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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

March 31, 2015

MEMORANDUM

SUBJECT: Science and Ethics Review of a Protocol for Field Testing of S.C. Johnson Skin-Applied Mosquito Repellent Products

FROM: Kevin J. Sweeney, Senior Entomologist
Registration Division
Office of Pesticide Programs

Kelly Sherman, Human Research Ethics Review Officer
Office of the Director
Office of Pesticide Programs

TO: Marietta Echeverria, Chief, Invertebrate-Vertebrate Branch 1
Registration Division (7505P)
Office of Pesticide Programs

REF: Palm, J. M., (2015) Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support their Use of the EPA Repellency Awareness Graphic. Unpublished document prepared by S.C. Johnson & Son, Inc. Entomology Research Center, Racine, WI. February 27, 2015. 676 p. (MRID 49580701) (D426139)

We have reviewed the referenced protocol for a field test of skin applied mosquito repellent products from both scientific and ethics perspectives. This review assesses the scientific aspects of the proposed research for an efficacy study to assess skin applied insect repellent products in terms of the recommendations of the EPA OPPTS 810.3700 Guideline, the EPA Repellency Awareness Graphic Guidance, and the EPA Human Studies Review Board. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board.

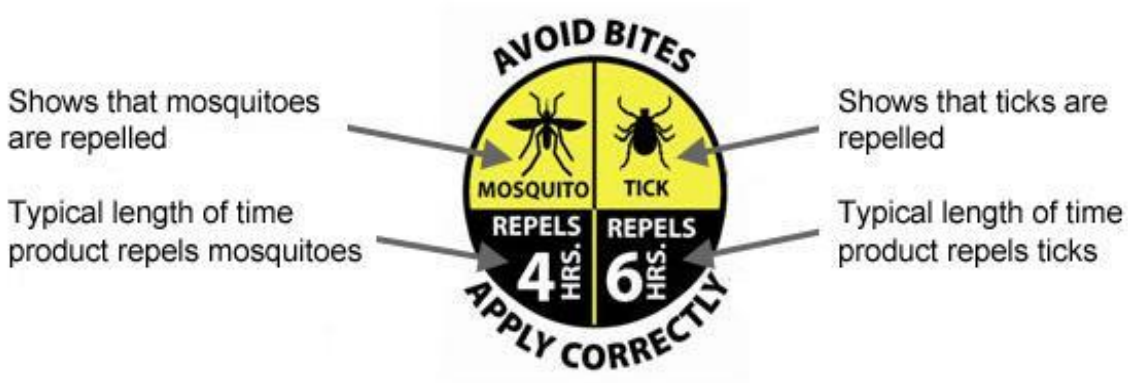
A. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 5. All elements of required documentation are provided in the submitted protocol package.

B. Summary Assessment of Ethical Aspects of the Proposed Research

Here is a summary of our observations about the ethical aspects of the proposed protocol. Supporting details are in the attachment.

1. **Societal Value of Proposed Research:** This study is designed to determine the complete protection time (CPT) of up to eighteen EPA-registered skin applied repellent products from S.C. Johnson & Son, Inc. in the field against wild adult mosquito populations using volunteer human subjects. Up to three different active ingredients will be tested and a variety of product types (e.g., lotions, sprays, aerosols, towelettes). Direct testing of the duration of efficacy is important because consumers, who rely on repellents to avoid mosquito bites, cannot readily assess the efficacy of a product independent of EPA's approval. EPA requires efficacy testing of these specific formulations to support their use of the EPA Repellency Awareness Graphic for mosquitoes on their product labels. This graphic is intended to help consumers easily identify the repellency time (based on the Median CPT) for mosquitoes (and ticks when requested). Labeling repellent products with the graphic that identifies the type of pest the product is expected to repel, and the amount of time the repellent will be effective, benefits society by informing consumers about the efficacy of various products when they are choosing a repellent product to purchase. The diagram below describes the graphic.



2. **Subject Selection:** Ten subjects (5 males and 5 females) will be treated with a test substance. There will also be two untreated control subjects (1 male and 1 female). Subjects will be between 18 and 55 years of age and will be recruited through a database of interested volunteers maintained by a professional recruitment firm. The protocol states that the pool of subjects will be demographically and ethnically

representative of the population in the area where the field testing will be conducted (southeast Wisconsin and southwest Florida, with the possibility of other locations). Johnson is requested to obtain further details about the demographics of the recruiting firm's list of potential subjects. The pool of people from which subjects for this research are selected should be representative of the population of potential repellent users in the United States.

3. **Risks to Subjects:** Risks to subjects include the risk of adverse reaction to the test substances; exposure to biting mosquitoes; the risk of exposure to mosquito-vectored diseases; general risks of being in the field; and unanticipated loss of confidentiality or privacy. Risks are minimized in the protocol by excluding candidates known to be sensitive to the test material; excluding candidates known to be hypersensitive to or phobic of mosquito bites; conducting the research in areas where the presence of mosquito-borne disease has not been detected within one month prior to the test date; training subjects to remove mosquitoes before they bite; providing a shaded, screened enclosure and beverages; using subject identification codes; and by incorporating procedures to keep the results of pregnancy testing private and permit discrete withdrawal. All practical steps to minimize subject risks have been taken, and the remaining risks have a low probability of occurrence.

4. **Benefits:** This research offers no direct benefits to subjects, but may provide indirect benefits to subjects and society by providing data that can be used by EPA to add the Repellency Awareness Graphic to skin applied insect repellent labels, thereby allowing for better protection of consumers from nuisance bites and bites that lead to arthropod-borne diseases. The graphic clearly informs consumers about the duration of repellent protection so that they can make informed choices about the repellent products they purchase and use.

5. **Risk/Benefit Balance:** No practical opportunities to further reduce risk to subjects while maintaining the robustness of the scientific design have been overlooked. The residual risk to subjects is low, and reasonable in light of the potential benefits of the data to society.

6. **Independent Ethics Review:** The Schulman Associated IRB (SAIRB) has reviewed and conditionally approved the protocol, informed consent form, and recruitment materials. SAIRB's final approval is conditioned on the sponsor obtaining EPA and HSRB review. After the HSRB review process is complete, the protocol and other documents should be revised by Johnson to incorporate comments from EPA and the HSRB, and then re-submitted to SAIRB for final approval before initiating the research. SAIRB is independent of the investigators and sponsors. Satisfactory documentation of SAIRB procedures and membership is on file with the Agency.

7. **Informed Consent:** The protocol contains a complete and satisfactory description of the process by which potential subjects will be recruited and informed, and the process for seeking their consent to participate. The most current draft of the consent

document (draft 3; conditionally approved by SAIRB) meets all requirements of 40 CFR §§26.1116 and 26.1117.

8. **Respect for Subjects**: Study documents will refer to individual subjects using a code number and subjects will not be identified in any published reports or presentations about this research. The protocol specifies procedures for discrete handling of the pregnancy testing. Candidates and subjects will be repeatedly informed that they are free to decline to participate or to withdraw at any time for any reason. Subjects who withdraw will be compensated for time spent up to the point of withdrawal. Medical care for research-related injuries will be provided by the sponsor at no cost to the subjects.

C. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply. A point-by-point evaluation of how this protocol addresses the requirements of 40 CFR 26 Subparts K and L and the criteria recommended by the HSRB is appended as Attachment 1.

EPA Ethics Comments

Before the research is initiated, the documents should be revised to address the comments below and any forthcoming comments from the EPA Human Studies Review Board. The revised materials should be submitted for review and final approval by the approving IRB:

- Please revise the benefits section of the Informed Consent Form as follows: *"You will not personally benefit from this study~~, other than the financial compensation~~."* The proposed payment to subjects is considered compensation for lost time and inconvenience, not a benefit of participating in the research. This study provides no direct benefits to subjects.

- Johnson should inquire with the recruiting firm about the demographics of the volunteer pool from which subjects will be recruited, and provide additional details in the protocol to support the statement that the pool of subjects will be demographically and ethnically representative of the population in the area where the field testing will be conducted. The pool of subjects should also be representative of the overall population of concern, which is repellent users in the United States.

- The protocol excludes Johnson employees from becoming subjects. Please amend the protocol and consent form to also exclude immediate family members of Johnson employees.

- Johnson should consider whether additional stopping rules should be added to the protocol. Examples of conditions which may be appropriate to trigger a stop to the research (either for

an individual participant or for the whole study) include: mosquito landing rate falls below threshold needed to challenge test material, wind speeds exceed a certain level, subject asks to withdraw, subject exhibits hypersensitivity to insect bites, subject exhibits sensitivity to the test material, medical management is invoked. The first two examples would apply to the entire study; the other examples would apply to an individual subject.

