the potential differences in dose. Dr. Hull-Sanders responded that EPA accepts the application method because it is very standardized, and a very even coverage, instead of asking the participants to spray themselves where they might not get a consistent dose. If a consumer is to utilize the product as it is intended, and as it is labeled, then it's pretty equivalent. Dr. Julia Sharp asked about a sentence where the words “attempting to bite” should be changed to “landing”. Dr. Hull-Sanders responded that EPA needs clarification on that. Dr. Scott Carrol said the point of giving that perspective was to articulate in a way that would give a sense of what subjects would be experiencing and in accord with the nature of the data being collected, that, or almost all subjects, in almost all exposure periods, until the point of product failure on a per individual basis, there will be no landing. Dr. Jennifer Cavallari asked if someone could clarify what a landing pressure above the threshold is. Dr. Fuentes said that would be a situation where there are an overwhelming amount of biting mosquitoes and it would be unsafe.

Ms. Arling of EPA OPP reviewed the ethical aspects of the study protocol. The sponsor will try to recruit up to 50 individuals willing to consent, and this will be done either by the research team or a recruitment firm, depending on the study location. Follow up will be conducted by phone and individuals will be asked basic eligibility questions, and will get an overview of the study. The study includes a maximum age cutoff of 60 because of the increased risk when exposed to certain diseases, and limits participation to English speakers based on the language of pesticide labeling and the staff language. This study excludes from participation pregnant and nursing women, and those who are allergic to, or sensitive to the test products or mosquito bites, or have a skin conditions that could be worsened by exposure to the test substance, as well as employees, students, and their family members of the researchers and sponsor. The protocol proposes limiting subject's participation to a single test day. Consent will occur in a one-on-one meeting with the study staff, and will cover the steps involved in this study, eligibility criteria, compensation, and subject's freedom to withdraw. And at the end of the process, those who are interested in proceeding, will be asked to sign a consent form and will be provided with a signed copy of that information. Each subject will be paid $20 per hour for their participation in the consent meeting, the training on aspirator use, the attractiveness test and the pre-test training on aspirator use. During the field test, subjects and untreated control subjects, will receive $200 for their first eight hours of each test day, and then an additional $25 per hour for any participation beyond eight hours. Risks include exposure to the test material, exposure to biting mosquitoes and mosquito-borne diseases, being outdoors during a test day, and the psychological stress associated with pregnancy testing. The protocol proposes to minimize these risks by excluding candidates who have known allergies to the test product, insect repellents, and common cosmetics. It also proposes to exclude subjects who have skin conditions that could be exacerbated by exposure to the test substance. The protocol proposes to exclude those subjects who have a known allergies or hypersensitivity, or who have a fear of mosquito bites. Additionally, the attractiveness test will be another opportunity to confirm that a subject won't have a severe reaction to a mosquito bite. During and after the test day, subjects can request a

topical antihistamine, if they need to address any mosquito bites they might get. Subjects will have access to water and snacks throughout the test day. They also will have access to a screened, shaded area with seating and study staff who are trained to identify signs of heat stroke and heat stress, and to render first aid or to make appropriate calls to get necessary medical attention. The primary beneficiary is the study sponsor, and eventually the public could benefit from the registration of a repellent that is effective at mitigating the risks of bites that reduce transmission of illnesses. The protocol includes effective methods for protecting subject's privacy, provides adequate compensation for the subject's participation, and makes clear throughout the protocol and throughout the consent materials that subjects are free to withdraw at any time, without forfeiting any benefits. Advarra was the overseeing IRB for this protocol , and they approved the original protocol and all amendments and the updates and materials again, with the December 23rd version of the protocol that was shared with the HSRB.

EPA's recommendations for the protocol regarding ethics were:

