August 21st, 2017

EPA-HSRB-16-3

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Subject: ~~October 19-20, 2016~~July 26, 2017 EPA Human Studies Review Board Meeting Report

Dear Dr. Kavlock~~Burke~~,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics review of the study entitled "Field evaluation of the three topically applied insect ~~repellant~~repellent products containing IR 3535 against mosquitoes in Florida." The Board's responses to the charge questions and detailed rationale and recommendations are provided in the enclosed final meeting report.

Signed,

Liza Dawson, PhD
Chair
EPA Human Studies Review Board

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INTRODUCTION

On July 26th, 2017, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to the following study: "Field evaluation of the three topically applied insect ~~repellant~~repellent products containing IR 3535 against mosquitoes in Florida."

REVIEW PROCESS

The Board conducted a public meeting on July 26th, 2017. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, 2017, pp 27255) This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale and consensus in response to the charge questions on ethical and scientific aspects of the proposed research.

Following welcoming remarks from Agency officials, the Board began its review of the study. At the meeting, the Agency staff presented their review of scientific and ethical aspects of the protocol, with each presentation followed by clarifying questions from the Board. The HSRB solicited public comments and then took up the charge questions under consideration. The Board discussed the science and ethics charge questions and developed a consensus response to each question in turn. For each of the charge questions, the Chair called for the Board to vote to confirm concurrence on a summary statement reflecting the Board's response.

For their evaluation and discussion, the Board considered presentations given by EPA staff at the meeting, oral comments from Agency staff and from the investigators during the meeting discussions, and the Agency's written reviews which were provided to the Board prior to the meeting.

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SCIENTIFIC REVIEW: CHARGE TO THE BOARD AND BOARD RESPONSE

Charge to the Board:

Is the protocol, "Field evaluation of the three topically applied insect ~~repellant~~repellent products containing IR-3535 against mosquitoes in Florida" likely to generate scientifically reliable data, useful for estimating the amount of time each of the products tested repels ~~mosquitos~~mosquitoes?

Board Response:

The HSRB has concluded that the protocol "Field evaluation of the three topically applied insect ~~repellant~~repellent products containing IR-3535 against mosquitoes in Florida" is likely to generate scientifically reliable data, useful for estimating the amount of time each of the products tested repels mosquitoes, provided the changes requested by EPA and the changes requested by the HSRB below are taken into account and implemented.

HSRB Detailed Recommendations and Rationale:

HSRB reviewed information provided in advance of the meeting, as well as the EPA scientific and ethics presentations provided at the meeting. The Board noted that EPA requested numerous changes in the protocol document, both major and minor, and the investigators have agreed to make all the changes as detailed in EPA memos and in the draft protocol document itself. The Board concurs with all the EPA recommendations presented at the meeting and in the prepared memos; these changes are also detailed in the meeting minutes and will not be reiterated here. In addition, the Board identified further details that need to be clarified or modified in the protocol. These issues fall into five categories: 1) provision of more background information in the protocol document; 2) clarifications regarding the study design; 3) clarification of planned statistical methods; 4) provision of further detail about study procedures; and 5) correction of minor discrepancies in the protocol document. The HSRB requests that these changes be made and submitted for EPA review prior to submission to the reviewing IRB. Each of these areas is discussed below.

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1. **Provision of more background information**

The exposure of subjects to the test compound will be within acceptable safety margins based on existing toxicology data and based on *Margin of Exposure* calculations as provided in the EPA scientific review. The source of the information about toxicology should be cited in the background section of the protocol and in the reference list. The active ingredient of these LivFul Inc products, IR3535 (Ethyl butylacetylaminopropionate) should be mentioned explicitly in the background section also.

The previous dosimetry studies which identified the amount for a standard dose of the product should be described and cited in the background section. This information provides the justification for the study using a standard dose in the exposure studies rather than some other method of dosing. These previous studies were mentioned by EPA staff at the HSRB meeting but were not described in the protocol document, nor were references provided in the reference list.