- The protocol and consent form must explain how compensation will be handled if a potential subject participates in the consent meeting, the training meeting, and/or the pregnancy testing, but then ultimately decides not to participate in the research.

- The protocol and consent form should be revised to include details about whether subjects will be transported by the researchers to and from the testing site. If the testing site is remote, and if Johnson intends to transport the subjects to the testing site, then Johnson should make arrangements to transport any subjects who withdraw back to the starting location within a short period of time after that subject indicates his or her desire to withdraw. If Johnson cannot make such arrangements, then a subject who withdraws should be paid for all of the time spent at the study site, even if he or she has chosen to withdraw early. Not compensating a subject for this type of time and inconvenience could unduly influence him or her to continue participating.

- The protocol provides that the entire consent document will be read aloud to potential subjects during the consent meeting. Given that the ability to read English is a requirement to participate, Johnson should offer subjects the option of reading the consent form themselves. If Johnson wishes to confirm understanding of the consent form, Johnson should draft several questions to be asked of each potential subject prior to them signing the consent form, and those questions should be included in the revised materials that are reviewed by SAIRB before the study is initiated.

40 CFR 26 Subpart Q, at §26.1703, as amended effective April 15, 2013, provides in pertinent part:

> EPA must not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

This protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA to rely on a study executed according to this protocol.

D. Summary Assessment of Scientific Aspects of the Proposed Research

"The objective of this study is to establish the complete protection time of up to eighteen EPA-registered repellent products ('test substances') from S.C. Johnson & Son, Inc. ('Johnson') in the field against populations of wild mosquitoes, using human volunteers. Testing will be

conducted at two geographically and ecologically distinct field sites" (p.8 of 676, §1.2). "The rationale is to provide data on the longevity of complete protection from mosquitoes landing with intent to bite people with one of Johnson's eighteen EPA-registered test substances (personal mosquito repellent products). Following this protocol, several individual GLP field studies will be conducted. Each study will include one or two of the eighteen EPA registered test substances listed in this protocol." (p. 10 of 676, §1.6.1)

"This data will be used to allow these products to use EPA's new Repellency Awareness Graphic for the labels. This system assigns duration of protection (in hours) on the EPA label, coupled with a graphic symbol for the target pest(s), which is the case for mosquitoes" (pp. 10-11 of 676, §1.6.1). "Repellency will be measured as the time between application of a test substance and the first confirmed landing. A 'Landing' occurs when a mosquito alights on the treated skin of a subject. A 'First Confirmed landing' is that which is followed by another Landing within a 5 minute exposure period or, when one Land occurs in such an exposure period and another Land occurs in the next exposure period" (30 minutes later)(p. 8 of 676, §1.2 and p. 46 of 676, §10.6.8). In this experiment the product dose will be standardized for product comparisons so the study as proposed has no dosimetry phase to determine the typical consumer dose of these products when applied by human subjects participating in the field studies.

This study will be conducted in accordance with EPA, FIFRA (Federal Insecticide, Fungicide and Rodenticide Act), and Good Laboratory Practice Standards (GLP); 40 CFR, Part 160 (October 1989). *"Each study will include all applicable GLP study information such as, GLP number, Test substance number(s), Study Director, etc." (p. 10 of 676, §1.6.1). "Johnson's independent Quality Assurance Unit (QAU) will perform all QAU duties." (p. 8 of 676, §1.4.1)*

1. Study procedures and design:

Study site locations: The studies will be conducted at two geographically distinct locations in the United States. The first field site will located in Southeastern Wisconsin and characterized by temperate forest. Collier County in the State of Florida will be the location of the second field site, which is characterized by semi-tropical saltmarsh bordering mangrove swamps and Royal palm hammocks. These sites are known to the study director and have different mosquito species composition (pp. 38-39 of 676, §10.1.2 and §10.1.3 of the protocol) that provide adequate representation of mosquito species and vectors in the United States. Mosquitoes will be aspirated from the untreated control subjects for identification.

If adequate densities of mosquitoes cannot be found at the above locations, alternative locations in the US may be used. All sites will be qualified by confirmation from county or state health staff or mosquito abatement district staff within one month prior to the test date and confirmation by the study staff of minimum landing pressures present prior to test initiation.

Johnson proposes that in the case where testing is to be conducted outside of the US mosquito season, testing may be conducted outside of the US. Site qualification will be the same as above. All human testing laws in the country will be followed and any required IRB

approvals in the country will be acquired prior to test subject recruitment, in addition to all US reviews and approvals (p. 38 of 676, §9.4). Previous repellent studies discussed with the HSRB have been done in the United States only.

Subject selection: §2.2.-§2.3.13.2 on pages 11-17 of 676 describe the process of subject recruitment, qualification, and selection**.** From a science perspective §2.3.13.1 and §2.3.13.2 on pages 16-17 of 676 are most relevant as they discuss confirmation of attractiveness of a potential subject to mosquitoes. Two approaches may be used, one in the laboratory and the other in the field. In the laboratory (p. 17 of 676, §2.3.13.1) potential subjects will insert their arm into a cage containing 50 *female* mosquitoes that are 5-10 days old. The subject must acquire five landings with an *Aede*s sp. mosquito in one minute or less. Once five landings have been achieved, the arm will be removed. Hands will be gloved and arms covered with a sleeve to protect the subjects from bites.

Treatments and replication: "*The test subjects will be selected at random from a pool of potential subjects. Assignment of the test substance to the subjects will be randomized. Randomization will use a treatment allocation table. The decision to use arms or legs will be based on the landing behavior of the species of mosquitoes present in the field. If two test substances are tested on one test day, assignments of these treatments will also be randomized amongst the test subjects"* (p. 40 of 676, §10.3.1 and §10.3.4).

As previously described, ten randomly chosen subjects will be allocated to a product treatment at each site. Subjects will be blinded to the identity of the test substance with which they are treated. The study staff will not be blinded to the treatments. Two more subjects selected from a pool of subjects proficient at aspirating mosquitoes will serve as the "untreated or negative controls". The data they collect will not be used to calculate the complete protection time. Instead, they will monitor mosquito landing pressure at the site throughout the test period to document that it was sufficient for repellent product evaluation.

Johnson discussed the justification for sample size in §12.3 on pp. 55-56 of 676 of the protocol where it refers to past EPA accepted protocols in which 10 subjects per treatment site was found to be acceptable. The Johnson protocol does not include a power analysis to address sample size.

The test system in this study proposes to conduct field studies in the States of Florida and Wisconsin where human subjects will be exposed to wild populations of mosquitoes. The experiment will include a product treatment group of ten subjects and an untreated group of two subjects who will monitor mosquito landing pressure and activity at each site (total of 20 and 4 subjects, respectively, for each product tested). A second product treatment group may be added to some of the field tests. A positive control substance will not be used.

Tables 1, 2, and 3 list the eighteen product treatments to be tested and a summary of the test design. Product names are listed in §3.1.1-3.1.18 on pages 26-29 of 676 of the protocol.

Table 1. Study Design –DEET Products

Repellent Product		Number of Field Sites[1]	Number of Subjects per Field Site	Number of Mosquito Species per Field Site[2]	Total Replicates per Product
EPA Reg. No.	Product Type				
4822-415	5% DEET Spritz	2	10	3 or more	20
4822-552	5.6% DEET Towelette	2	10	3 or more	20
4822-395	7% DEET Spritz	2	10	3 or more	20
4822-380	15% DEET Aerosol	2	10	3 or more	20
4822-543	15% DEET Aerosol	2	10	3 or more	20
4822-167	25% DEET Aerosol	2	10	3 or more	20
4822-258	25% DEET Towelette	2	10	3 or more	20
4822-399	25% DEET Spritz	2	10	3 or more	20
4822-572	25% DEET Aerosol	2	10	3 or more	20
4822-397	30% DEET Aerosol	2	10	3 or more	20
4822-276	98.25% DEET Spritz	2	10	3 or more	20

[1] Field sites located in Southeastern Wisconsin and in Collier County, Florida.
[2] Field site should have species from at least three mosquito genera to include species that vector disease to humans. The number of species per field site will vary by location and day of testing.

Table 2. Study Design – Picaridin Products

Repellent Product		Number of Field Sites[1]	Number of Subjects per Treatment per Field Site	Number of Mosquito Genera/ Species per Field Site[2]	Total Replicates per Product
EPA Reg. No.	Product Type				
4822-536	5% Picaridin Spritz	2	10	3 or more	20
4822-535	5% Picaridin Lotion	2	10	3 or more	20
4822-556	20% Picaridin Spritz	2	10	3 or more	20
4822-564	20% Picaridin Aerosol	2	10	3 or more	20

.[1] Field sites located in Southeastern Wisconsin and in Collier County, Florida.
[2] Field site should have species from at least three mosquito genera to include species that vector disease to humans. The number of species per field site will vary by location and day of testing.

