



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND  
POLLUTION PREVENTION

June 12, 2020

**MEMORANDUM**

**SUBJECT:** Ethics Review of Completed Study titled “Single group trial to determine the complete protection time of an insect repellent formulation containing 30% Citriodiol® (Oil of Lemon Eucalyptus) against three species of ticks”

**FROM:** Michelle Arling, Human Research Ethics Review Officer  
Office of the Director  
Office of Pesticide Programs

**TO:** Robert McNally, Director  
Biopesticides and Pollution Protection Division  
Office of Pesticide Programs

**REF:** Jones, Robert T. (2019) Single group trial to determine the complete protection time of an insect repellent formulation containing 30% Citriodiol® (Oil of Lemon Eucalyptus) against three species of ticks. Sponsored by Citrefine International Ltd. Study Completed November 14, 2019. Unpublished Report Updated and Submitted April 23, 2020. 4562 pages. MRID 51132201.

I have reviewed available information concerning the ethical conduct of the referenced research study, “Single group trial to determine the complete protection time of an insect repellent formulation containing 30% Citriodiol® (Oil of Lemon Eucalyptus) against three species of ticks”. The documents submitted to the Environmental Protection Agency (EPA) describe the implementation and results of a laboratory study based on EPA guidelines OSCPP 810.3700: Insect Repellents to be Applied to Human Skin. The primary objective of the research was to determine the efficacy of this skin-applied repellent against three species of ticks in a lab setting. The secondary objective was to determine the typical consumer dose for the product used via pump spray.

After reviewing all available documentation, I have determined that the conduct of this study met applicable ethical standards for the protection of human subjects of research and that the requirements for documentation of ethical conduct of the research were satisfied. If the research is determined to be scientifically acceptable, I find no barrier in regulation to the EPA’s reliance on this study in actions under the Federal Insecticide, Fungicide, or Rodenticide Act

(FIFRA) or the Federal Food, Drug, and Cosmetic Act (FFDCA). If the research is not scientifically valid, it would not be ethical to rely on it.

In addition, under 40 CFR 26.1604, EPA is required to seek input from the Human Studies Review Board (HSRB) for intentional exposure human studies covered by EPA's Human Studies rule that are initiated after April 7, 2006. EPA will share this study and all associated support documents, as well as EPA's science and ethics reviews of the study with the HSRB for their review. This memorandum and its attachments constitute EPA's ethics review.

### **Completeness of Submission**

The materials provided by the Arthropod Control Product Test Centre (ARCTEC) at the London School of Hygiene and Tropical Medicine (LSHTM) satisfied the requirements of 40 CFR 26.1303. A checklist indicating how each requirement has been satisfied is provided in Attachment 1.

### **Summary Characteristics of the Research**

Citrefine International Ltd. (Citrefine) sponsored this study in order to determine the complete protection time (CPT) or duration of efficacy of a skin-applied repellent containing 30% Oil of Lemon Eucalyptus (OLE). The study report summarizes two distinct phases of the study. First, a consumer dose rate was determined by having subjects make 3 applications of the product to their forearms and calculating the average amount applied by each subject and across all 25 subjects enrolled in this phase. A total of 25 individuals participated in this phase. Second, the dose calculated during the first phase was used to test the efficacy of a product containing 30% OLE applied to human skin against ticks in a lab setting. A total of 91 test days were initiated, and the data from 75 test sessions were included in the results for this phase. Overall, a total of 188 potential subjects were identified through recruiting, 70 people consented to participate in one or both phases of the study, and 65 individuals participated in at least one testing event. The study was initiated on November 16, 2018. The consumer dose phase began on February 6, 2019 and ended on February 27, 2019. The repellent testing phase began on May 8, 2019 and ended on October 18, 2019. The study was completed on November 14, 2019.

Human subjects were used because no reliable models or surrogates have been found to adequately predict the duration of efficacy of topically-applied insect repellents. The repellent test product (OLE) has been registered by EPA and has already been found to present little or no risk when used as directed. The precautions taken to mitigate hazards associated with the study were consistent with the approved protocol.