2. **Clarifications regarding the study design**

It has been clarified for this protocol that no dose determinacy will be performed for any application type (i. e., wipe, pump or spray). Standard doses will be applied to skin surface area. These are doses likely/expected to be delivered by the application types. These standard doses were agreed on based on previous testing conducted for pump, spray and wipe methods of application. The study sponsor is asked to remove reference to weighing the wipes before and after application, and to ensure that throughout the document it is clear how any dose is applied to the area consistently. The study sponsor should also ensure there is no confusion on how the chemical formulation is applied. It is applied directly and not in a wipe, pump or ~~spray~~ lotion method. The protocol is assessing the CPT of formulation doses expected when using a wipe, pump or ~~spray~~ lotion application method. Documentation of previous studies relating the standard doses to the product types should be included in an attachment to the protocol.

For the measurement of CPT, some clarity is needed on the confirmatory landing time period in the protocol. The ideal and more accurate phrasing seems to be the language used by EPA in the meeting and found on slide 16:

Endpoint for efficacy is 'First Confirmed Landing' on a treated subject, which is:

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a. A landing that follows another landing within a ~~5-minute~~5-minute exposure period,~~-~~ or
b. A landing in an exposure period immediately following an exposure period in which a landing occurred.

The protocol has phrased it two ways as found on Page 26; "time at which one landing occurs in a 5-minute period followed by a second landing within the same 5-minute period or in the next 5-minute period which occurs 30 minutes later" and "the CPT is defined as the time between application of the ~~repellant~~repellent product and the occurrence of the fist landing in a 5-minute test followed by a confirmatory landing within 30 minutes or two landings within the same ~~5 minute~~5-minute period" (page 9).

The study team should clarify throughout the protocol what the exposure period is and what the rest period is. For example, if the rest period is 25 minutes, then the exposure and rest period are 30 minutes together. The study team should also include in the protocol the contingency plan should the 5 bites in a 5-minute period not be achieved by the controls and whether the study would end for that day in that instance. The team should include in the protocol whether the researchers will try to conduct the study during the expected months of high bite pressure, in the warm and/or wet months, and include in the protocol any specifications regarding the season or timing of the study.

3. Clarification of statistical methods

The basic statistical design and data analysis have been laid out and accepted by HSRB on meetings for other insect repellent studies over the last several years. With regard to the data analysis, the use of the Kaplan-Meier survival function to estimate median complete protection time (CPT) is reasonable. The treatment of subject withdrawals as censored observations is acceptable as well.

The EPA recommendation to increase the study day from 12 to 16 hours is reasonable given that subjects are not exposed to ~~mosquitos~~mosquitoes for the first two hours after application of the product. The criteria for determining if a study day produces "~~Valid~~ valid results for a test day" are confusing. The first criterion of "no more than three consecutive periods missed due to

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weather delay or inadequate landing pressure" is clear, but the second criterion stated in terms of the percentage of exposure periods not meeting the required landing pressure is unclear and needs to be restated.

The second criterion of "no more than 15% of non-consecutive exposure periods missed due to weather delay or inadequate landing pressure" is unclear and needs to be reworded to avoid any misunderstanding. For example, if there is no exposure during the first 4 periods (2 hours) and the 5th, 7th and 9th periods have adequate pressure, the first criterion would not apply but the second criterion as stated apparently would make the results for that day invalid (3/9 > 0.15). If the intention of this criterion was to base it on the entire 16-hour day, then missing a total of 5 periods, no 3 of which were consecutive, would invalidate that day. In that case, perhaps a statement such as the preceding would avoid any confusion.

Page 8 of EPA's Guidelines on Insect Repellent Efficacy Testing (OPPTS 810.3700) mentions that withdrawal of test subjects from the study before failure may compromise validity; the protocol should address how this would be handled. Right censoring is mentioned for use when subjects fail to experience failure (no landings in the test time). Right censoring is not mentioned for withdrawal. Censoring is mentioned for withdrawal (i.e., use the time of withdrawal as the CPT). Guidelines suggest that research try to avoid failure to achieve the study endpoint by applying ingredient 2 to more hours before testing occurs, given that reaching a failure point is more scientifically desirable than right censoring that point. EPA's Guidelines on Insect Repellent Efficacy Testing~~OPPTS810.370~~ mention~~s~~ right censoring and withdrawal in one paragraph but it does not specifically link the two. Censoring (using the time of withdrawal) is acceptable in the analysis for withdrawal and right censoring for failure; the protocol should include additional language on handling failures and withdrawal and censoring to address these points. EPA has mentioned that no more than 6 of the 13 subjects should be censored and this should also be specified in the protocol.