Table 3. Study Design –p-Methane-3, 8-Diol (PMD) Products

Repellent Product		Number of Field Sites[1]	Number of Subjects per Field Site	Number of Mosquito Species per Field Site[2]	Total Replicates per Product
EPA Reg. No.	Product Type				
4822-526	8% PMD Towelette	2	10	3 or more	20
4822-515	10% PMD Lotion	2	10	3 or more	20
4822-528	10% PMD Spritz	2	10	3 or more	20

[1] Field Sites located in Southeastern Wisconsin and in Collier County, Florida.
[2] Field site should have species from at least three mosquito genera to include species that vector disease to humans. The number of species per field site will vary by location and day of testing.

Dosage and product application: Each subject will have one forearm or lower leg (calf) treated with the repellent product to be tested. The choice of forearm or lower leg treatment will be made by the study director or designated staff on the day of the test based on the landing behavior of mosquitoes present at the site. As a result, the surface area of the forearm and lower leg will be measured for every subject. Surface area calculation is described in §6.1.1.1 and §6.1.1.2 on pages 32-33 of 676 of the protocol and will be calculated as follows:

Area = C * D

For the forearm, 'C' equals the circumference of the forearm (based on the mean of four equidistant measurements made between the wrist and the elbow) and 'D' equals the distance between the wrist and the elbow. For the lower leg, 'C' is the mean of four equidistant measurements made between the area just above the laterally protruding ankle bone and at the crease of the knee. The distance 'D' is measured from just above the ankle bone to the crease of the knee (p. 60 of 676, Appendix I).

Johnson is proposing a fixed dosage rate of 1 gram of product per 600 cm^2 (1.67 mg/cm^2). Johnson is not proposing a dosimetry phase to determine a 'typical consumer dose' by dose titration, which would be based on the grand mean of triplicate applications made by the test subjects. Johnson stated five reasons for using a fixed dose rather than a titrated dose (pp. 33-34 of 676, §7.1.1 – §7.1.2.5):

"(1) Influence of outliers: A single outlier data point can unduly influence the mean of 10 doses applied by subjects;

(2) Inter-test variability: Choice of dosing from dosimetry often results in selecting different doses for different tests since the groups of subjects will apply varying doses. This can obscure the cause of any different outcomes from two otherwise identical tests. This risk is avoided by using a set dose;

(3) Dose effect: Varying doses make it impossible to determine if performance difference is driven by the dose or the test products;

(4) Time and cost: Dosimetry introduces additional time and cost to a study compared to a set dose; and

(5) Relation to actual consumer use: To maintain the integrity of a scientific efficacy study the dose used should remain consistent. Keeping as many variables consistent from one test to the next and one test substance to the next is a more scientifically robust method of testing. A set dose can be related to known consumer behavior. Based on a handful of tests where dosimetry was employed, the standard dose falls within the range of values arrived at via dosimetry. Dosimetry allows the possibility of an atypical result."

In order to apply the target dose of 1.67 $mg.cm^2$ the following formula will be used:

[Area of the Limb/600 cm^2] * 1 gram = weight (amount) of product to apply

The application of repellent product to the skin of each subject will depend on the product type.

- For pump sprays, the test substance container is placed on a balance and the balance is tared. The required weight is drawn up by pipette while observing the digital display on the balance and applied to the skin of the subject.
- For aerosol sprays, the test substance container is placed on a balance and the balance is tared. The test substance is then sprayed from the container directly onto the skin. After the spray, the sample is returned to the balance and the amount applied is determined. If the amount is below the required weight, more test substance is sprayed onto the limb targeting the required weight as closely as possible.
- For lotions, the test substance container is placed on a balance and the balance is tared. The required weight of the test substance is then removed by spatula or similar implement-carefully observing the balance read out.

Treatments will be made by study staff. §7.1.4-§7.1.6 on pages 34-35 of 676 describe preparations before treatments are made. The target dose weight and actual weight applied will be recorded on a data sheet (p. 61 of 676, Appendix II). Margin of Exposure (MOE) estimates are based on an assumed 70 kg subject and the acute dermal LD_{50} value for each product at the limit dose of greater than 2,000 mg/kg. Based on the dose rates presented by Johnson, the MOE values for the tested active ingredients will exceed EPA's level of concern of MOE = 100. Specific MOE values will be provided for each product when the study is conducted.

In §10.3.3 on page 40 of 676 the study director mentions that more than one test substance may be tested per day. However, there is no mention of how treatments might be allocated to subjects or if the same subjects may be used for more than one treatment but on different days.

Mosquito landing assessment: As is typical for these types of field studies since the introduction of West Nile virus into the USA in 1999, mosquito landings will be used instead of bites to assess repellent efficacy. All subjects will be given a battery powered aspirator to use for collecting mosquitoes landing on the exposed skin of their limb and will be trained in their use. The treated subjects will form pairs, based on a previously assigned order. Untreated subjects will do the same. Just prior to an exposure period, the study staff will lead subjects to the test site. They will take up an assigned position at least 20 feet apart from other pairs. When testing occurs after daylight hours the subjects will be provided a head lamp and instructed how to use it. (pp. 43-44 of 676, §10.6.1-§10.6.2)

As directed by study staff, all subjects will observe their treated limbs for five minutes. Subjects will quickly aspirate mosquitoes landing on the exposed limb before they bite. Subjects will report landings to the study staff at the completion of an exposure period. Aspirated mosquitoes will be labeled and retained for identification and recounting. Five-minute exposures will continue every 30 minutes until repellent failure occurs or until directed to stop by the study staff. Times between exposure periods will be spent in a protected area, such as a screened enclosure.

The two negative control subjects (one male and one female) at each site will monitor mosquito landings (Referred to a "biting pressure" in the protocol) to document that a minimum of five mosquitoes are landing on their untreated exposed limb in five minutes. They will conduct five minute landing assessments every 30 minutes. When they have received five landings in five minutes or less they will cover their exposed limbs. If the minimum standard is not met (For one or both subjects?), the study director may allow further exposure of these subjects in the expectation that the minimum landing rate will resume. Johnson proposes that no more than 10% of the landing values recorded by the untreated controls can be less than the minimum of five mosquito landings in five minutes. This is equivalent to 1-2 exposure periods per test. The protocol does not address what data values, if any, will be recorded or if the data recorded during these times will still be used in calculating CPT.

Some of the test substances are expected to have a long CPT. For those test substances, the study director may choose to treat the subjects, then delay the start of the test, a practice common to repellent testing. This reduces unnecessary exposure to mosquitoes. Subjects will be kept in conditions similar to the test site and protected from mosquitoes and sunlight.

2. Endpoints and Measures:

Repellency will be measured as complete protection time. *"Subject specific Complete Protection Time (CPT) will calculated as time from application of each test substance to a subject and the 'First Confirmed Landing' on that subject." "A 'Landing' occurs when a mosquito alights on the treated skin of a subject. A 'First Confirmed landing' is that which is followed by another Landing within a 5 minute exposure period or, when one Land occurs in such an exposure period and another Land occurs in the next exposure period (30 minutes later)."* Subjects with repellent failures will be removed from the field test when a First Confirmed Landing occurs. The test will be terminated as determined by the study director.

.

3. Data Analysis:

The objective of the data analysis is to estimate the Median Complete Protection Time. Complete Protection Time (CPT) will calculated as time from application of each test substance to a subject and the first confirmed land on that subject. The Median CPT of all test subjects will be calculated using the Kaplan-Meier estimator, which is advantageous since CPTs may not be normally distributed. Kaplan-Meier is more conservative than competing parametric methods (Weibull and Normal) in that the Median CPT is likely to be lower and the 95% confidence interval around the median CPT is likely to be wider. Kaplan Meier estimator has been accepted by EPA and the HSRB for the Median CPT calculation in past repellent efficacy studies and is also recommended by the World Health Organization for CPT calculation from these non-parametric data sets. "The duration of protection for each test substance will be the lowest median CPT from the test locations." This value will be rounded down to the closest full hour (p. 57 of 676, §12.4.4).

E. **Compliance with Applicable Scientific Standards**

This protocol adequately addresses the following elements according to applicable scientific standards:

- Prerequisite acute toxicity research to characterize toxicological profile of the formulation and calculate margin of exposure (MOE).
- Experimental design
- Pre-training of subjects

EPA Science Comments

The following elements in the protocol require revision/amendment before the research goes forward:

- Inclusion of field testing sites outside of the United States (p 38 of 676, §9.4). The protocol proposes to include field sites outside of the US to enable testing to be conducted outside of the US mosquito season. However, the protocol does not specify those possible sites or identify the endemic mosquito species at those sites. Before proceeding with research under this protocol at sites outside of the United States, the sites and endemic mosquito species need to be identified and approved by U.S. EPA. Additional information that would be helpful to EPA in determining if a non-US site is appropriate includes: mosquito species composition, host seeking behavior, disease vector potential, habitat, and climate in comparison to the proposed US sites. Also, how does Johnson proposed to bridge such data to US mosquito species to meet the criteria for the Repellency Awareness Graphic?