### **Required Reviews and Oversight of the Research**

Oversight of the research was conducted by two institutional review boards (IRB): Western Institutional Review Board (WIRB) and the London School of Hygiene and Tropical Medicine (LSHTM) Interventions Research Ethics Committee. The IRBs entered into a reliance agreement for dual IRB oversight, signed by WIRB on August 2, 2017 and by LSHTM's IRB on July 25, 2017 (pp. 612-613). In this document:

*Both IRBs agree[d] to the following conditions for shared oversight:*

- 1. If either IRB makes a finding of serious or continuing non-compliance, or suspends or terminates the research, it will notify the other IRB of these actions and provide a summary of the reasons.*
- 2. If either IRB receives a subject complain relevant to the oversight of the other IRB, the IRB will notify the other IRB and provide information regarding the subject complaint.*
- 3. Both IRBs will approve the consent form, the protocol, and other aspects of the research, and both IRBs will provide continuing oversight of the research for the duration of the study.*
- 4. Both IRBs will follow their own written procedures. (p. 612)*

The WIRB is registered with the Office of Human Research Protections (FWA#: 00005790). The WIRB holds full accreditation from the Association for Accreditation of Human Research Protection Programs. Satisfactory documentation of the WIRB's procedures and membership were provided to EPA.

The LSHTM Interventions Research Ethics Committee is registered with the Office of Human Research Protections (FWA#: 00003028). Satisfactory documentation of the Ethics Committee's procedures and membership were provided to EPA.

The research was conducted outside of the United States, in London, England. The LSHTM Interventions Research Ethics Committee is bound by a Federal-wide assurance, which is an assurance of compliance with the U.S. federal regulations for the protection of human subjects in research, i.e., the Common Rule, codified by EPA at 40 CFR 26, Subpart A. The Ethics Committee's Terms of Reference note that "[t]he committee endeavours to ensure that all studies carried out by LSHTM staff and students meet [U.S. standards for the protection of human subjects in research] by reviewing projects against the four essential ethical principles: beneficence, non-maleficence, justice and autonomy. In addition, the research project must be based on good quality, valid science, risks must be minimised, and not exceed the potential benefits to the individual or community." (LSHTM Ethics Committee Terms of Reference, p. 2) In reviewing research, the Ethics Committee is committed to complying with 21 CFR 56, among other regulations and international standards. These standards are substantially similar to those in the Common Rule and EPA's rule for the protection of human subjects, and require the IRB to ensure that risks are minimized and reasonable in relation to anticipated benefits, that selection of subjects is equitable, and that informed consent is appropriately obtained and documented.

Documentation regarding final IRB approval of the protocol and subsequent correspondence between the researchers and the IRB is included with the materials provided to the HSRB members in Appendix 16.6 to the Study Report.

### **Ethics-Related Chronology**

Following EPA and HSRB review of the protocol, the Study Director addressed all comments and resubmitted the protocol to the WIRB and to the LSHTM Ethics Committee for approval.

A draft protocol approved by the WIRB was submitted to EPA for review. The protocol and EPA’s review<sup>1</sup>, dated March 30, 2018, were discussed at a public meeting by the HSRB on April 24, 2018. Per the final HSRB meeting report, dated July 10, 2018, the HSRB concluded that “with the modifications recommended by the EPA and the HSRB, the study is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L.”<sup>2</sup>

In follow-up to the HSRB meeting, the researchers revised the protocol and related materials to address comments, including the EPA and HSRB comments described in Attachment 2, and submitted the revised documents to the WIRB and to the LSHTM Interventions Research Ethics Committee for review and approval prior to initiating the study. The WIRB approved the protocol on October 5, 2018 (p. 632), and the LSHTM Interventions Research Ethics Committee approved the protocol on November 9, 2018 (p. 754). The study was closed out by the WIRB on November 13, 2019 (p. 744) and the LSHTM Interventions Research Ethics Committee accepted the close-out of this study on November 12, 2019 (p. 800).

## Recruiting

Recruitment was conducted in substantial compliance with the protocol. The protocol called for enrolling no fewer than 25 subjects, assuming all would complete both the dosimetry phase as well as repellent efficacy testing with all 3 species of ticks, and up to 100 subjects, assuming each subject only participated in 1 testing event. Recruitment occurred in three rounds. In total, 188 people expressed an interest in participating, and a total of 70 people attended the screening visit, consented to enroll, and completed the health questionnaire. See the summary table below.