1) That the protocol include a discussion of the risks and precautions that will be taken to protect subjects and research staff from exposure to COVID-19, such as wearing masks and socially distancing, following all appropriate federal, state and local guidance, following up with subjects after their participation, engaging in a reading before the test day, and establishing a mechanism for contact tracing if necessary.
2) The protocol proposes that subjects wear Tyvek suits during the test day. EPA recommends that subjects wear light, loose fitting clothing, along with a head net and gloves on the test day, to protect their skin that's not being exposed as part of the experiment, because the wearing of Tyvek suit does present an increased risk of heat related illness.
3) The protocol is unclear about assigning subjects as control or test subjects. There are two consent forms provided, separated by the role that a subject would play in the study, and in some places the protocol proposes that subjects know before they consent to participate, that they will be a test or control subject. EPA recommends that these roles are randomly assigned, following consent, and that the consent process cover the risks to both tests and control subjects, and the consent form is written in a way that's relevant to anyone who participates in this study. EPA also recommends randomly selecting control subjects, again, from that pool of subjects, following consent.
4) Expand the consent process so that it will include demonstrations of how the test substance will be applied, what the aspirator is and how it is used, and how the attractiveness test will be conducted, as well as how a five minute exposure period would occur for both the test and control subjects.
5) To include in the protocol how the researchers will confirm that subjects understand the risks and benefits, and the study design. For example, following the consent process, subjects could be asked the standard set of questions to ensure that they adequately understand what they're agreeing to.
6) That the protocol include a discussion of how and when the subjects age will be verified, and to clarify that pregnancy testing will be conducted when female subjects are exposed to mosquitoes in the lab, as well as prior to the application of the test substance.

7) That the protocol include more information about the preparation for and timing of the study day, such as when subject will arrive, what steps will be taken upon arrival, such as checking subjects' skin for any scrapes or abrasions that would impact their eligibility, and confirming other eligibility criteria, and providing information about how subjects will be transported to the field site.
8) Revise the protocol to include more information about adverse events: how they'll be evaluated, who will be evaluating them, and how they will be reported, if necessary, to the IRB.
9) That the protocol be revised to describe what the 10-minute break that occurs every hour is and how it will occur, and the impact it will have on the timing of the exposure periods. Also, EPA recommends clarification about how long alternates will be expected to remain at the test site, and until what point an alternate can be enrolled in place of a withdrawn test subject.
10) That the compensation amounts page for withdrawing subjects be clarified in the protocol. This is related to whether a subject withdraws before the eight hour period, would the subject be paid a prorated rate, or paid for their whole time up to that eight hour cutoff?
11) That the protocol specify how individuals will be paid, whether that's by cash or check or prepaid card, if it's at the end of the test day or at some interval following the test day, and if it's going to be in-person or by mail. That information should be included in the consent form.
12) The protocol and consent note that subjects' social security numbers will be requested, and EPA recommends either providing justification for requesting that information, or removing this request.
13) Revise the consent form to include all elements outlined in the human studies rule, including a summary of the key information of the study upfront, more information about subjects' withdrawal, and the use of withdrawn subjects' data.

With EPA's recommended changes addressed, it is expected that the requirements of the human studies rule in subpart K will be addressed, and the requirements to consult with the HSRB at section 26.1203 will also be satisfied. The risks of test subjects have been minimized effectively and are reasonable in light of the expected benefits and the knowledge likely to be gained.

The Board had no questions about the ethics presentation.

The Chair asked if there were public comments and there were none.

The HSRB’s scientific review was presented by Board members Drs. Tom Lewandowski Dr. Lisa Corey, and consultant Dr. Kendra Lawrence. Dr. Lewandowski had some concerns about the dermal absorption study that was mentioned and said it would be helpful if EPA had more input on the design of the study. Dr. Sadaf Shaukat said that EPA was originally thinking a dermal absorption study would be useful, but after further collaboration with some of EPA senior scientists, because they are using a dermal loading rate and EPA had determined that there is no observed systemic toxicity with this chemical, EPA no longer needs a dermal absorption study.

Dr. Lewandowski suggested that the protocol be revised to indicate an absorption study isn't needed and Dr. Hull-Sanders agreed. Dr. Lewandowski said that EPA's requests for additional COVID protections were not that specific. Dr. Hull-Sanders said that the protocol is meant to be a general protocol for studies moving forward. Ms. Arling said EPA has to look at every protocol for proposed human research independently, so even if this were a protocol that could be used as a model for future research, it would have to be revised to be specific to the study that will be conducted and reviewed by EPA. So, she did not think there is the risk of rendering it obsolete once COVID ends and there is value in having an acknowledgement of the additional risk and just a note that both subjects and researchers will be protected. Dr. Corey had a question about the end user application rate and how that might vary. Dr. Corey said it would be helpful to increase the justification of how that applies in this field setting to the actual user. Dr. Corey recommended to evaluate the diversity in the species of mosquitoes in each area ahead of time to be sure that after going through all of this, we're actually getting enough data from the different species to have usable information for labeling or any other types of conclusions that come out of the study. Dr. Corey said maybe moving forward, it would be useful for EPA to let us know if there has been some change from the protocol that we were asked to review ahead of time. Dr. Kendra Lawrence said the study states any subjects who are judged to be in poor physical health will not be included in this study and she thought that statement was rather vague and not very specific. It wasn't clear who was going to be judging any potential subjects who are in poor physical health and what that criteria would be based on and it would be more helpful to either eliminate comments like that in the protocol and just rely on what's in the inclusion and exclusion criteria. Dr. Lawrence did not see excluding potential participants who have experienced a heat-related illness in the past and recommended that be included as an exclusion criteria to minimize the risks of heat stress-related events. Dr. Lawrence had a small recommendation where it talks about standard first aid materials that could be available, just to maybe specify that those are commonly acquired over the counter materials versus standard first aid.