- Field site qualification should describe in more detail how the study director will know if the selected site did not have mosquito-borne disease transmission activity for at least one month prior to the start of the test.

- Change "mosquito biting pressure" to "mosquito landing rate" as subject bites are not counted or recorded in this study.

- The justification for sample size requires further elaboration and explanation.

- Describe how the data will be analyzed if the number of test subjects at the end of the test is less than ten. In other words, what if subjects withdraw? If alternates replace them, how will Johnson account for this change of subjects in the data analysis?

- Describe treatment allocation when, and if, testing is conducted on consecutive days with different products and when more than one test substance is tested per day. The protocol needs to be amended to describe these possibilities or forbid them. Will more than one test substance only be tested on the same day with an additional group of test subjects? Will test substance testing occur over consecutive days with the same subjects and different products or not? If yes, how will treatments be allocated and will there be a time period when a

subject may not participate in the next test if they were previously treated with another test substance?

- The protocol states that up to 10% of the exposure periods in a test may have less than the minimum landing (biting in the protocol) pressure of five mosquitoes landing in five minutes or less. Will treatment exposures occur during periods of insufficient landing pressure? If treatment data are collected during these periods, how will they be used in CPT calculation? If they are not used, how will the lack of data points be considered in the K-M analysis and calculation of Median CPT?

- The exact conditions for delaying the start of the test for test substances with expected longer CPTs should be fully described. For instance, what expected CPT value is the threshold for delaying exposure to mosquitoes in the field? What percentage of the CPT may be delayed for more efficacious repellents?

- State/justify why no positive control substance is to be used.

- Dose: In this protocol, all product types are proposed to be tested at the same dose, 1 g/600cm^2, and a dosimetry phase is not proposed. This is a departure from the design of repellent efficacy studies that that have been reviewed and approved by EPA and the HSRB in recent years, which have experimentally determined the dose. Based on an analysis of the dosimetry results from repellent studies reviewed by EPA and the HSRB since 2006, EPA considers the following to be the appropriate product doses for studies conducted under this protocol: lotion – 0.9 g/600cm^2, pump spray 0.4 g/600cm^2, and aerosol 0.8 g/600cm^2. If Johnson disagrees with these doses, a dosimetry phase should be conducted to justify a different dose.

- Product application is not fully described. After weighing the set dose, how is the product applied to the limb for pump sprays and lotions? For instance, is the required amount left in the container and the pump used to spray it on the limb? For lotions, the amount to be applied is removed with a spatula instead of a larger syringe so transfer to the subject might be easier? For aerosols, Johnson could estimate the delivery of the prescribed amount of product by counting the number seconds needed to deliver the dose to the limb and determine the amount applied per second of spraying to more closely estimate the application amount? How does this compare to the product's label directions? Will study staff spreading the lotion with a gloved hand?

- All raw data must accompany all study submissions.

- Appendix III – Land Data Form. Identification of which limb was treated needs to be added to this data sheet.

- Data compilation and processing. Little detail is provided in the protocol on how the data from these sheets will be compiled and processed before entry into Excel, JMP, or SAS, etc.

Attachments:

1. Summary Review of Protocol (protocol dated 2/12/15)
2. §26.1111 Criteria for IRB approval of research
3. §26.1116 General requirements for informed consent
4. §26.1117 Documentation of informed consent
5. §26.1125 Criteria for Completeness of Proposals for Human Research

EPA Protocol Review

Title: Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support their Use of the EPA Repellency Awareness Graphic

Date: February 27, 2015

Principal Investigator and any sub-investigators: Julie M. Palm, Sr. Associate, Entomology

Participating Laboratory:
S.C. Johnson & Son, Inc.
Entomology Research Center
15 Four Mile Road
Racine, WI 53402

Sponsor:
S.C. Johnson & Son, Inc.
1525 Howe Street
Racine, WI 53403

IRB:
Schuman Associates IRB
Sawgrass Plaza, Suite 120
1530 Sawgrass Corporate Parkway
Fort Lauderdale, FL 33323

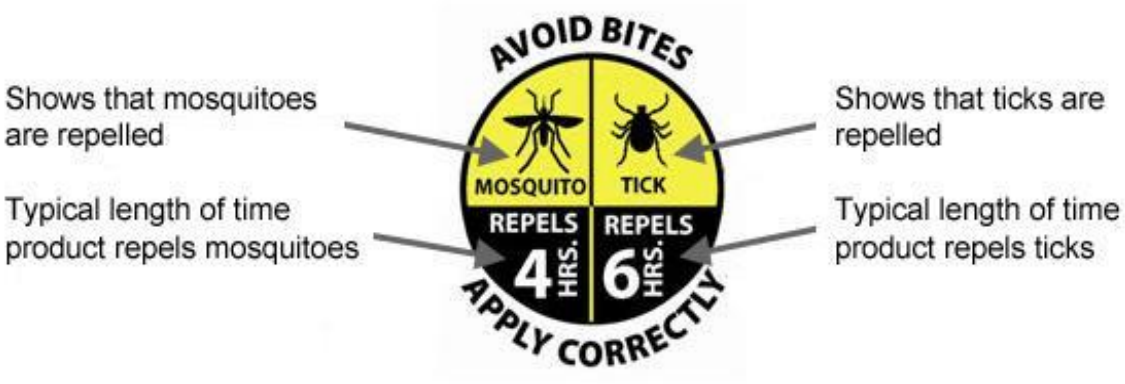
1. Societal Value of Proposed Research

(a) What is the stated purpose of the proposed research?

"*This data will be used to allow these products to use EPA's new Repellency Awareness Graphic for the labels. This system assigns duration of protection (in hours) on the EPA label, coupled with a graphic symbol for the target pest(s), which is the case for mosquitoes*" (pp. 10-11, §1.6.1).

This study is designed to determine the complete protection time (CPT) of up to eighteen EPA registered skin applied repellent products from S.C. Johnson & Son, Inc. in the field against wild adult mosquito populations using volunteer human subjects. Up to three different active ingredients will be tested and a variety of formulation types. Direct testing of the duration of efficacy is important because consumers, who rely on repellents to avoid mosquito bites, cannot readily assess the efficacy of a product independent of EPA's approval. EPA requires efficacy testing of these specific formulations to support their use of the EPA Repellency Awareness Graphic for mosquitoes on their product labels. This graphic is intended to help consumers easily identify the repellency time (based on the Median CPT) for mosquitoes (and ticks when requested). Labeling

repellent products with the graphic that identifies the type of pest the product is expected to repel, and the amount of time the repellent will be effective, benefits society by informing consumers about the efficacy of various products when they are choosing a repellent product to purchase. The diagram below describes the graphic.



(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?

To determine the Median Complete Protection Times of eighteen S.C. Johnson & Son, Inc. personal repellent products.

(c) How would the study be used by EPA?

EPA will consider the study to satisfy product specific efficacy data requirements for use of the EPA Repellency Awareness Graphic on the eighteen S.C. Johnson & Son, Inc. personal repellent labels.

(d) Could the research question be answered with existing data? If so, how? If not, why not?

EPA requires product-specific efficacy data conducted to assess skin applied insect repellent products in terms of the recommendations of the EPA OPPTS 810.3700 Guideline and EPA Repellency Awareness Graphic Guidance. Previous testing of these products against mosquitoes under the proposed use pattern do not meet these recommendations for repellent efficacy.

(e) Could the question be answered without newly exposing human subjects? If so, how? If not, why not?

Human subjects are required because they represent the target system for the test material, and sufficiently reliable non-human models for repellency testing have not been developed.

2. Study Design

(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?

"The objective of this study is to establish the complete protection time of up to eighteen EPA-registered repellent products ('test substances') from S.C. Johnson & Son, Inc. ('Johnson') in the field against populations of wild mosquitoes, using human volunteers. Testing will be conducted at two geographically and ecologically distinct field sites" (p.8, §1.2). *"The rationale is to provide data on the longevity of complete protection from mosquitoes landing with intent to bite people with one of Johnson's eighteen EPA-registered test substances (personal mosquito repellent products). Following this protocol, several individual GLP field studies will be conducted. Each study will include one or two of the eighteen EPA registered test substances listed in this protocol" (*p.10, §1.6.1).

(b) Can the study as proposed achieve that objective or test this hypothesis?