	Contacted	Consented	Study Phase
Round 1	75	38	2 dosimetry only 11 repellent efficacy only 25 dosimetry and efficacy
Round 2	49	24	24 repellent efficacy only
Round 3	64	8	8 repellent efficacy only

Recruitment was conducted in London, England. According to the study report, recruitment advertisements included posters, emails, postings on Craigslist, and Gumtree (an

<sup>1</sup> Fuentes, Bohnenblust, Arling. Science and Ethics Review of a Protocol for Laboratory Evaluation of Skin-Applied Tick Repellent Product Containing OLE. March 30, 2018. [https://www.epa.gov/sites/production/files/2018-04/documents/1a\\_ole\\_tick\\_repellent\\_protocol\\_science\\_and\\_ethics\\_review\\_final\\_3-30-18.pdf](https://www.epa.gov/sites/production/files/2018-04/documents/1a_ole_tick_repellent_protocol_science_and_ethics_review_final_3-30-18.pdf)

<sup>2</sup> Dawson, Liza. April 24-26, 2018 EPA Human Studies Review Board Meeting Report. July 10, 2018. p. 6. [https://www.epa.gov/sites/production/files/2018-07/documents/final\\_hsrb\\_report\\_from\\_april\\_2018.pdf](https://www.epa.gov/sites/production/files/2018-07/documents/final_hsrb_report_from_april_2018.pdf)

online classified/community website). The IRB-approved advertising materials provided a brief explanation of the study, indicated that compensation would be provided, and included email and phone contact information. See Appendix 16.2 for the advertisements.

Those who responded to the advertisements were informed of the eligibility criteria, indicate whether they believed they were eligible, and asked whether they wished to continue enrollment in the study. Those who indicated they were eligible and interested were assigned a subject number and added to a recruitment list. Once the target number of individuals were on the list (e.g., 75 potentially eligible and interested candidates in recruitment round 1), the list was randomized and prospective subjects were invited to participate in a screening and consent meeting.

### **Consent and Enrollment**

All participating subjects completed the informed consent process detailed in the study protocol and signed the IRB-approved consent form. (Appendix 16.2, pp. 130-137) Screening and consent meetings were held at the Insectaries and in a room at the LSHTM on a one-on-one basis. Upon arrival, candidates' ages were verified by reviewing a government-issued identification. Next, the Study Director or a designated member of the research team familiar with the protocol and consent materials provided a copy of the consent form to the candidate with instructions to read the entire document. When the candidate was finished, the researcher leading the meeting went over relevant information orally, including "the study, its purpose, the subject's potential role in the study, the potential duration of testing, the identity and function of the repellent to be used, potential hazards associated with the study, and [sic] steps taken to mitigate these hazards, the inclusion/exclusion criteria, and the procedures for reporting adverse events." (p. 20) Additionally, the researcher described the test procedures step by step, and informed females of the requirement and procedures for pregnancy testing on each day of testing. The consent form and presentation highlighted that participation was completely voluntary and explained the process for withdrawal by the subject and the criteria for withdrawal by the Study Director.

Following this presentation of information, candidates were asked if they had any questions. Candidates who remained interested in participating were asked a standard set of questions (*see* pp. 94-95) to ensure they comprehended the study and the consent form. Those who demonstrated comprehension were invited to sign the consent form and enroll in the study. All subjects received a copy of their signed consent forms. After signing the consent form, subjects completed a screening questionnaire form. (p. 138) Then a member of the research team confirmed eligibility through completion of the first four pages of the Case Report Form. (pp. 139-142)

Subjects met the inclusion criteria outlined in the protocol and stated in the study report. (p. 20) Subjects were eligible to participate if they were capable of following instructions and giving informed consent, between 18 and 65 years old, a non-smoker or willing to refrain from smoking as instructed, able to stand unsupported for at least 5 minutes at a time, willing to have hair around the wrist clipped, and able to speak and understand English. People were not eligible to participate if doing so would pose a risk to their health (allergic or sensitive to tick bites,

allergic to the test substance, skin disorders and/or open cuts/scrapes on the legs, previous anaphylaxis, compromised immune system), if they participated in another study within the past 72 hours, or if they had a phobia of ticks or tick bites. Additionally, pregnant or nursing women, employees (and their spouses) of ARCTEC and the study sponsor, and those who were supervised by or students of any faculty member involved in the study were not eligible to enroll.