4. Provision of more detail about study procedures

The Board notes that EPA requested that pathogen testing be extended to all relevant ~~mosquito~~ vector-borne illnesses (EPA Science and Ethics Review, page 12). Section 8.1.3 should include

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the methodology for testing for all relevant vector-borne illnesses, unless the qPCR method is the same, in which case this should be noted.

The protocol should include a description of the demographics of the area in accordance with OPPTS 810.3700 which mentions that "protocols should describe the demographic characteristics of the pool from which subjects will be recruited." The Board notes that excluding non-English speakers may affect the demographics of the study participants, and the resulting demographic characteristics of participants should be documented. The Board did not express concern that exclusion of non-English speakers would adversely affect the validity of the study.

Much of the scientific rigor of the project relies on the biting pressure of mosquitoes and the ability of participants to aspirate, that is, capture, the mosquito. A short description of this process should be included in the protocol. The training on aspiration and the ability by subjects to detect a landing will be very important to the scientific soundness of the project, and the process of aspiration is not found in the OPPTS 810.3700 guidelines. This information could be included as an attachment to further describe what the training consists of and how difficult or easy the process is. Page 20 of the protocol briefly mentions ""insect catch landing training," and further information could be added in this section. EPA has also requested this additional information on training.

It is not clear why each participant who has the material applied is accompanied by a person from the research team that will help them aspirate, however the controls (those not receiving the applied materials) are teamed with each other. Given that this may affect the accuracy of aspiration for the controls that determine bite pressure, it would be appropriate to also pair the controls with a member of the research team, unless there is a justification for handling treated subjects differently from controls. The OPPTS 810.3700 guidance guidelines mentions that subjects can work in pairs;, however, a discrepancy between treated and untreated subjects would require some explanation.

The Board discussed the question of the consumption of food types during the 24 hour24-hour period before testing, and the lunch that subjects will be allowed to bring the day of testing. Although there is mention of the influence of spicy food on CPTattractiveness to mosquitoes, HSRB the Board agreed that the only requirements for what subjects consume the day before or

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the day of testing are that the study participants avoid alcohol and tobacco smoke. HSRB suggest refrigeration be provided for the lunch that subjects bring with them.

The soap to be provided is mentioned in the consent form on page 3. It is important to also mention in this in the protocol and to provide soap for all subjects (control and treated) to ensure consistency. The Board notes page 28 of OPPTS 810.3700 states that "The treated area should be washed with unscented soap, rinsed with a solution of ethanol or isopropyl alcohol in water and dried with a clean towel." In discussion with EPA, the Board determined that rinsing with ethanol or isopropyl alcohol should be implemented in this study in case subjects applied skin products at home prior to the testing day. Also, the use of unscented soap should be consistent.

The protocol mentions that following the pregnancy test the participants will be provided a discreet means to dispose of the test. OPPTS 810.3700, page 17 mentions that no positive pregnancy test should be recorded. The language in protocol and consent form should specifically include this statement. The study team should also clarify whether study participants are allowed to take the test home if they choose.

The protocol provides some additional guidance on instructions for study participants between experiments in field and in the lab, for example, on page 9 and 27, it describes instructions to avoid rubbing limbs together after treatment with the repellent product. However, the protocol should include additional advice on not contacting surfaces between experiments and not allowing clothing to contact the area when using the bathroom.

5. Resolving discrepancies in the protocol document

There is a need to ensure that all documents (protocol, consent form, and appendices) match in their phrases and comments, especially following changes requested by EPA and HSRB.

Documents need to be reviewed to ensure that the right number of subjects needed for each product testing is specified. The number 6, instead of 5 needed as alternative, is still listed in certain areas of the document, for example on page 17, section 8.3.1 which lists 6 alternates per day.

Commented [AM1]: Did they also recommend that the study sponsor provide participants with lunch and snacks?