The Board's statistical review was given by Dr. Julia Sharp. Dr. Sharp said that she is unclear on the recorded values one or two for when there are dozens of zero landing values, and suggested that be clarified. Dr. Sharp said on page 33, there's mention of a first landing confirmed by a second landing within the same five minutes exposure period or by a second landing occurring in the next exposure period, including when that exposure period occurs after a pause in conducting exposure periods. and was curious about what that pause was and how long of a pause before recording that first confirmed landing. Dr. Hull-Sanders said EPA interprets that pauses to be where they would stop momentarily due to bad weather or due to low landing pressure parts. EPA has asked that the study sponsor continue to test at least during low landing pressure periods, except for bad weather. EPA hopes that there's not a pause in testing and it will either be a continuation or a stopping altogether. Dr. Sharps suggests adding a clarification that if at least 50% of the subjects have data that are right-censored, the mCPT (median CPT) will not be computed. Also Dr. Sharp said there are two field studies here and the statistical analyses will be done on each of those field studies separately, and the data should not be combined. Dr. Hull-Sanders agreed and EPA will add those comments.

The HSRB voted unanimously in favor of the following response to the science charge question: The research proposed in the protocol field efficacy of an oil of lemon eucalyptus and methyl nonyl ketone based repellent spray against mosquitoes is likely to generate scientifically reliable data useful for estimating the amount of time the product tested repels mosquitoes provided the comments and recommendations provided by EPA and HSRB are adequately addressed.

Dr. Mark Aulisio presented the HSRB's ethics review of the study. Advarra gave approval and Advarra is a fully accredited. Dr. Aulisio said that given EPA's science and ethics recommendations are addressed, this ethics review endorses all of EPA's ethics comments as articulated in EPA's science and ethics review, MIM-006 16 to 18, and the protocol will be in substantial compliance with CFR 40 Part 26, Subpart K. Children and pregnant or nursing women are excluded and pregnancy tests will be administered to women who are potential participants and the test results will be in private and confidentially discussed by a female member of the research team. Other study participants will either be male or female, but between the ages of 18 and 60. So, the proposed study is in substantial compliance with 40 CFR Part 26, Subpart L and ultimately based on this review of the available information provided by HSRB, by EPA to the HSRB by EPA, it is Dr. Aulisio's opinion that the research proposed contingent upon addressing EPA ethics comments as articulated in EPA science ethics review, MIM-006 16 to 18 will be in substantial compliance with the requirements of 40 CFR part 26, subparts, K and L. The Board voted unanimously in the affirmative to the following response to the ethics charge question: "the research proposed in the protocol fields efficacy test of an oil of lemon eucalyptus and methyl nonyl ketone based repellent spray against mosquitoes is likely to meet the applicable requirements of 40 CFR Part 26, Subparts K and L, if the recommendations made by the EPA and HSRB are adequately addressed.

This concluded the Board's session for April 20, 2021 and the meeting was adjourned.

April 21, 2021 Meeting

Meeting was called to order at 1:00 p.m.by Tom O'Farrell, designated federal official (DFO) for the HSRB. Roll was taken and the following members and observers were present:

HSRB members	EPA staff members
Jennifer Cavallari, Sc.D. (Chair) Alesia Ferguson, Ph.D. (Vice-Chair) Philip Day, Ph.D. Thomas Lewandowski, Ph.D. Mark Aulisio, Ph.D. Janice Britt, Ph.D. AJ Allen, Ph.D., M.D. Ann Um, Ed.D. Lisa Corey, Ph.D. Lindsay McNair, M.D. George Milliken, Ph.D.	Michelle Arling (EPA, OPP) Clara Fuentes, Ph.D. (EPA, OPP) Helen Hull-Sanders, Ph.D. (EPA, OPP) Shannon Borges (EPA, OPP) Angela Gonzales (EPA, OPP) Tom O'Farrell (EPA, OSAPE)
Members of the public, representatives of research sponsor and research team Cass Kaplinsky (Carrol-Loye Biological Research) Scott Carroll (CLBR) Shawn King (CLBR) Ralph Washington Jr. (CLBR) Lara Hall (Bergeson and Campbell, P.C.) Dana Lateulere (Bergeson and Campbell, P.C.) Stephanie Watson (Mimikai) David Nielson (CLBR) Moriah Garrison (CLBR)	

Dr. Tom O'Farrell provided an introduction to the meeting and outlined the Federal Advisory Committee Act (FACA) procedures and took role of the meeting participants.