## Demographics

Of the 65 subjects who consented and participated in at least one test day, 33 were females and 32 were males. For the consumer dose phase, 13 females and 12 males participated. For the repellent efficacy testing phase, 26 females and 29 males participated, 15 of whom had also participated in the consumer dose phase. All subjects were at least 18 years old.

## Randomization and Test Day Procedures

Both phases of the testing were conducted by ARCTEC in London. The consumer dose testing phase occurred “in an outside, sheltered space adjacent to the Barbara Sawyer Insectaries.” (p. 24) For the consumer test, subjects donned safety goggles and an apron and washed their forearms. Then, subjects were provided a container of the product along with the label, and asked to read the label and make a practice application according to the product labeling. After the practice application, subjects washed and dried their arms. Then researchers placed 3 gauze bracelets each 3 centimeters wide on one forearm spaced equally from wrist to elbow. Subjects applied the test substance to that forearm, then the bracelets were removed by a researcher wearing gloves and placed in a bag. This procedure was repeated twice more to yield data for 3 applications. To calculate the consumer dose, the researchers averaged the amount applied across each subject for each application by subtracting the pre- and post-application weight of each bracelet, then averaged the application amount across all subjects to arrive at a consumer dose of  $0.793 \mu\text{L}/\text{cm}^2$  to be used in the second phase of the study. Due to an error in data entry (the data for only 24 out of the 25 subjects were averaged), repellent efficacy testing up to July 4, 2019 was conducted with a consumer dose rate of  $0.801 \mu\text{L}/\text{cm}^2$ ; this was reported as a protocol deviation.

The repellent efficacy test was conducted inside a lab at the Barbara Sawyer Insectaries building at LSHTM, using three species of ticks: *Amblyomma americanum*, *Ixodes scapularis*, and *Rhipicephalus sanguineus*. Testing was originally scheduled to include *Dermacentor variabilis*, but due to lack of questing behavior testing with this species was discontinued after 5 test sessions. This species was replaced with *Rhipicephalus sanguineus*. Testing with *Amblyomma americanum* involved 31 visits, and 25 completed test days; 3 tests were stopped due to excessive missed time points, 2 subjects withdrew from testing, and 1 test ended early because the subject requested to stop testing before achieving CPT or reaching the maximum testing time. Testing with *Ixodes scapularis* involved 25 visits, all of which resulted in completed tests. Testing with *Rhipicephalus sanguineus* involved 30 visits, and 25 completed test days; 5 tests were stopped due to excessive missed time points.

For the test, a table was set with 3 trays – one for holding ticks, and one for each of the subject’s hands. Researchers measured subjects’ forearms and calculated the surface area in

order to determine the proper amount of test substance to be applied. Subjects' forearms were washed with unscented soap and water, then if necessary, hair was clipped from the wrist to 3 centimeters up the forearm to allow ticks to walk on the skin surface. Subjects' arms were marked with two lines, a boundary line at the wrist (the edge of the treated area) and a release line (3 centimeters toward the fingers from the boundary line). Researchers measured the consumer dose using a calibrated micropipette and applied it from wrist to elbow on a single forearm. Starting at 15 minutes post-application, the efficacy testing began. Testing started with the subject placing the untreated or control hand into the tray, putting fingers flat on the bottom and laying the palm on the hand rest. A tick was placed onto the subject's hand at the release line with the mouth facing the arm and the movement was monitored. If the tick moved up the arm from the release line and crossed the boundary line within 3 minutes, it was considered "actively questing" and testing proceeded. The actively questing tick was moved from the control arm to the release line of the treated arm, which was placed in another tray and arranged in the same manner. When the actively questing tick began moving on the treated arm, the timer was started. A tick was classified as "not repelled" if it moved from the release line to the treated area and remained in the treated area for at least 1 minute. A tick that did not cross the boundary line and remain in the treated area for at least 1 minute (crossing back into the untreated area, falling off the arm entirely) were classified as "repelled".

Testing continued every 15 minutes from the time of application until a confirmed crossing occurred (a second tick classified as "not repelled" within 30 minutes of a first tick being classified as "not repelled"), or for up to 10 hours. If an actively questing tick was not identified within 10 minutes of starting the process, the time period was missed. Subjects were allowed to move around between the test periods, and skipped one test period during the day in order to have lunch. To ensure the integrity of the repellent, subjects were instructed to use hand sanitizer instead of washing with soap and water during the test period.

