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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

September 22, 2015

MEMORANDUM

SUBJECT: Science and Ethics Review of a Protocol for Laboratory Testing of S.C. Johnson Skin Applied Tick Repellent Products

FROM: Kevin J. Sweeney, Senior Entomologist
Registration Division

Eric Bohnenblust, Ph.D., Entomologist
Registration Division

Maureen Lydon, Human Research Ethics Review Officer
Office of the Director *(On Detail*)

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

REF: Styer, K. (2015) Protocol Submission Package for Testing of S.C. Johnson Personal Tick Repellent Products to Support their Use of the EPA Repellency Awareness Graphic. Unpublished document prepared by i2LResearch USA, Inc., Baltimore, Maryland. July 28, 2015. 353 p. (MRID 49686701) (D428880)

We have reviewed the referenced protocol for a laboratory test of skin applied tick 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 (HSRB). 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

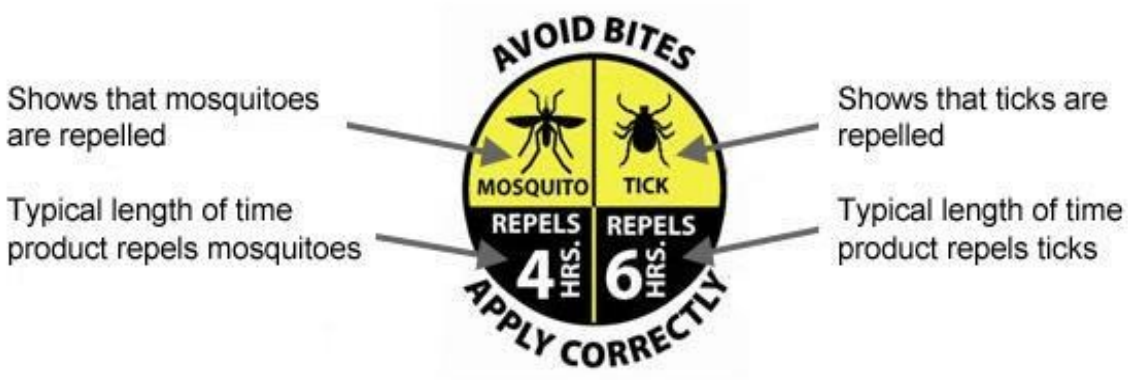
The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 8. All

elements of required documentation are provided in the submitted protocol package and separate materials provided by the Schulman Associates Institutional Review Board (SAIRB) directly to the U.S. Environmental Protection Agency (EPA).

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 attachments.

1. **Societal Value of Proposed Research:** This study will determine the complete protection time (CPT) of up to eighteen EPA-registered skin applied repellent products from S.C. Johnson & Son, Inc. on volunteer human subjects in a laboratory against three tick species. Up to three different active ingredients will be tested, along with a variety of product types (e.g., lotions, spritz, aerosols, and towelettes). Direct testing of the duration of efficacy is important because consumers, who rely on repellents to avoid tick 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 ticks on their product labels. This graphic is intended to help consumers easily identify the repellency time (based on the Median CPT). 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 sample diagram below describes the graphic (and includes a fictional example of repellency hours which are not intended to apply to the study products).



2. **Subject Selection:** Ten subjects (5 males and 5 females) will be treated with a test substance. Each test subject will serve as their own untreated control. There will be two alternate test subjects (one male and one female). Subjects will be between 18 and 55 years of age. As described in the protocol language revised to address EPA's comments, subjects will be recruited for each study to best represent the demographics of U.S. repellent users, based on Neilson data identified in the protocol. Revised §2.3.6 of the protocol describes the targets for each sub-population of U.S. repellent users. Test

subjects will be recruited via advertising, through digital and social media, from the Baltimore, Maryland area where the testing will be conducted. A Spanish language advertisement will also be posted on line using the same digital and social media, along with an online Spanish language newspaper that advertises within the recruitment area. The advertisements will contain a link to a study-specific secure website where interested subjects can learn more about the study and, if interested, complete a pre-screening qualification form; the form will be automatically uploaded into a secure and encrypted portal to which i2LResearch employees will have access. Every effort will be made to achieve the demographic composition described in revised §2.3.6. Individuals from the recruitment pool will be contacted to determine whether they meet the basic inclusion criteria and will be given a brief outline of the study. If they are interested in enrolling in the study, they will meet with i2L staff for a training session to learn more about the details of the study and their potential role in it, review the inclusion/exclusion criteria, confirm their understanding of the informed consent document, and receive answers to their questions. The training program is outlined in detail in §2.2.5 of the revised protocol language. All subjects who meet the requirements for participation and agree to participate in the study will signed the informed consent document, which will include contact information in case subjects have additional questions in follow-up to their training.