The Board reviewed the protocol "Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-based Repellent Spray with Ticks under Laboratory Conditions" by Mimikai.

The Agency's scientific review of this study was presented by Drs. Clara Fuentes and Helen Hull-Sanders of EPA's Office of Pesticide Programs (OPP). Dr. Hull-Sanders presented first. The test product contains 11% oil of lemon eucalyptus (OLE) and 7.75% methyl nonyl ketone, MNK, as active ingredients. The objective of this study is to determine the complete protection time (CPT) of the skin applied repellent. Repellency testing will be conducted in the lab with 25 subjects per tick species. The proposed ticks are *Amblyomma americanum, Ixodes scapularis*, and *Dermacentor variabilis*. The product will be tested at an application rate of 0.5

grams per 600 centimeters squared. Data provided from this research will be used by the EPA to characterize efficacy against ticks for three tick species and provide reliable data for the support of efficacy claims against ticks on product labels. Mimikai and Carrol-Loye had submitted a protocol dated February 17, 2020 to the EPA for review. The EPA had identified some deficiencies to the submission and the revised protocol was resubmitted to the EPA. This review today is based on the revised protocol dated December 23rd, 2020. The time point of repellency failure is measured by a tick crossing three centimeters onto treated skin and remaining on that treated skin for one minute, followed by a confirmatory crossing from a second tick within 30 minutes apart. The length of repellency is measured by the median CPT, which is the summary of individuals CPTs across all subjects throughout the test. The EPA follows the repellency awareness guidance for skin applied insect repellent producers in setting the CPT. The CPT is estimated for the product against each tick species. The guidance recommends selecting the most conservative CPT of the three tick species rounded down to the nearest integer for product labeling.

Dr. Fuentes continued the presentation. The formulation side is a back involved spray and the product will be applied at a rate of 0.5 grams per 600 squared centimeters of the skin surface area. The amount of product applied to test subjects will be measured biometrically adjusted to the skin surface area of each subject forearms, so that all subjects receive the same rate of application. The test substance will be evenly applied to subjects' non-dominant arms. Multiple technicians will make the applications simultaneously wearing gloves and using a finger to apply the test substance. The active ingredient in OLE is p-methane-3,8-diol, abbreviated as PMD. OLE contains 65% of PMD. And the product proposed for registration contains 11% OLE. The no adverse effect level for chronic dermal exposure to PMD is 1000 milligrams per kilogram per day and the lowest adverse effects level is 3000 milligrams per kilogram per day. This is based on the 90 day dermal study in rats. The maternal and developmental no adverse level is 3000 milligrams per kilogram per day in rabbits. The margin of exposure or MOE was not calculated because there were no points of concern identified. The PMD is non-mutagenic and it is not genotoxic. The other active ingredient in the product is methyl nonyl ketone, abbreviated as MNK. The no adverse effect levels for dermal irritation is 100 milligrams per kilogram per day with no systemic effect. These findings are from a 21-day dermal irritation study in rabbits. MNK is non-mutagenic and not genotoxic. The product contains 7.75% by weight of MNK. The margin of exposure or MOE is calculated using a dermal loading rate from the 21 day dermal study in rabbits, which is 100 milligrams per kilograms per day, based on moderate to severe dermal irritation at a dose of 300 milligrams per kilogram per day, with no systemic effects. Since the only effect is dermal irritation with lack of systemic toxicity, the uncertainty factor can be reduced and the risks can be estimated using the dermal loading rather than the body weight. The uncertainty factor was reduced by a factor three due to the lack of systemic effect, and also due to less intra- and inter-specific variation between and among species for localized irritation response, resulting in a level of concern LOC equal to 10. The risk was estimated using the dermal loading rate for the 21-day dermal study divided by the loading rate of product application proposed for testing. This resulted in an MOE of 52, which is larger than the LOC of 10 and these results indicate that there is no unacceptable risk to subjects. The toxicity profile of

the product is toxicity category four for all routes of exposure and the product is not a skin sensitizer.