At the end of the test day, subjects washed their arms thoroughly with unscented soap and water, provided with their compensation, and reminded to contact the Study Director with any questions. The study staff followed up with each subject within 48 hours of the test day in order to determine whether the subject experienced any adverse effects and to ask whether the subject wanted to continue testing.

The test day procedures were conducted in substantial compliance with the ethical aspects of the protocol.

### **Safety Precautions**

The study followed the measures outlined in the protocol to minimize identified risks to subjects during testing, including adverse reactions to the test substance, adverse reaction to tick bites, potential transmission of tick-borne disease, potential stress from finding out the results of a pregnancy test, and unintentional release of confidential information. The screening criteria were used to minimize risks of adverse reactions to the test substance by only enrolling subjects without a known sensitivity or allergy to the test substance or any skin-applied insect repellents. In addition, subjects with localized skin disorders on the forearms that could be exacerbated by exposure to the test substance were excluded.

Prior to entering the Insectary building, subjects were provided with a sheet informing them of the risks of potential exposure to mosquitoes and ticks within the facility and the risks of entering a hot, humid environment, and how to minimize those risks. See p. 16. Ticks were placed one at a time on subjects' arms and monitored closely to minimize the chance for the tick to move further onto the host for a suitable location to attach (e.g., armpit). Ticks were removed if they appeared to bite and attach to the subject. Ticks were sourced from pathogen-free colonies at Oklahoma State University Tick Rearing Facility and a subset from each batch were tested for pathogens in order to eliminate the risk of transmission of tick-borne disease. Each tick was used only once with a single subject and was destroyed after being placed on a subject's arm.

### **Adverse events**

There were 8 adverse events during the course of the study. The Study Director followed the protocol process for following up with subjects after each test day, and continuing follow up until the adverse events were resolved. The adverse events were reported as necessary to WIRB and the LSHTM Ethics Committee. None of the adverse events were serious.

Six of the adverse events were related to bites by ticks or mosquitoes. One subject experienced swelling on the arm following study participation, and was directed by the study's medical monitor to visit a doctor. The subject received a diagnosis of "toxic effect of venom of other arthropods." (p. 72) The subject recovered with no lasting effects. One subject experienced a suspected tick bite, which was identified by a red area around the site and itching. The subject used anti-itch cream and the incident resolved. Four subjects each experienced a mosquito bite from colony-reared mosquitoes being used for other studies in the Insectaries building.

Two subjects experienced general ill feeling following study participation. One was fatigued and had a headache and fever. She noted that the study coincided with an exam period, so the symptoms could be related to her stress. The medical monitor determined this incident was not related to study participation. The second subject reported feeling dizzy after participating in the study, and followed up with a medical professional who said, "her dizziness was due to a possible dehydration or a drop in blood pressure as a result of the laboratory temperature." (p. 71) Both of these were determined not to be study related and the subjects recovered and did experience any lasting effects.

### **Female Subject Screening**

During recruitment and enrollment, women were asked about whether they were pregnant, lactating, or nursing. In addition, prospective subjects were asked to complete a questionnaire that included "If female, are you pregnant, nursing, or intending to become pregnant?" (p. 501) If a subject responded affirmatively, she was not eligible to participate. Female subjects' continued eligibility to participate was verified at the start of each test day by completing pregnancy testing according to the procedures outlined in the protocol. Pregnancy testing was conducted in by the female subject alone, and the subsequent discussion with a female member of the research team occurred in a private setting. This procedure was verified each test day through the completion of the case report form. (pp. 139-181)

## **Confidentiality**

The study followed the measures outlined in the protocol regarding confidentiality. The Trial Coordination Centre is registered under the General Data Protection Regulation. Subjects were identified by numbers on study documentation, rather than by name. Study records are stored on a password-protected computer server. Pregnancy tests were conducted in private and the results were only communicated with the Study Director or female member of the study team to confirm eligibility of female subjects to participate.

## **Compensation**

Each subject received compensation consistent with the protocol and informed consent document. Compensation was £20 for attending the consent and screening appointment. Subjects who participated in the consumer dose test were paid £20 for that session. Subjects participating in the repellent efficacy testing were paid £7.50 per hour, rounded up to the next hour.