3. **Risks to Subjects:** Risks to subjects include the risk of adverse reaction, either irritation or allergic reaction, to the test substances; exposure to ticks; the risk of exposure to tick vectored diseases; unanticipated loss of confidentiality or privacy; and fatigue and/or physical discomfort from the length of the test day. Risks are minimized in the protocol by excluding candidates known to be sensitive to the test material; excluding candidates known to be sensitive or allergic to ticks bites; conducting the research with disease free ticks; technician removal of ticks before they bite; using subject identification codes to help ensure privacy; and incorporating procedures to keep the results of pregnancy testing private and permit discrete withdrawal. To try to address fatigue and physical discomfort, the study sponsor will provide breakfast, lunch and dinner to participating subjects as described in the revised protocol, breaks and opportunities to stretch during the test day, and support for the subject's arm as it's held at an angle during the exposure period. Also, there will be a two-day break between test days. 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 allow the addition of the Repellency Awareness Graphic to skin applied tick repellent labels. 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, thereby allowing for better protection of consumers from nuisance bites and bites that lead to arthropod-borne diseases.

5. **Risk/Benefit Balance:** Based on the revised protocol language submitted in response to EPA comments, 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 viewed as low and reasonable in light of the potential benefits of the data to society.

6. **Independent Ethics Review:** The Schulman Associates IRB (SAIRB) has reviewed and conditionally approved the protocol and informed consent form. SAIRB's final approval is conditioned on the sponsor obtaining HSRB review, comments and approval. After the HSRB review process is complete, the protocol and other documents must be revised by the author and sponsor 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. Documentation of SAIRB procedures and membership is on file with the Agency.

7. **Informed Consent:** The protocol contains a description of the process by which potential subjects will be recruited and informed, and the process for seeking their consent to participate. The draft of the consent document (conditionally approved by the SAIRB pending HSRB review/approval) and the revised draft (in Attachment 3), which was prepared by the author in response to EPA comments, meet the 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. Multiple opportunities exist to ask questions and receive information in response. Subjects who withdraw will be compensated for time spent up to the point of withdrawal as described in the protocol. Medical care for research related injuries will be provided through the sponsor at no cost to the subjects. As described in the revised protocol language, meals will be provided to participating subjects at the test site consistent with the length of each test day.

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 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. Attachment 1 provides 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.

EPA Ethics Comments

Before the research is initiated, the documents should be revised to address EPA's ethics comments in this section, EPA's science comments, and any forthcoming comments from the

EPA Human Studies Review Board. S.C. Johnson and i2LResearch agreed to address all of EPA's comments; Attachment 2 includes the revised language proposed by S.C. Johnson (hereafter "Johnson") and i2LResearch in response to EPA's comments. HSRB members are encouraged to read through Attachment 2 to understand the proposed revisions. After HSRB review and comment, the revised materials must be submitted to the SAIRB for final approval.

EPA's ethics comments are listed below (in order of the pertinent sections of the draft July 28, 2015 protocol to which they apply):

1) For purposes of clarity, please expand upon the following statement in Section 2.2.2: **"**Each tick species will be tested separately from the other two tick species over the course of two test days, each lasting up to 18 hours (test period) for a total of 6 test days (3 testing periods) per study."

2) Johnson and i2L Research will require a 2 hour training session for study participants prior to the test day in order for subjects to "learn more about the study and their potential role in it, go over the inclusion/exclusion criteria, and receive answers to any questions they may have." EPA's science and ethics review resulted in the same recommendation regarding the training session; the protocol should be explicit with regard to the training outline and specific topics to be addressed.

3) Regarding the recruitment process described in sections 2.3.3 – 2.3.6 (on pages 15 – 16 of the draft protocol), Johnson and i2LResearch decided to recruit participants instead of relying on a "pool of individuals who have expressed interest in testing with i2L." As a result, please provide a revised and detailed description of the recruitment process for inclusion in the revised protocol. The recruitment process should include advertisements in one or more local Spanish language newspapers. 40 CFR Section 26.1125(c) requires that the sponsor submit any advertisements proposed to be used; the advertisement language must be provided for EPA and HSRB review. Following EPA and HSRB review, the advertisement must be reviewed and approved by the IRB, along with all other changes to the protocol.

4) The last statement in section 2.3.6 (above the chart, on page 17 of the protocol) indicates that, "If the individual desires, this discussion may also take place by telephone or email." OPP recommends deleting or revising this statement because it conflicts with the statement in section 2.4.1 (on page 19) that prior to participating in any study-related procedure, each potential subject will meet in person with the Study Director or another designated staff member.