CPT is defined as time of protection from time of product application to the first confirmed crossing on a subject. The crossing occurs when a tick crosses the boundary line onto the treated skin. The first crossing is confirmed when a second confirmatory crossing occurs within 30 minutes of the first crossing. The product will be tested on a sample size of 25 subjects, 12 of one sex and 13 of another sex per tick species. Both control and test arms will be arranged identically with equally spaced longitudinal lines, three centimeters apart. Ticks of one species will be individually screened on the subject's untreated arm. Once a questing tick is identified, the questing tick will be individually transferred for exposure to the treated arm within a 15-minute interval. This procedure will be repeated sequentially with ticks of different species within 15-minute intervals. Each subject will test three tick species in three or more days of testing. Tick movement is recorded within three minutes from the time of the tick being released on the release line. A tick is not repelled when it crosses three centimeters onto treated the skin within three minutes. The tick is repelled when it does not cross the reference line more than three centimeters toward the elbow onto treated skin, or it changes its direction upon approaching the treated line area and moves away. The CPT is measured as a single time point per subject per tick species. The test will be stopped when the consented duration time for testing is reached, or the subject asks to withdraw, or for safety reasons such as medical management is invoked, or there's hypersensitivity to ticks or to the product. Testing will stop for the subjects who achieve the CPT for tick species tested, or if the subject becomes unattractive to ticks during the testing. The Kaplan-Meier survival analysis will be used to estimate the median CPT for each tick species across 25 subjects with a 95% confidence interval. The Kaplan-Meier survival analysis is advantageous since the CPTs data may not be normally distributed. The experimental design, the pre-training of subjects and the risk minimization are adequately addressed in the protocol.

Dr. Hull-Sanders continued the presentation. EPA gave the following recommendations for the study:

1) The criterion for subject replacement when a subject fails to screen for one or two tick species should be established and that the criterion for treatment of data from withdrawn subjects who will not be replaced should also be established.
2) The protocol be revised such that a subject will be stopped from testing for only a single species when exposure periods are missed due to a single tick species failing the screen, and that the protocol be revised to note that testing with a specific tick species will be stopped when more than five exposures, at least three, and up to five subjects are missed due to ticks failing the screen on the untreated arms.
3) That alternate tick species for *Dermacentor variabilis* be included, namely *Dermacentor andersoni* and *Rhipicephalus sanguineus*.
4) That the protocol specify that unfed female ticks will be used for testing.

5) That the repulsion criteria be revised for a not repelled tick as defined in the 810.37 guidelines. A not repelled tick crosses three centimeters onto treated skin and remains on that treated skin for one minute.
6) That the protocol revise section 3.3.2 and 4.8.2, establishing 72 hours between each test day. That section 3.3.2, item 13, be revised for the people not spending time outdoors so it does not apply for exclusion from participation in the laboratory tests. Also, the Agency recommends removal of references pertaining to the mosquito protocol.
7) The Agency would like to know how many ticks species will be tested each day specifically.
8) That the informed consent form be amended, this is two, three and four on page 44, to replace low fragrant soap with unscented soap for arm preparation.
9) Stopping test per tick species when more than half of the subjects have reached CPT for that species.

If amended to address the concerns raised in the EPA review, the field's efficacy test of an oil of lemon eucalyptus, and a methyl nonyl ketone-based repellent spray against ticks under laboratory conditions is likely to yield scientifically reliable information, satisfying the following scientific criteria. It would produce important information that cannot be obtained except from research with human subjects. It has clear scientific objectives and the study design would produce adequate data to achieve those objectives.

The Board asked questions about the science presentation. Dr. Alesia Ferguson asked was there information on how they're going to ensure that subjects are coming from different demographic backgrounds? How will that effort be made? Dr. Hull-Sanders said that is usually in the ethics section. Dr. Cavallari asked to confirm that only one species of tick is being tested on a subject on any given day per subject. Could different subjects be exposed to different types of species? How would that be determined? If that was going to be randomly determined who gets which tick species, how many tick species were going to be tested in a day? Dr. Fuentes agreed that we need more clarification on that. In one section of the protocol it says that it will be one species per day, but then it is also explaining that it will be more than one species tested per day, multiple species tested per day. Dr. Cavallari asked if Dr. Hull-Sanders mentioned that different tick species have different questing behavior. Dr. Hull-Sanders said they actually have seen registrants come back in with a revised protocol because one species did not quest correctly. They only obtain the *Dermacenter Variablilis* and that those, for whatever reason, did not behave at all and they had to replace them with a different species and come back to the Board.