## **Withdrawal**

Subjects were informed that they were free to withdraw from the study at any point, including during the testing period, without forfeiting any benefits to which they were entitled. This was communicated during the consenting process and at the beginning of each test day. A subject who consented to participate in the consumer dose testing phase withdrew prior to participating. Another subject ended his participation early on one test day in order to attend another engagement, though he returned to participate fully in another test day.

## **Protocol Amendments and Reported Deviations**

The protocol was amended five times. All amendments were made in accordance with the regulation and the policies of WIRB and the LSHTM Ethics Committee and became effective upon review and approval of the IRBs. The first two amendments were made before any testing began. The first amendment addressed comments from the HSRB and EPA following the April 2018 meeting. The second amendment made administrative changes. The third amendment occurred between the consumer dose phase and the repellent efficacy testing phase. It made administrative changes, updated the participant information sheet to change the details for the study director to match the protocol, and changed the solvent. The fourth and fifth amendments were made during the repellent efficacy testing phase. The fourth amendment added two additional species of ticks for testing and an additional supplier of ticks, and made administrative changes. The fifth amendment was made to clarify the protocol requirements for missed time points. Time points were missed when a questing tick could not be identified within 10 minutes. The amendment clarified that a test would be repeated if more than 6 time points were missed for this reason, and that a subject who failed a test with more than 2 species would be withdrawn and replaced. This amendment also clarified that data from subjects who withdrew prior to 9 hours of testing and who missed more than 6 time points would not be used and that data from subjects who withdrew after at least 9 hours of testing would be used with the subject's consent. None of these amendments directly impacted the health, safety, or welfare of the subjects. EPA's science

review concluded that these amendments did not negatively impact the scientific validity of the research.

There were several deviations to the protocol that involved subjects, described on pp. 41-46 of the Study Report, and in Appendix 16.3. They are discussed below.

A deviation related to the calculation of the consumer dose applied to testing with subjects up to July 4, 2019. Following the completion of the consumer dose testing phase, the average dose to be applied during the repellent testing phase was calculated as  $0.801 \mu\text{l}/\text{cm}^2$ . This dose only included data from 24 out of 25 of the subjects who performed the consumer dose testing. The consumer dose reflecting data from all 25 subjects is  $0.793 \mu\text{l}/\text{cm}^2$ . The difference is  $0.008 \mu\text{l}/\text{cm}^2$ , within the standard error of  $\pm 0.217 \mu\text{l}/\text{cm}^2$  permitted in the protocol. The higher dose was used in 38 tests conducted May 8, 2019 through July 1, 2019. Additionally, because the dose for subject 593092 was carried over between visits rather than recalculated for each visit, it was used in two additional tests for involving this subject (August 28, September 19). Upon discovering the error in consumer dose calculation, additional QA checks were put into place to ensure that all data collected are included in tables prior to performing calculations or analysis.

Several deviations were related to the application of the test substance. For subject 593039, the application was made to the left arm of the subject rather than the right arm. The subject's forearm measurements were slightly different, resulting in an overapplication of 0.5%. This amount is within the standard deviation of the standard dose derived from the consumer phase. For subject 593067, the randomization schedule dictated application to the right arm, but application was made to the left arm. The report notes that the correct dose amount for the left arm was applied.

Several deviations occurred in which testing was terminated due to ticks' lack of questing behavior before the CPT was achieved or the testing time limit of 10 hours was reached. Termination constituted a deviation prior to implementation of amendment 5, which specified that up to 6 time points could be missed before the test had to be stopped.

A deviation occurred with subject 593120. This subject was engaged in a test and requested to end before CPT was achieved or the maximum test time was reached. Under the protocol, this would be considered a withdrawal. However, the subject indicated he needed to leave to attend a meeting and wished to continue his enrollment in the study. The subject returned and completed a test day with the same species at a later date. As a result of this deviation, two changes were made. Subjects were asked at the beginning of the test day whether they were available for up to 10 hours of testing, and the reminder emails sent to subjects included a note that testing could extend beyond 7 pm.

Other deviations included slightly exceeding the prescribed temperature (25 Celsius) on several instances, having humidity out of the prescribed range in the test area and tick storage areas, initiating a time point for testing with subject 594054 5 minutes early in one instance, using a previous version of the Case Reporting Form during one subject test, not clipping the wrist hair of all subjects at the start of each visit, and missing a time point for one subject during one test (593107).