The objective cited may be achieved by the study as proposed if the protocol is revised and amended to explain, in more detail, the following items noted on pages 12-14 of this review.

2.1 Statistical Design

(a) What is the rationale for the choice of sample size?

The rationale for the sample size appears on pp. 55-56 of 676 (§12.3). The researcher's justification for sample size is based on EPA accepted repellent protocols recommended by the HSRB including: Carroll-Loye Biological Research SPC-001, HSRB review of October 2007; and No Mas 003, HSRB review October 2010.

(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

Ten subjects (5 males and 5 females) will be treated with the test substance. Two additional subjects (one male and one female) will serve as the negative control for each test set as described on pp. 47-48 of 676 in §10.7.1 and §10.7.2. The controls are appropriate to monitor the mosquito landing rate (biting pressure) of mosquito populations at the test site. The data collected from these subjects will not be used in

the calculation of the Median Complete Protection Time. A positive control will not be used.

(c) How is the study blinded?

The subjects will be blinded to the test substances with which they are treated as described in on p. 41 of 676 in §10.4. The test substances will be coded both numerically and with colors, to link each test substance to the data sheet and to the subject who will receive it. The numerical codes will be written on each test substance sample and on the respective data sheets. Colored tape or marker will be used for the different colors.

(d) What is the plan for allocating individuals to treatment or control groups?

"*The test subjects will be selected at random from a pool of potential subjects. Assignment of the test substance to the subjects will be randomized. Randomization will use a treatment allocation table. The decision to use arms or legs will be based on the behavior of the species of mosquitoes present in the field. If two test substances are tested on one test day, assignments of these treatments will also be randomized amongst the test subjects"* (p. 40 of 676, §10.3.1 and §10.3.4).

(e) Can the data be statistically analyzed?

Yes.

(f) What is the plan for statistical analysis of the data?

The objective of the data analysis is to estimate the Median Complete Protection Time. Complete Protection Time (CPT) will calculated as time from application of each test substance to a subject and the first confirmed land on that subject. The Median CPT of all test subjects will be calculated using the Kaplan-Meier estimator, which is advantageous since CPTs may not be normally distributed. Kaplan-Meier is more conservative than competing parametric methods (Weibull and Normal) in that the Median CPT is likely to be lower and the 95% confidence interval around the median CPT is likely to be wider. Kaplan Meier estimator has been accepted by EPA and the HSRB for (Median) CPT calculation in past repellent efficacy studies and is also recommended by the World Health Organization for CPT calculation from these non-parametric data sets. "The duration of protection for each test substance will be the lowest median CPT from the test locations". This value will be rounded down to the closest full hour (p. 57 of 676, §12.4.4).

(g) Are proposed statistical methods appropriate to answer the research question?

The analysis will provide the overall Median Complete Protection Time. As proposed, the analysis addresses CPT values and associated uncertainties.

(h) Does the proposed design have adequate statistical power to definitively answer the research question?

The sample size of 10 subjects per treatment is consistent with past studies reviewed by EPA and the HSRB since 2006 and is a compromise between statistical power and cost.

2.2 How and to what will human subjects be exposed?

Subjects will be exposed to mosquito and tick repellent products that are registered by the US EPA. The application of these products to the skin of subjects in this study will be consistent with the directions for use on these products, and therefore the use has been determined to be safe. The active and inert ingredients have undergone EPA review and fulfilled the requirements needed for EPA registration as repellent products for contact skin use (p. 30 of 676, §3.3). Additional information on each product is provided in Appendix VI and VII of the protocol on pages 69-310 of 676 and in Tables 1, 2, and 3 in this review.

(a) What is the rationale for the choice of test material and formulation?

Efficacy data to satisfy product performance requirements and to support label claims for this product are required by EPA for registration. EPA requires submission of product performance data for all products claiming efficacy against public health pests. EPA recommendations in EPA OPPTS Guideline 810.3700 and the EPA Repellency Awareness Graphic are to be met to add the Repellency Awareness Graphic to a product label.

(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?

A dosimetry phase is not proposed in this experiment. Instead, Johnson is proposing a set dosage rate of 1 gram of product per 600 cm^2 (1.67 mg/cm^2). The study will not have a dosimetry phase to determine a 'typical consumer dose' by dose titration, which would be based on the grand mean of triplicate applications made by the test subjects. Johnson stated five reasons for using a set dose rather than a titrated dose (pp. 33-34 of 676, §7.1.1 – §7.1.2.5):

"(1) Influence of outliers: A single outlier data point can unduly influence the mean of 10 doses applied by subjects;

(2) Inter-test variability: Choice of dosing from dosimetry often results in selecting different doses for different tests since the groups of subjects will apply varying doses. This can obscure the cause of any different outcomes from two otherwise identical tests. This risk is avoided by using a set dose;

(3) Dose effect: Varying doses make it impossible to determine if performance difference is driven by the dose or the test products;

(4) Time and cost: Dosimetry introduces additional time and cost to a study compared to a set dose; and

(5) Relation to actual consumer use: To maintain the integrity of a scientific efficacy study the dose used should remain consistent. Keeping as many variables consistent from one test to the next and one test substance to the next is a more scientifically robust method of testing. A set dose can be related to known consumer behavior. Based on a handful of tests where dosimetry was employed, the standard dose falls within the range of values arrived at via dosimetry. Dosimetry allows the possibility of an atypical result."

Johnson proposed: "In order to apply the target dose of 1.67 mg.cm^2 the following formula will be used:

[Area of the Limb/600 cm^2] * 1 gm = weight (amount) of product to apply"

EPA is recommending the following product specific doses based on an analysis dosimetry data for repellent studies reviewed by EPA and the HSRB since 2006:

The following formula should be used to determine the amount of product to apply:

[Area of the Limb/600 cm^2] * X or Y or Z grams = weight (amount) of product to apply

X = 0.9g for lotions. (Target dose is 1.5 mg/cm^2)

Y = 0.4g for pump sprays. (Target dose is 0.67 mg/cm^2)

Z = 0.8g for aerosols. (Target dose is 1.34 mg/cm^2)

The application of repellent product to the skin of each subject will depend on the product type.

- For pump sprays, the test substance container is placed on a balance and the balance is tared. The required weight is drawn up by pipette while observing the digital display on the balance and applied to the skin of the subject.

- For aerosol sprays, the test substance container is placed on a balance and the balance is tared. The test substance is then sprayed from the container directly onto the skin. After the spray, the sample is returned to the balance and the amount applied is determined. If the amount is below the required weight, more test substance is sprayed onto the limb targeting the required weight as closely as possible.

- For lotions, the test substance container is placed on a balance and the balance is tared. The required weight of the test substance is then removed by spatula or similar implement-carefully observing the balance read out.

  Treatments will be made by study staff. §7.1.4-7.1.6 on pages 34-35 of 676 describe preparations before treatments are made. The target dose weight and actual weight applied will be recorded on a data sheet (p. 61 of 676, Appendix II).

(c) What duration of exposure is proposed?

The exposure is a 5-minute period every 30 minutes for either one arm or one leg of each subject. The exposure periods will be repeated until the product treatment fails on the treated subject.

2.3 Endpoints and Measures

(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?

Endpoints/Measures for efficacy evaluation:
"Subject specific Complete Protection Time (CPT) will calculated as time from application of each test substance to a subject and the 'First Confirmed Landing' on that subject." "A 'Landing' occurs when a mosquito alights on the treated skin of a subject. A 'First Confirmed landing' is that which is followed by another Landing within a 5 minute exposure period or, when one Land occurs in such an exposure period and another Land occurs in the next exposure period (30 minutes later)." The Median CPT of all test subjects will be calculated using the Kaplan-Meier estimator.

Subjects with repellent failures will be removed from the field test. The test will be terminated as determined by the study director.

The endpoints are appropriate to the questions being asked and address uncertainty associated with the samples size, between subject variation, mosquito land values, and the overall Median Complete Protection Time value.

The data form for each 5 minutes exposure is presented in Appendix III on page 62 of 676.

(b) What steps are proposed to ensure measurements are accurate and reliable?

- Standard Operating Procedures (SOPs) will be in place that must meet Good Laboratory Practices requirements.
- Study staff will train subjects for capturing (aspirating) mosquitoes landing on their exposed skin.
- Study staff will treat the skin of the exposed limb with the test substance.

- Study staff will lead subjects to and from the study sites and ensure that subjects work in pairs at pre-assigned locations within the study site.
- Study staff will monitor the start and stop times for each exposure period.
- Study staff will monitor the negative control subjects to make sure that the minimum mosquito landing rate (biting pressure) is met for each exposure period. Subjects may be moved within the test area to a location where landing rates may be higher if necessary.
- Study staff and the study director will track test substance samples, closely monitor the testing, environmental conditions and data recording.
- Alternate subjects will be enrolled to ensure adequate sample size.
- Counts of mosquito landings and the total number of mosquitoes captured will be determined. All mosquitoes captured through aspiration from the exposed skin will be identified to species.
- A Quality Assurance Unit will be in place to monitor all study activities and data collection.