Commented [DL([2]: I believe the board decided not to suggest providing lunches due to the complications of people's different dietary needs.

Commented [AM3]: Delete highlighting

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In different places in the protocol there are discrepancies regarding the timing of contacting participants after the testing. The protocol mentions contacting participants within 48 hours, on page 3, to determine if any adverse event has occurred. In other sections of the protocol 72 hours is mentioned as a follow-up point to contact for further participation, and on ~~Page~~ page 27 for adverse events. The ~~72 hour~~72-hour time frame is also listed in the recruitment materials. EPA has indicated that the ~~72~~ 48-hour time period is in error, and should be removed. There are some inclusion/exclusion criteria that can be seen as basic and some that that will occur based on capability of the participants as the study proceeds, such as ability to operate an aspirator. It may be helpful to separate these types of inclusion criteria into two groups in the protocol document. For the Adverse Event Monitoring Questionnaire, use of the term "A&E" is more common in British healthcare. The Board recommends substituting the term "Urgent Care and/or Emergency Room" instead of A&E.

ETHICS REVIEW: CHARGE TO THE BOARD AND BOARD RESPONSE

Charge to the Board:

Is the research described in "Field evaluation of the three topically applied insect ~~repellant~~repellent products containing IR 3535 against mosquitoes in Florida" likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response

When 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 Part 26.

HSRB Detailed Recommendations and Rationale:

The board agrees with the suggestions and changes made by EPA Protocol Version 5, dated April 23, 2017 (file name "Protocol_field_V5_05102017_OPP comments_6-29-2017"). This report will not repeat EPA's recommendations as the sponsor and PI have agreed to incorporate the changes.

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40 CFR 26 subpart K requires that studies initiated on or after April 7, 2006 involving intentional exposure of human subjects to a pesticide be reviewed and approved by an institutional review board (IRB) that meets the membership and review criteria listed in that subpart. This research is being independently reviewed by the University of Florida Institutional Review Board, which meets the requirements.

40 CFR 26 subpart K mandates studies minimize risk to subjects, equitably select subjects, seek and appropriately document informed consent, make adequate provisions to ensure safety of subjects, and protect the privacy of subjects and confidentiality of data.

Risk Minimization:

The study team has done an excellent job in minimizing physical and emotional risk to participants. The team will work closely with the local monitoring agencies to verify that study sites are free from Zika and West Nile virus. The ~~board~~ Board agreed that testing should occur for other diseases if warranted, consistent with the EPA recommendation. ~~if the risk of Dengue Fever and Chikungunya are negligible in northern Florida, so there is no need to test for other vector-borne illnesses.~~ Shade and seating in a screened area with refreshments provided address the concerns for comfort and safety between exposure periods. Recommendations on proper clothing, provision of head nets and gloves, and training on mosquito aspiration decrease risk during exposure periods. The ~~board~~ Board recommends consistency in the protocol regarding the inclusion criteria of self-reported good general health and exclusion criteria of having a history of cardiac, pulmonary, dermatologic, or anaphylactic problems (study synopsis and sections and 4.2).

Equitable Selection:

The ~~b~~Board agrees with the sponsor and EPA that excluding non-English speakers does not compromise the scientific validity of the study, as language does not affect attractiveness to ~~mosquitos~~mosquitoes, and does not unfairly disadvantage non-English speakers, since there is no direct benefit to study participants derived from the repellency testing.

Commented [LD4]: EPA has stated that monitoring for those diseases should also take place (EPA Science and Ethics Review, page 12), so our comment here is inconsistent with EPA's stipulations.

Commented [AM5R4]: With the minor edits, I think the Board's recommendations and EPA's comments can both be resolved in a consistent manner.

Commented [DL([6R4]: I am suggesting a more strongly worded concurrence with EPA's recommendation, focusing on the need to do testing if there is some risk, rather than a presumption that there is no risk. I believe this is consistent with the Board's view on this point.