None of these deviations negatively impacted the subject's health or welfare. EPA's science review concluded that these deviations did not negatively impact the scientific validity of the research.

### **Applicable Ethical Standards**

The following provisions of 40 CFR 26 Subpart Q define the applicable ethical standards which are summarized below:

**§26.1703:** EPA shall not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

**§26.1705:** For research conducted outside of the United States, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with procedures that are at least as protective of subjects as all applicable provisions of subparts A through L of this part or another agency's codification of the Common Rule.

In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) applies. This passage reads:

In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

### **Findings**

Pregnancy testing of female subjects was conducted on each day of testing. No pregnant or lactating women were enrolled in the study. All subjects who participated in study were at least 18 years old. Therefore, 40 CFR §26.1703 does not prohibit reliance on this research.

40 CFR §26.1705 requires that EPA determine that the study, which was performed outside of the United States, was performed in substantial compliance with procedures that are at least as protective as those in EPA's regulations for the protection of human subjects. After reviewing all available information, I conclude that this study was conducted in substantial compliance with standards as protective as those in EPA's regulations.

As documented in Attachment 1 to this review, the central requirements of 40 CFR §26 subpart M, §26.1303 to document the ethical conduct of the research were addressed.

The requirement of FIFRA §12(a)(2)(P) that human subjects of research be "fully informed of the nature and purposes of the test and of any physical and mental health

consequences reasonably foreseeable therefrom,” and “freely volunteer to participate in the test,” was met for this study.

## **Conclusion**

This study reports research conducted in substantial compliance applicable regulatory standards, and with a protocol for research that was reviewed by EPA and the HSRB according to the standards at 40 CFR 26, Subpart P. In its conduct, this study met applicable ethical standards for the protection of human subjects of research. Requirements for documentation of ethical conduct of the research were satisfied. From EPA’s perspective, if this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA’s reliance on it in actions under FIFRA or §408 of FFDCa. This research and EPA’s reviews will also undergo review by the HSRB.

Cc: Ed Messina

Robert McNally

Shannon Borges

Clara Fuentes

Helen Hull-Sanders

Menyon Adams

Attachment 1: §26.1303 Completeness Checklist

Attachment 2: Responsiveness to EPA and HSRB Ethics Comments on Draft Protocol

## Attachment 1

### § 26.1303 Checklist for Completeness of Reports of Human Research Submitted for EPA Review

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

	Requirement	Y/N	Comments
(a) Copies of all of the records relevant to the research specified by § 26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of <ul style="list-style-type: none"> <li>• all research proposals reviewed,</li> <li>• scientific evaluations, if any, that accompany the proposals,</li> <li>• approved sample consent documents,</li> <li>• progress reports submitted by investigators, and</li> <li>• reports of injuries to subjects.</li> </ul>	Y	Appendices 16.1, 16.2, 16.6
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show <ul style="list-style-type: none"> <li>• attendance at the meetings;</li> <li>• actions taken by the IRB;</li> <li>• the vote on these actions including the number of members voting for, against, and abstaining;</li> <li>• the basis for requiring changes in or disapproving research;</li> <li>• a written summary of the discussion of controverted issues and their resolution.</li> </ul>	Y	Appendix 16.6
	§1115(a)(3): Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in §26.1109(f)(1).	Y	Appendix 16.6
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	Y	Appendix 16.6
	§1115(a)(5): A list of IRB members in the same detail as described in § 26.1108(a)(2).		Appendix 16.6
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a)(3) and (4).	Y	WIRB provided to EPA LSHTM Ethics Committee attached to memo
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(c)(5).	N/A	
	§1115(a)(8): The rationale for an expedited reviewer's determination under §26.1110(b)(1)(i) that research appearing on the expedited review list described in §26.1110(a) is more than minimal risk.	N/A	
	§1115(a)(9): Documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of this subpart.	Y	Appendix 16.6
(b) Copies of all of the records relevant to the information identified in § 26.1125(a)-(f)	§1125(a)(1): The potential risks to human subjects	Y	Appendix 16.1
	§1125(a)(2): The measures proposed to minimize risks to the human subjects;	Y	Appendix 16.1
	§1125(a)(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	Appendix 16.1
	§1125(a)(4): Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Appendix 16.1
	§1125(a)(5): The balance of risks and benefits of the proposed research.	Y	Appendix 16.1
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Appendix 16.2
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	Appendix 16.2
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.	Y	Appendix 16.1
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	Appendix 16.6
§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.	Y	Appendix 16.6	
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research	Y	Appendix 16.2	
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.	N/A		