Ms. Arling reviewed the ethical aspects of the study protocol. The recruitment will occur in the greater Sacramento area through print and digital advertising. The materials will have a brief description of the study and information about how to contact the study group to get more information about the study. Those who express an interest will receive more information about the study by email or phone and will be asked some preliminary screening questions. This protocol proposes to use 25 subjects per tick species along with eight alternate subjects, a total of 33 individuals per tick species. The intention is to have each subject test all three ticks species. Children under 18 years old are excluded, excluded as well as pregnant and nursing women.

Only those who are able to speak and read English are eligible to participate, in part because of the language of the study staff. Anyone who might be more susceptible to tick bites or the effects of exposure to the test substance are excluded from participation. A staff person will meet one-on-one with an interested party to discuss the study, covering how the study would be conducted, the eligibility criteria, compensation, and freedom to withdraw. After this discussion, if the subject is interested in continuing, the study staff will read the consent form to or with the candidate. Each subject will be paid $20 per hour for taking part in the consenting training and pre-test training and then $200 for the first eight hours of each test day and $25 per hour for participation beyond eight hours. Exposure to ticks and tick-borne diseases will be minimized by using lab raised, pathogen-free ticks, and having subjects trained on observing tick behavior and when to remove ticks prior to their enrollment in a test day. Also, the ticks will be closely monitored during the test phase and removed if they show any signs of attaching. Subjects who have allergies to repellent, test material ingredients, and common cosmetic ingredients will be excluded from participation. Those who have localized skin disorders that could be exacerbated by exposure to the test substance will also be excluded. The study sponsor will benefit by being able to register their product and the public could benefit from the registration of an effective skin applied repellent that would mitigate the risks of tick bites and transmission of tick-borne illnesses. The protocol includes effective methods for ensuring that subjects' identities and privacy are protected, including maintaining records in locked cabinets and discreet handling for pregnancy testing. Any expenses for injury or illness incurred as a result of study participation will be paid by the study sponsor. The version of the protocol that was provided to EPA and the HSRB dated December was reviewed by the IRB and approved along with all of the supporting materials.

EPA’s recommendations regarding the ethical considerations for the study were the following:

1) Revise the protocol to acknowledge any COVID related risks that will be present at the time that the study is conducted and to detail the precautions that will be taken to protect both the subjects and the study staff.
2) Include information in the protocol about how adverse events will be evaluated and reported to the IRB, as well as information about who will make these determinations and what their qualifications are.
3) Before the test day, state that someone who is qualified will check the subject's skin where the treatment will be applied to ensure that it is sound, and there's no disqualifying conditions that would render them ineligible.
4) EPA recommends that the protocol include a thorough description of what will be covered during the consent meeting in the discussion with the subjects and we recommend that this include a step-by-step demonstration of all of the study activities.
5) Following the consent process and before obtaining the informed consent of the subjects, EPA recommends that the protocol include information about how the subjects' comprehension of the consent form and the study process will be demonstrated.

6) That the protocol clarify how subjects who withdraw will be compensated and whether it will be a pro-rated amount or the full payment if they participate for up to eight hours. The protocol should provide more detail on how and when individuals will be paid and that this information also be included in the consent form, so it's clear to the subjects what to expect.
7) That the request for subjects' social security numbers, which is outlined in the consent form, be removed or that adequate justification for requesting this information is included.
8) Revising the consent form to include all elements of the human study's role, primarily including a brief description of the study at the front of the consent form.

This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, and the data will be submitted to EPA under FIFRA. The primary ethical standards are the human studies rule at 40 CFR 26, Subparts K and L; and FIFRA. A full evaluation of how these standards are met is included in the attachment to EPA's review. Moving to slide 18 and compliance with these ethical standards. With EPA's recommendations addressed, the requirements of the human studies rule will be satisfied as well as the requirement at 26.1203 to consult with the HSRB. EPA found that the risks have been effectively minimized and are reasonable in light of the expected societal benefits. There are no deficiencies relative to the human studies rule or FIFRA. With the recommendations addressed, the protocol will meet the applicable requirements of 40 CFR Part 26, the human studies rule.