(c) What QA methods are proposed?

Johnson's independent Quality Assurance Unit (QAU), under the leadership of Michael Caringello, will perform all QAU duties. Specifically, the QAU will inspect each study at intervals adequate to ensure study integrity, and maintain written and properly signed records of each periodic inspection showing the date of inspection, the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for re-inspection, all inspection findings will be sent to management and the Study Director Any problems which are likely to affect study integrity found during the course of an inspection shall brought to the attention of the Study Director and management immediately. The QAU will review and sign the final report for accuracy and compliance with GLPs and the protocol. (pp. 8-9 of 676, §1.4)

(d) How will uncertainty be addressed? Will point estimates be accompanied by measures of uncertainty?

Complete Protection Time (CPT) will calculated as time from application of each test substance to a subject and the first confirmed land on that subject. The Median CPT of all test subjects will be calculated using the Kaplan-Meier estimator, which is advantageous since CPTs may not be normally distributed. Kaplan-Meier is more conservative than competing parametric methods (Weibull and Normal) in that the Median CPT is likely to be lower and the 95% confidence interval around the median CPT is likely to be wider. Kaplan-Meier estimator has been accepted by EPA and the HSRB for (Median) CPT calculation in past repellent efficacy studies and is also recommended by the World Health Organization for CPT calculation from these non-parametric data sets. "The duration of protection for each test substance will be the lowest median CPT from the test locations. This value will be rounded down to the closest full hour (p. 57 of 676, §12.4.4).

3.1 Representativeness of Sample

(a) What is the population of concern?

The population of concern consists of people who would purchase and use mosquito repellents. Little information is available to characterize this population, but it is presumed that repellent users are highly diverse in age, gender, physical size, general health, attractiveness to mosquitoes, and other characteristics. The pool from which subjects are recruited is stated in the protocol to be demographically and ethnically representative of the population in the area where the field testing will be conducted. However, there are no details provided to substantiate this statement, nor is there information about whether the pool is representative of the U.S. population or the population of repellent users.

(b) From what populations will subjects be recruited?

Subjects will be recruited by a recruiting firm. This firm maintain a database of contacts of people generally interesting in participating in research studies in various areas including Wisconsin and Florida. The firm will telephone individuals from the database to compile a list of potentially interested subjects. The protocol states that the initial pool of subjects will be demographically and ethnically representative of the population in the area where the field testing will be conducted.

(c) Are expected participants representative of the population of concern? If not, why not?

There is no information provided about the demographics of the initial group of potential volunteers that will be contacted by the recruiting firm, and therefore there is not sufficient information to determine if expected participants are representative of the population of concern.

EPA Comment: Johnson should inquire with the recruiting firm about the demographics of the volunteer pool and provide additional details in the protocol to support the statement that the pool of subjects will be demographically and ethnically representative of the population in the area where the field testing will be conducted. Ideally, the pool of subjects will also be representative of the overall population of concern, which is repellent users in the United States, not just the population in the area where the testing is conducted.

(d) Can the findings from the proposed study be generalized beyond the study sample?

Yes. Each test substance tested will be evaluated at two geographically-separate sites.

3.2 Equitable Selection of Subjects

(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?

The inclusion/exclusion criteria are complete and appropriate.

"Individual Inclusion/Exclusion Criteria:

- *The subjects must be within the ages of 18-55 and can provide proof of age by a driver's license, passport, or other valid identification.*
- *The subjects must be able to read and speak English fluently.*
- *Subjects must not be employees of Johnson.*
- *Subjects must have a reliable form of transportation to get to and from the test and training locations.*
- *The subjects must be willing to be exposed to and potentially bitten by mosquitoes and not known to be hypersensitive to mosquito bites. All measures possible will be taken to prevent mosquito bites.*
- *The subjects must not have a known sensitivity or allergy to mosquito bites, Elastikon (or equivalent) tape, latex, insect repellents, or skin care products.*
- *The subjects must be free of skin disease, skin problems, such as eczema, psoriasis, or atopic dermatitis.*
- *Subjects must feel they are healthy enough and do not have any heath conditions that would make them unable to sit in a chair for long periods, with breaks for limb stretching and movement at reasonable intervals, able to stand continuously for five minutes and be outdoors for several hours where high temperatures, high humidity and sweating are possible.*
- *Subjects must be willing to participate in testing outdoors where high temperatures, high humidity and sweating are possible.*
- *The subjects must be willing to refrain from using alcohol 12 hours before the test, and refrain from nicotine, and fragrance products (e.g., soap, perfume, cologne, hair spray, lotion, etc.) during the test.*
- *The subjects must be willing to follow the study procedures as explained and be willing to sign an ICD.*
- *The Female subjects must not be pregnant or be breast-feeding. Within 48 hours prior to participation in testing Female subjects will be required to perform an over the counter pregnancy test that will be supplied by the Sponsor.*
- *Confirmation (during their training session) will be needed before the field testing that mosquitoes are attracted to subjects' untreated skin in one of the two following ways:*
    - *In a lab setting, potential test subjects will confirm mosquitoes are attracted to subjects' untreated skin by inserting an untreated forearm into a 2' x 2' x 2' test cage with approximately 50 adult female mosquitoes, that are approximately 5-10 days old. To qualify test subjects must acquire five lands within a one minute exposure with an Aedes species. If five lands are acquired before the end of the exposure period, the exposure period will be stopped. The arm will be protected with a sleeve the proboscis cannot penetrate and the hand is protected with a glove.*

- *If a laboratory is not available, potential test subjects will confirm mosquitoes are attracted to subjects' untreated skin in a field setting. Potential test subjects will be exposed to a wild population of mosquitoes and must acquire five lands in 5 minutes on the forearm or lower leg. If five lands are acquired before the end of the exposure period, the exposure period will be stopped. No skin will be exposed for this qualification. A full bug suit (or similar) consisting of a material the proboscis cannot penetrate and screened mesh over the face area will protect the entire body. The hands will be protected with gloves and the feet with higher cut shoes or boots."* (p. 14-16)

(b) What, if any, is the relationship between the investigator and the subjects?

The protocol excludes people who are employees of S.C. Johnson are excluded from becoming subjects.

EPA Comment: The protocol and consent form should be amended to also exclude the immediate family of S.C. Johnson employees.

(c) Will subjects be recruited from a vulnerable population?

No.

(d) What process is proposed for recruiting and informing potential subjects?

"Subjects will be recruited from the general public at three times greater than the number required for any one study. A Recruitment Firm will initially contact potential subjects and compile a pool of potentially interested subjects. This pool will be demographically and ethnically representative of the population in the area where the field testing will be conducted. Subjects will be recruited over telephone. Potential subjects will be given a brief outline of the study. If they are interested in potentially enrolling in the study, they will be given a time, date and phone number to talk with member of the study staff learn more about the study and there role in it, go over the inclusion/exclusion criteria, and answer any further questions they may have.

"Subjects that meet the inclusion/exclusion criteria and are still interested in enrolling in the study, they will be given a time, date and location to meet with the Study Director or Principle Investigator for further information, as described under 'Consenting' below (Section 2.4). If the subject would like to provide the study director with an email or mailing address, the ICD will also be sent to them via email or mail to review prior to the training session." (pp. 12-13)

(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?

Subjects will be recruited by a professional Recruiting firm. There will be no communication between the researchers and the potential subjects' employers, which minimizes the potential for coercion or undue influence. In addition, employees of the sponsor, S.C. Johnson, are excluded from participation.

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for the subjects?

"Subjects will be paid $60.00 for participating in an approximately 3-4 hour training session prior to the field testing.

"For each field test day, subjects will be paid $15/hr for the test day. If a test day exceeds 8 hours, subjects will be paid $18.00 for each additional hour beyond the first 8 hours, rounded up to the nearest hour.

"The alternates, if they are not needed on the test day to replace an absent or withdrawn test subject, will be paid $50 to compensate for being inconvenienced.

"A back up date will be planned in case of rain. Should the original test date be cancelled due to inclement weather, subjects will be compensated for their time and inconvenience, and will be invited to volunteer as a test subject for the Rain Date. They will receive $60 for having been available for the original date. They will receive the standard payment for participation the Rain Date." (pp. 13-14)

(b) Is proposed remuneration so high as to be an undue inducement?

No.

(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects?

No.

(d) How and when would subjects be paid?