## Attachment 2

### Responsiveness to EPA and HSRB Ethics Comments on Draft Protocol

<b>EPA Recommendation</b>	<b>Action taken by Study Sponsor</b>
Make editorial revisions and minor edits as recommended in EPA’s written comments dated March 30, 2018.	The protocol and consent form were revised according to EPA’s comments.
Revise the protocol to note that dosimetry/consumer dose testing will occur with the actual consumer product and that subject will be instructed to make the applications after reviewing the label.	The study sponsor addressed this comment in the final IRB-approved protocol and consent materials. See Appendices 16.1 and 16.2.
Update the protocol to reflect the number of subjects and alternates necessary to ensure statistically-valid results for both the consumer dose and repellent efficacy testing phases of the study.	The study sponsor revised the protocol to reflect this recommendation. See Appendix 16.1.
Remove the discussion of tick paralysis as a risk to subjects as the ticks will not be allowed to bite or feed for an extended period if they do attach.	The revised protocol does not include these risks. See Appendix 16.1.
Revise subject compensation to provide a flat sum for participation in the consent meeting and consumer dose testing, and an hourly rate (no less than minimum wage) rounded up to the next hour for participation in the repellent efficacy testing phase.	The revised protocol notes that subjects will be compensated £20 for participating in the consent meeting, £20 for participating in the consumer dose testing, and £7.50/hour rounded up to the next hour for participating in the repellent efficacy testing phase. p. 111.

<b>HSRB Recommendation</b>	<b>Action taken by Study Sponsor</b>
<p>Revise eligibility criteria:</p> <ul style="list-style-type: none"> <li>to add to inclusion criteria “not pregnant or intending to become pregnant <u>during the study.</u>”</li> <li>to clarify that only those with known allergens to ingredients in the test product, rather than any repellent product, will be excluded</li> </ul>	<p>The protocol includes these revisions, see p. 99.</p>
<p>Clarify provisions for meal breaks and how handwashing before and after eating would disturb product application on the forearm.</p>	<p>The protocol includes language that “participants will be instructed not to disturb the product during the resting period” and explains that one period can be missed for a meal break. p. 106.</p> <p>See Appendix 16.1. for revisions to the protocol.</p> <p>The consent form notes that hand sanitizer will be provided during the test for use in lieu of handwashing in order to avoid disturbing the product application. p. 133</p>
<p>In section 10.3.2, clarify whether Epi-Pens will be available.</p>	<p>Section 9.4.2 of the final protocol notes that Epi-Pens “will not be routinely available.” p. 108.</p>
<p>Clarify the procedure for determining whether an adverse event is related to study participation as well as the party responsible for making this determination.</p>	<p>Section 9 of the protocol notes that the medical monitor will be asked to review information on adverse events and to determine the severity and whether the adverse event was related to study participation. p. 107.</p>
<p>Clarify the section on ethical approval of the protocol to include compliance with 40 CFR Subparts K-L, to indicate how a disagreement between the two overseeing ethics committees will be handled, and to clarify that all protocol amendments will be submitted to the overseeing ethics committee.</p>	<p>The protocol was revised to address these recommendations. See pp. 109-110. Additionally, an agreement between WIRB and the LSHTM Interventions committee outlined how their relationship would be governed. pp. 612-613.</p>

<b>HSRB Recommendation</b>	<b>Action taken by Study Sponsor</b>
<p>In the consent form section titled “Risks and discomforts”, the issue of laboratory raised ticks is mentioned: “there is no risk of getting a disease from a tick bite during this study because the ticks we will use are raised in a laboratory....” Revise to add “and are disease-free” after “laboratory”.</p>	<p>This language was included in the protocol (p. 97) but inadvertently left off of the consent form.</p>
<p>Contact information for questions about rights as a research subject lists WIRB, which is one of the reviewing IRBs. The Board suggests it would be more appropriate to list the LSHTM ethics committee given that it is the locally reviewing board and may seem more accessible to study participants from the London area</p>	<p>The consent form was revised to add contact information for both overseeing bodies. p. 136.</p>