The Board then asked questions about the ethics presentation. Dr. Alesia Ferguson asked how they were going to ensure demographic distribution. Ms. Arling said her recollection is that the protocol says that there'll be general recruitment from the area and that demographic information on the subjects who enroll will be provided in the report. Dr. Fergusons suggested that there should be a couple sentences about how exactly it will be done. Dr. Phil Day asked if there could be more clarity on how the study director determines when the site is unsafe and the study should be stopped. Dr. Hull-Sanders said it refers to when there are adverse weather conditions at outside field sites and that might be a copy and paste error. Dr. Scott Carrol confirmed that it is a copy and paste error. Dr. Carrol said that the instances of the word mosquito referred to a discussion regarding where they would provide context about what is better known in mosquitoes regarding arthropod preferences for individual hosts, rather than being a copy and paste error. Where there's an absence of information about individual host choice preferences in ticks, they did allude to what is known for mosquitoes to give greater context. Ms. Arling also noticed there's some indication of referring to the participants' limb and the leg and the recording form mentioned a leg and should be corrected just to the arm for the tick protocol.

There were no public comments.

The HSRB’s scientific review was presented by Board members Drs. Janice Britt and Ferguson. Dr. Britt said most of the comments the had were addressed by EPA. Dr. Britt said should it be clarified that ticks are used to up to twice on a subject, first tested for questing and then they are used if questing is successful? Dr. Hull-Sanders said it should read that ticks are

used for one testing period. It should be very clear that a tick is only used on a single person for a single testing period and not used again. Dr. Ferguson suggested to add a sentence that says why study participants over the age of 60 were not allowed to participate. Dr. Cavallari suggested that it be clear that only one tick species will be used on any given one subject per day.

The statistical review of the study was given by Dr. Ann Um. The proposed design and methods are great, and the sample size is 25 people, which is great. The Kaplan-Meier survival analysis will be used. It is most appropriate for estimating the Median CPT. The proposed method and proposed design are appropriate for answering the Research question and the protocol can generate scientifically reliable data.

The Board voted unanimously in favor of the follow response to the science charge question "The research proposal proposed in the protocol efficacy test of an oil of lemon, eucalyptus, and methyl nonyl ketone based repellent spray with ticks under laboratory conditions is likely to generate scientifically reliable data useful for estimating the amount of time the product test repels ticks provided the comments and recommendations provided by the EPA and HSRB are adequately addressed".

Dr. AJ Allen presented the HSRB's ethics review of the study. This is a study that was originally submitted in 2018 by the Sponsor for a review by the EPA and the HSRB. At that point in time, it was noted that there was an unacceptable bridging of toxicity data to fulfill the toxicity data requirements. The protocol was then withdrawn in March of 2019. The Sponsor subsequently, reformulated the product as outlined in the EPA Scientific Review and submitted a new protocol, MIM series of seven, which is the one currently reviewed. Originally, it was dated the 17th of February 2020 and had been reviewed by Advarra. EPA identified deficiencies in that protocol, so the Sponsor corrected those, the amendment, and submitted an amended protocol dated the 23rd of December 2020 to Advarra for review and approval. The Sponsor then submitted that amended protocol and updated the review documents to the EPA for its Review and for this HSRB Review. The procedures for recruiting, screening, selecting, training, and if needed, withdrawing and replacing study participants are described in the protocol and the EPA Scientific Review. Conditions under which the participants will participate in testing, putting actions taken to minimize risks to the participants where possible in procedures for measuring CPT for ticks, including the analysis are also described in the protocol and EPA Scientific Review. Both OLE and MNK are registered with the EPA for use in skin applied repellents at or both concentrations used in the repellent. The EPA Scientific Review found the risks due to exposure to be low. Those are further lowered via several exclusion criteria as described in the EPA Review. The EPA Review summarized five risks to participants that were discussed in the protocol related to exposure: test material exposures, ticks, and tick-borne illnesses, physical stress, and test conditions. The psychological risks associated with disclosure, pregnancy testing results, and those risks and actions taken to minimize them are all outlined in the EPA Science and Ethics Review. Specifically, the protocol excludes pregnant and lactating women and individuals under the age of 18. The consent form appears to be generally appropriate with some exceptions that were noted in the EPA Ethics Review for correction. Dr. Allen said once the different comments and recommendations from the EPA and from HSRB have been

satisfactorily addressed, this protocol is likely to meet the applicable requirements for 40 CFR 26 and subparts K and L. Dr. Allen recommend that the Board respond affirmatively to the charge question. Dr. Ferguson suggested to add a couple of sentences on how the recruitment will really ensure a diverse population in the pool of applicants. The Board voted unanimously to the following response to the ethics charge question: that for research proposed in the protocol, efficacy tests of an oil of lemon, eucalyptus and methyl nonyl ketone based repellent spray with ticks under laboratory conditions is likely to meet the applicable requirements of 40 CFR part 26 subparts K and L, if the recommendations made by the EPA and HSRB are adequately addressed.

This concluded the Board's session for April 21, 2021 and the meeting was adjourned.