"Subjects will be instructed that they will be asked to pick up their monetary compensation at the Recruitment Firm, the next following business day after their participation in the training session and also after their participation in the study. All subjects will be paid an additional $15 to compensate for their time and travel to the recruitment firm." (p. 14)

4. Risks to Subjects

4.1 Risk characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test material?

Subjects will be exposed to mosquito and tick repellent products that are registered by the US EPA. The application of these products to the skin of subjects in this study will be consistent with the directions for use on these products, and therefore the use has been determined to be safe. The active and inert ingredients have undergone EPA review and fulfilled the requirements needed for EPA registration as repellent products for contact skin use. (p. 30 of 676, §3.3) Additional information on each product is provided in Appendix VI and VII of the protocol on pages 69-310 of 676 and in Tables 1, 2, and 3 in this review. Margin of Exposure (MOE) estimates are based on an assumed 70 kg subject and the acute dermal LD_{50} value for each product at the limit dose of greater than 2,000 mg/kg. Based on the dose rates presented by Johnson, the MOE values for the tested active ingredients will exceed EPA's level of concern of MOE = 100. Specific MOE values will be provided for each product when the study is conducted.

(b) What is the nature of the risks to subjects of the proposed research?

"There are five types of hazard associated with this type of study:
A) Adverse reaction to the test substances
B) Exposure to biting mosquitoes
C) Exposure to mosquito-vectored diseases
D) General risks of being in the field, including (but not limited to): exposure to high levels of heat and humidity for 12+ hours, possible presence of wild animals (e.g. snakes, ticks), and risk of injury due to uneven terrain
E) Unanticipated loss of confidentiality." (pp. 15-16)

(c) How do proposed dose/exposure levels compare to the established NOAELs for the test material?

The test materials are EPA-registered mosquito repellent products and they will be used consistent with the Directions for Use on the product labels. Therefore, EPA considers the exposure to the test substance that would be received by a subject to be safe.

(d) What is the probability of each risk associated with the research? How was this probability estimated?

No numerical probability is estimated, but risks have a low probability of occurrence. Risks are minimized in the protocol by excluding candidates known to be hypersensitive to or phobic of mosquito bites; conducting the research in areas where

mosquito-borne disease has not been detected within one month prior to the test date; excluding candidates known to be sensitive to the test material; applying stopping rules if conditions at the site become unsafe; and by incorporating procedures to keep the results of pregnancy testing private and permit discrete withdrawal.

4.2 Risk minimization

(a) What specific steps are proposed to minimize risks to subjects?

Risk of adverse reaction to test substance

"Subjects will be told that if anyone experiences any skin reaction, experiences an injury, or simply feels unwell, he or she should inform Study staff right away. Such subjects will immediately be given appropriate care, may be withdrawn from testing, and may be transported to a local hospital if necessary. The closest hospital to the training and test sites and directions to the closest hospital will be identified prior to the training or test date.

"Subjects may ask for standard first aid items such as bandages, antiseptics, and mild topical and oral antihistamines at any point during the study, though they will not be able to apply topical antihistamines to the treated areas of their skin while still taking part in the test. They may also request qualified first aid assistance at any time." (p. 23)

Risk of exposure to biting mosquitoes:

"No subjects with known allergies to mosquito bites will be allowed to participate as a test subject. Subjects will receive specific training on how to remove mosquitoes from their skin before they bite. In addition, treated subjects will only expose one forearm or one lower leg for mosquitoes to land on.

"The untreated control subjects will be at greater risk of being bitten, since they will not have any repellent test products applied to their exposed skin. Therefore, when they have received five lands in a 5-minute exposure (the minimum necessary to ensure adequate biting pressure), they will cover their exposed limbs by rolling down their sleeve or pants leg." (p. 21)

Risk of exposure to mosquito-vectored diseases

"In the US, mosquitoes can transmit various disease-causing organisms to humans, notably the West Nile virus ('WNV'). According to the CDC, most people who contract WNV (approx. 80%) do not develop symptoms. The remaining 20% may show symptoms of tiredness, headaches, body aches, fever or a rash. Slightly less than 1% of persons will show more serious symptoms. Several forms of encephalitis-causing organisms can be vectored by mosquitoes but at a lower frequency than WNV. There is also a smaller risk of transmission of dengue virus, malaria protozoa

and chikungunya. All subjects will be instructed as to what symptoms of these diseases may look like, so they may seek informed medical care in the very unlikely event they contract any of these diseases and become symptomatic.

"To reduce the risk of contracting any mosquito-borne diseases, the study will be conducted in areas where the presence of mosquito-borne disease has not been detected by county or state health staff or mosquito abatement district staff within one month prior to the test date. All subjects will be trained to quickly and adeptly remove mosquitoes from each other (using a hand-held aspirator device) during the 5 minute periods when they expose small areas of their skin to mosquitoes." (p. 22)

General risks of being in the field

"Study staff will provide food and non-alcoholic beverages on site, and will encourage subjects to drink regularly in order to keep hydrated. A screened enclosure will be provided to keep subjects away from mosquitoes between text exposure periods and shade will also be provided to protect them from direct sun.

"Staff will be cognizant of the types of wildlife they may find in the area, and will move subjects away from areas where they find potentially harmful organisms such as fire ants or snakes. Staff will also encourage subjects to perform frequent 'tick checks' (and will assist if necessary) to remove any acquired ticks before they have opportunity to bite." (p. 22-23)

Risk of Unanticipated loss of confidentiality

"All efforts will be taken to maintain the confidentiality of the pregnancy tests results. The test will be performed by the potential subject in a private setting. The results will be verified by the subject only. After completion of the pregnancy test, a female member of the study staff will ask in a private setting if the potential subject is still interested in participating in the study. If they are no longer interested they do not need to explain why. If the test subject is interested in participating, the results will be verified by a female of the study staff in a private manner. The results will be kept confidential, will not be recorded, and will not be disclosed to anyone. The Female staff member will only notify the Study Director or Principle Investigator which females will be and will not be participating in the study.

"All efforts will be taken to maintain the confidentiality by protecting the subjects' personal information in the following ways. Each subject will be assigned a code number. Only subjects' code numbers will appear on data sheets. The subjects' names will not appear in the report. The study records will be maintained at the study site in locked cabinets and electronic files kept on a password-protected computer server. No one outside Johnson, the study staff, the IRB, or certain governmental agencies (such as USEPA) will have access to subjects' personal information." (p. 24)

(b) What stopping rules are proposed in the protocol?

The protocol states: "*The Study Director or Principle Investigator will stop, and if needed reschedule, the test day if temperatures exceed 105°F, or other unanticipated weather arises that poses unsafe conditions to remain outdoors."* (p. 53)

EPA Comment: Johnson should consider whether additional stopping rules should be added to the protocol. Examples include: biting pressure falls below threshold needed to challenge test material, wind speeds exceed a certain level, subject asks to withdraw, subject proves unattractive to target species, subject exhibits hypersensitivity to insect bites, subject exhibits sensitivity to the test material, medical management is invoked. The first two examples would apply to the entire study; the other examples would apply to an individual subject.

(c) How does the protocol provide for medical management of potential illness or injury to subjects?

"Johnson will have at least two First-Aid qualified study staff members and supplies on site to monitor subjects for medical problems. In the case of medical emergency, Study Staff will call 911, ask for emergency assistance, and follow instructions given by the emergency dispatcher (including, if necessary, waiting for an ambulance for transport the subject to the nearest hospital)." (p. 19)

(d) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

The consent form states: *"If you have any questions about this study or suffer a research-related reaction, call the Study Director listed on the front page of this consent form, or Safety Call at (866) 344-3932 available 24-hours."* There is no time limit given. (p. 319)

(g) How and by whom will medical care for research-related injuries to subjects be paid for?

The consent form states:

"***Compensation for Injury.*** *In the unlikely event that you are injured as a result of your participation in this study, medical care will be made immediately available. The sponsor will reimburse you for the costs of this care. All adverse effects will be followed until resolution is reached. If you believe you have suffered any physical or mental adverse effects as a result of your participation in this study, the sponsor will address your claims according to the applicable workers compensation laws and regulations. There are no plans to provide other compensation beyond that which is listed in this informed consent document. You will not lose any of your legal rights or release the Sponsor, the study doctor, the study staff, or study site from liability for mistakes or intentional misconduct by signing this consent document.*" (p. 318)

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

There are no direct benefits to subjects. The consent form states: *"You will not personally benefit from this study, other than the financial compensation."* (p. 319)

EPA Comment: The consent form should be revised to delete the phrase: "other than the financial compensation" from the Benefits section. Compensation is not considered a benefit of study participation.

(b) What benefits to society are anticipated from the information likely to be gained through the research?

The consent form states: *"The benefit to society is the gaining of knowledge regarding the efficacy of personal mosquito repellents."* (p. 319)

(c) How would societal benefits be distributed? Who would benefit from the proposed research?