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The ~~b~~Board agrees that the inclusion and exclusion criteria contribute to the scientific and safety aspects of the proposal, with the exception of the exclusion criterion of prior participation in "any intervention study (other than an insect repellent study) in the previous 3 months" (found in study synopsis page 4). The ~~board~~ Board stated that any type of intervention study in the previous 3 months, including insect repellent studies, should be an exclusion criterion. Discussion with the study sponsor indicated that the concern is that participants recruited for this study would not be able to participate in multiple sessions of this study. The subsequent allowance for participating in a biting insect study in the previous ~~48~~ 72 hours allows individuals to participate in multiple sessions of this study. The board recommends that the second exclusion requirement be altered to "Participated in any other intervention study in the previous 3 months."

Informed Consent:

Sections 17 and 19 of the informed consent form seem to be template language used in medical intervention studies that include patients that typically occur at the University of Florida or Shands Hospital. Much of this template is inappropriate for an insect repellent study with healthy volunteers being conducted outside the confines of a hospital. Specifically, the researchers will not be creating protected health information and there is no reason to be sharing study information with health professionals at the University of Florida or Shands Hospital. The ~~b~~Board recommends the following changes:

Section 17. How will your health information be collected, used, and shared?

- First Paragraph, first sentence: delete "create"
- Second paragraph, should read:
  "Your protected health information may be collected, used, and shared with others to determine if you can participate in the study. This information will be gathered from you via a health questionnaire. More specifically, the following information may be collected, used, and shared with others:"

Section 19. Who will be allowed…

Move second bullet to last and should read: "in the event of a medical emergency, medical professionals at the University of Florida or Shands Hospital.

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The consent form should include information regarding how many bites, if any, subjects are likely to receive, as recommended by OPPTS 810.3700. The potential number of bites would have to be mentioned for control and those receiving treatment, and for field study and the study on attractiveness.

Section 4.4 of the protocol mentions that participants can withdraw without giving a reason and without forfeiting benefits based on their participation. This section of the protocol should also include the information that if they withdraw for a medical reason, they will be compensated in full for the day.

Safety:

The study team provides a number of measures to ensure a safe environment for this field study. The Board agrees with EPA that more information need to be provided about the "First Aider" who will be called in the case of emergency. Typically, in EPA exposure studies, investigators have trained medical personnel on site for the entire exposure time.

The Board also recommends some changes with regard to reporting Adverse Events (AE) and Serious Adverse Events:

- Section 6.2. Reporting Procedures: First sentence change "should" to "will."
- Section 6.2.2 Serious AEs. All SAEs should be reported to UF IRB for independent review, not just those deemed related and unexpected by Dr. Weeks. The final two sentences should read, "AE questionnaires meeting the SAE definition will be submitted to the Principal Investigator, Dr. Emma Weeks with 24 hours and she will report them to the UF IRB within 5 days of becoming aware of the event.

Privacy and Confidentiality:

As stated in the informed consent section above, portions of the protocol use phrases more suitable to medical intervention trials on patients being cared for by Shands Hospital rather than a repellent exposure study. Specifically, there is no need to routinely share protected health information ~~HPI~~ with the University of Florida (outside of the IRB) and Shands Hospital.

Commented [AM7]: Protected health information? Suggest spelling out.

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Section 11.3.3. of the protocol should be changed in the same fashion as section 19 of the informed consent form.

Some notes for HSRB board members from the Chair:

Three comments were taken out:

- One about the overall toxicity—just suggested including in background section that toxicity profile poses no concerns due to prior evidence.
- Comment from scientific review: Be aware of guidance on storage of test materials, page 7 of OPPTS 810.270 (i.e., ambient temperature and humidity before use)—*did not seem to be a concrete recommendation*
- Comments from scientific review: EPA has a question on who decides which leg to be tested. This could be randomized if in any way they feel this affect the study outcome (i.e., bite rate)? –*already included in EPA comments, they requested randomization*

One potential question regarding testing for other pathogens other than West Nile and Zika. EPA review states that EPA is requesting testing for other pathogens, specifically Dengue and Chikungunya, and that the protocol team has agreed. It appears this testing would be done by the team and not done by local mosquito control districts (according to meeting minutes). The ethics section of our review indicates concurrence with original plan to only test for WNV and Zika. This discrepancy would need to be resolved.

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