Respectfully submitted:

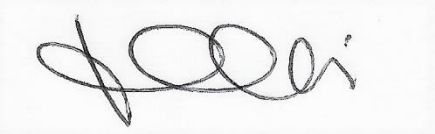
7/19/2021

X Thomas O'Farrell

Signed by: THOMAS O'FARRELL

Thomas O'Farrell, Ph.D.
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:



Jennifer Cavallari, Sc.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

Jennifer Cavallari, Sc.D., CIH
Associate Professor
Department of Public Health Science
University of Connecticut School of Medicine
Farmington, CT

Vice Chair

Alesia Ferguson, Ph.D.
Associate Professor
Department of Built Environment
North Carolina A&T University
Greensboro, NC

Members

Janice Britt, Ph.D.
Managing Scientist
ToxStrategies, Inc.
Tallahassee, FL

Lisa Corey, Ph.D.
Toxicologist
Intertox, Inc.
Seattle, WA

George Milliken, Ph.D.
Consultant
Milliken Consultants
Manhatten, KS

Thomas Lewandowski, Ph.D.
Principal
Gradient
Seattle, WA

Mark Aulisio, Ph.D.
Professor
Case Western Reserve University
Cleveland, OH

Albert J. Allen, M.D., Ph.D.
Senior Medical Fellow
Eli Lilly
Indianapolis, IN

Eun Um, Ed.D.
President and CEO
AMSTAT Consulting
Bethesda, MD

Julia Sharp, Ph.D.
Associate Professor
Colorado State University
Fort Collins, CO

Lindsay McNair, M.D., Ph.D.
Chief Medical Officer
WIRB-Copernicus
Princeton, NJ

Philip Day, Ph.D.
Assistant Professor
University of Texas, Southwestern
Dallas, TX

Consultants 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 Registers Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10017-40-ORD]

Human Studies Review Board; Notification of Public Meetings

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA), Office of Research and Development announces the 2021 public meetings dates of the Human Studies Review Board (HSRB) to advise the Agency on the ethical and scientific review of research involving human subjects.

DATES: Four three-day virtual public meetings will be held on:

1. January 26-28, 2021;
2. April 20-22, 2021;
3. July 20-22, 2021; and
4. October 19-21, 2021.

Meetings will be held each day from 1 p.m. to 5:30 p.m. Eastern Time. Separate, subsequent teleconference meetings are planned for the HSRB to finalize its Reports of the three-day meetings that proceed these dates on March 18, 2021; June 17, 2021; September 16, 2021; and December 14, 2021; all from 2 p.m. to approximately 3:30 p.m. Eastern Time.

ADDRESSES: These meetings are open to the public and will be conducted entirely virtually and by telephone. For detailed access information and meeting materials please visit the HSRB Website: https://www.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), Thomas O'Farrell at the following telephone number: (202) 564-8451 or by email at: ofarrell.thomas@epa.gov.

SUPPLEMENTARY INFORMATION:

Background

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

Meeting access: These meetings will be open to the public. The full agenda with access information and meeting materials will be available seven calendar days prior to the start of each meeting at the HSRB Website: https://www.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, Thomas O'Farrell, 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 listed under **FOR FURTHER INFORMATION CONTACT** at least 10 days prior to each 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. To pre-register to make oral comments, please contact the DFO, Thomas O'Farrell, listed under **FOR FURTHER INFORMATION CONTACT**. Requests to present oral comments during the meetings will be accepted up to Noon Eastern Time, seven calendar days prior to each meeting date. 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 the meetings 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. For the Board to have the best opportunity to review and consider your comments as it deliberates, you should submit your comments prior to the meetings via email by Noon Eastern Time, seven calendar days prior to each meeting date. 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 the DFO, Thomas O'Farrell listed under **FOR FURTHER INFORMATION CONTACT**. There is no limit on the length of written comments for consideration by the HSRB.

Topics for discussion. The agenda and meeting materials will be available seven calendar days in advance of each meeting at https://www.epa.gov/osa/human-studies-review-board.

Meeting minutes and final reports. Minutes of these meetings, summarizing the topics discussed and recommendations made by the HSRB, will be released within 90 calendar days of

each meeting. These minutes will be available at https://www.epa.gov/osa/human-studies-review-board. In addition, information regarding the HSRB's Final Reports, will be found at https://www.epa.gov/osa/human-studies-review-board or can be requested from Thomas O'Farrell listed under **FOR FURTHER INFORMATION CONTACT**.

Dated:

Jennifer Orme-Zavaleta,
EPA Science Advisor.