One beneficiary of the research is the sponsor, S.C. Johnson, which is seeking the Repellency Graphic across the company's line of topically-applied repellent products. Indirect beneficiaries would include users of these products who may benefit from additional information about the period of effectiveness of these products.

(d) What is the likelihood that each identified societal benefits would be realized?

The testing is likely to demonstrate the complete protection time for each of the tested products.

6. Risk/Benefit Balance

(a) How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

The protocol reduces risks to subjects without reducing the robustness of the scientific design. The resulting residual risk to subjects is very low. The potential benefits from availability of additional information about the efficacy of skin-applied repellent products are likely to be realized, and make the residual risks to subjects in this proposed research reasonable.

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Schulman Associates Institutional Review Board, Inc. (SAIRB)

(b) Is this IRB independent of the investigators and sponsors of the research? Yes

(c) Is this IRB registered with OHRP? Yes

(d) Is this IRB accredited? If so, by whom?

SAIRB has full AAHRPP accreditation.

(e) Does this IRB hold a Federal-Wide Assurance from OHRP?

Yes.

(f) Are complete records of the IRB review as required by 40 CFR 26.1125 provided?

Yes.

(e) What standard(s) of ethical conduct would govern the work?

This is a protocol for third-party research involving what EPA has interpreted to be intentional exposure of human subjects to a pesticide. The study is being conducted with the intention of submitting the resulting data to EPA under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA). Thus, the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

8. Informed Consent

(a) Will informed consent be obtained from each prospective subject?

Yes.

(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR 26.1117?

Yes.

(c) Do the informed consent materials meet the requirements of 40 CFR 26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research?

Yes.

(d) What is the literacy rate in English or other languages among the intended research subjects?

Ability to speak and read English is a requirement for participation.

(e) What measures are proposed to overcome language differences, if any, between investigators and subjects?

N/A

(f) What measures are proposed to ensure subject comprehension of risks and discomforts?

Frequent opportunities to ask questions during the consent process.

(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

"Prior to participating in any aspect of the study (including training), each potential subject who has expressed interest in participating in the study and has met the inclusion/exclusion criteria will meet with the Study Director or Principle Investigator. The subjects will be provided with copies of the ICD and will then be asked to listen while the entire document is read to them.

"The Study Director or Principle Investigator will ask the subjects if they have any questions. Any questions will be answered.

"If a subject still wishes to enroll in the study, he or she will be asked to sign their copy of the ICD. His or her signature will be witnessed by the Study Director, Principle Investigator or Sub Investigator. Each subject will then be given a photocopy of his or her signed ICD." (pp.17-18)

EPA Comment: Given that the ability to read English is a requirement to participate, Johnson should offer subjects the option of reading the consent form themselves. If Johnson wishes to confirm understanding of the consent form, Johnson should draft several questions to be asked of each potential subject prior to them signing the consent form. These questions should be included in the revised materials that are reviewed by SAIRB before the study is initiated.

(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

Candidates are offered repeated opportunities to decide not to participate; participants are offered repeated opportunities to withdraw. Exclusion factors rule out participation by employees of the sponsor. Recruitment of alternate subjects reduces the likelihood that subjects might be reluctant to withdraw.

9. Respect for Subjects

(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?

Subject-identifying information will be recorded only once; all subsequent data records and reports will refer to individual subjects only by an arbitrary code. *"The information obtained from subjects taking part in this test will be used by Johnson and will become part of a report. This report (as well as all study-related records) will not be publically available, and will be kept as confidential as possible under local, state, and federal laws and regulations. The study results generated following this protocol are not intended for publication; however, if any of the study- related data are published, subjects' identities will remain confidential.*

"In addition, the subjects' identities will be protected in the following ways. Each subject will be assigned a code number. Only subjects' code numbers will appear on data sheets. The subjects' names will not appear in the report. The study records will be maintained at the study site in locked cabinets and electronic files kept on a password-protected computer server. No one outside Johnson, the study staff, the IRB, or certain governmental agencies (such as USEPA) will have access to subjects' personal information." (p. 19-20)

Provision is made for discrete handling of the pregnancy testing that is required of female subjects on the day of testing. *"Within 48 hours prior to participation in testing Female subjects will be required to perform an over the counter pregnancy test that will be supplied by the Sponsor. The test will be performed by the test subject in a private setting. The results will be verified by the test subject only. After completion of the pregnancy test a female member of the study staff will ask in a private setting if the potential subject is still interested in participating in the study. If the test subject is interested in participating, the results will be verified by a female of the study staff in a private manner. The results will be kept confidential, will not be recorded, and will not be disclosed to anyone other than the test subject and the Study Director or Principle Investigator."* (p. 16)

(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

The informed consent form states: *"Participation in this study is voluntary. You may refuse to take part in this study or withdraw at any time without penalty or loss of benefits to which you may be otherwise entitled. You agree to inform the Study Director or Principal Investigator if you intend to withdraw from the study."* (p. 319)

Subjects are informed about their right to withdraw during the consent meeting and in the consent form.

(c) How will subjects who decline to participate or who withdraw from the research be dealt with?

Payment:
The protocol contains details about how payment will be handled if subjects withdraw from the research. It states that if subjects withdraw for a non-health related reason, they will only be paid for the hours they have participated in the research. It does not specific, however, if subjects will be compensated for time or inconvenience if they participate in the consent meeting or the training session but ultimately decide not to participate.

> EPA Comment: The protocol and consent form should state whether subjects will be compensated for participating in the consent meeting, the training meeting, and/or the pregnancy testing if they ultimately decide not to participate in the research.

Other issues:
The protocol does not specify how subjects will be treated if they withdraw after the research is underway.

> EPA Comment: The protocol also does not specify if subjects will be transported by the researchers to and from the testing site, or if subjects will travel to the testing site on their own. If the testing site is remote, and if Johnson plans to transport the subjects to the testing site, then Johnson should make arrangements to transport any withdrawn subjects back to the starting location. If Johnson cannot make such arrangements, then a subject should be paid for the time spent at the study site, even if he or she has chosen to withdraw early. To do otherwise could unduly influence the subjects to continue participating.

Attachment 2

§ 26.1111 Criteria for IRB approval of research
Field Testing of SC Johnson Mosquito Repellent Products
to Support their Use of the EPA Repellency Awareness Graphic

Criterion	Y/N	Comment/Page Reference
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	N/A	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	Y	
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	N/A	

§26.1116 General requirements for informed consent
Field Testing of SC Johnson Mosquito Repellent Products
to Support their Use of the EPA Repellency Awareness Graphic

Criterion		Y/N	Comment/Page Reference
No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative		Y	
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		Y	
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		Y	
No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence		Y	
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	Y	
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Y	
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	Y	
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Y	
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	Y	
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	Y	
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	Y	
(b) When appropriate, one or more of the following elements of information shall also be provided to each subject	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	Y	
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Y	
	(3) Any additional costs to the subject that may result from participation in the research	Y	
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	Y	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	N/A	
	(6) The approximate number of subjects involved in the study	Y	
(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		Y	

§26.1117 Documentation of informed consent
Field Testing of SC Johnson Mosquito Repellent Products
to Support their Use of the EPA Repellency Awareness Graphic

Criterion	Y/N	Comment/Page Reference
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.	Y	Consent form pp. 311-321
(b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or	Y	Consent form meets requirements of §26.1116; the procedure described in protocol §2.4 [if the EPA request that subjects be given the opportunity to read the consent form themselves is implemented] provides adequate opportunity for each subject to a gain full understanding of it before it is signed.
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	N/A	

40 CFR 26.1125 Submission of proposed human research for EPA review
Field Testing of SC Johnson Mosquito Repellent Products
to Support their Use of the EPA Repellency Awareness Graphic

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

	Requirement		Y/N	Comments/Page Refs
The following Information, to the Extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 20-21
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 21-24
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	pp. 25
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	See Rationale and intended use of data- Section 1.6.1 - Page 10 See Rationale for human testing- Section 2.1.1.1 – Page 11
		(5) The balance of risks and benefits of the proposed research.	Y	p. 21-24
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	pp. 311-321
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 11-18 pp. 322- 323 pp. 324-326
	§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	pp. 17-18 pp. 311-321
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 329- 672
	§1125(f): Official notification to the sponsor or investigator. . . that research involving human subjects has been reviewed and approved by an IRB.		Y	The research has been conditionally approved, pending EPA and HSRB review. p. 642
all information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	pp. 6-68 pp. 311-321
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	pp. 671-672
	(3) Records of continuing review activities.		n/a	
	(4) Copies of all correspondence between the IRB and the investigators.		Y	pp. 329-672
	(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y Y	pp. 673-676
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		N	On file with EPA
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	n/a for protocols