5) In order to strengthen the **consent process and Informed Consent Document**, EPA recommends the changes noted below. The revised consent form which Johnson and i2LResearch proposed in response to EPA comments is in Attachment 3.

    a) In order to confirm each subject's understanding of the consent form, Johnson and i2LResearch should draft several questions to be asked of each potential subject prior to the subjects signing the consent form; those questions should be included in the revised materials that are reviewed by the HSRB and SAIRB before the study is initiated. One of the questions should address freedom to withdraw from the study.

b) The draft protocol indicates that participants sign the consent form once, regardless of the number of studies in which they participate. EPA recommends that participating subjects read and sign the consent form more frequently and asks Johnson and i2LResearch to propose an approach.

c) EPA recommends that a section on "Test Material" and the identity of the pesticide and the nature of its pesticidal function be included in the consent form. As a result of this, please delete the language in protocol section 7.4 on blinding of subjects as to identity of test substance.

d) In the consent form, under "purpose of study," it says the Johnson and i2LResearch wish to conduct "five to eighteen research studies." This is the first place where the number "five" is used. EPA recommends consistency between the protocol and the consent form.

e) In the draft consent form, under "suitability," second paragraph, EPA recommends referring to "allergies or sensitivities" to tick bites.

f) In the consent form, under "study duration and number of subjects," when referencing the number of days of the study and number of testing periods, please be consistent with the proposed revisions to the protocol, specifically section 2.2.9.

g) Under "study duration and number of subjects," at the end of the first paragraph, please add the following language: "Each test subject can only take part once in any two-day testing period. Subjects who become test subjects in two studies within one week will have different arms treated for each study to avoid the risk of carry-over of the first treatment to the second study."

h) Please insert the detailed description of the training program in the consent form.

i) In the consent form, at the end of the procedures section, please insert language about a fifteen minute lunch break and fifteen minute dinner break. Please reference that breakfast, lunch and dinner will be provided. The breaks and providing breakfast during the preparation time, and lunch and dinner during the test day, are necessary due to the length of the test day.

j) At the end of the "discomfort and hazards/risks" section, EPA recommends adding the sentence, "There is also the fatigue and discomfort associated with a long testing day."

k) Please update the compensation figures in the consent form consistent with EPA's comments on compensation amounts. (See EPA comment #7.)

l) In the introduction to the consent form, please remove the reference to "alternative procedures" described in the consent form because such procedures are not discussed.

m) Please reference the updated preparation time, in addition to the potential length of the testing period, in the consent form.

n) In the consent form's section on study duration and number of subjects, there is a reference to "zero to five female subjects plus five to zero male subjects." EPA recommends that you replace this with a statement that both male and female subjects will participate.

o) EPA recommends deleting the section in the original draft consent form entitled, "Research Participation Information." This section lists 5 different websites that subjects can check for information about participation in human research studies in general. Although EPA appreciates the intent of Johnson and i2LResearch, given that these websites do not focus on the tick repellent study for which subjects are being recruited, EPA believes this section is unnecessary. Only the information directly relevant to the tick repellent study should be included in the consent form to avoid unnecessary time being spent by subjects researching other material.

p) The definition of the repellant breakdown/failure in the consent form needs to match the definition in the revised protocol.

q) The consent form and phone scripts must be updated consistent with any other revisions to the protocol approved by EPA and the HSRB.

6) EPA recommends that the training session require that each subject provide proof of age with a driver's license, passport or other valid identification; Johnson already identified this inclusion factor in the protocol, but the protocol needs to specify at what point the identification will be checked. EPA recommends that occur during the training session and at the beginning of each study, on the first day that a subject arrives for participation.

7) Section 2.5 of the protocol states that, for each test day, test subjects will be paid $99.00 for any length of participation up to 9 hours and if a test day exceeds 9 hours, subjects will be paid $16.50 (time and a half) for each additional hour, rounded up to the nearest hour. The compensation of $11 per hour is not comparable to similar recent human studies. OPP recommends that S.C. Johnson increase compensation to $13 per hour up to 8 hours and if a test day exceeds 8 hours, subjects will be paid $19.50 (time and a half) for each additional hour, rounded up to the nearest hour. The protocol currently states that subjects will be paid $25 for taking part in the training session. Section 2.2.5 (page 14) indicates that the training session will be about two hours. Given that the training session will be two hours in length, $30 seems like reasonable compensation and would be comparable to other protocols/studies.

8) Regarding the inclusion/exclusion criteria, EPA recommends the following changes:
"2.6.7. The subject must have no known allergies or sensitivities to tick bites.
2.6.9. The subjects must not be hypersensitive to repellent or latex or ~~other~~ skin care products. The subjects must be free from skin disease, skin problems such as eczema, psoriasis or atopic dermatitis."

9) EPA recommends that the pregnancy test be conducted within 48 hours prior to the test day. We understand that it's necessary to conduct other preparation work on the day of testing, but

Johnson can take steps to reduce the length of the day by having the pregnancy test completed in advance.

10) Please update section 2.7.3 under "restrictions," to indicate that there must be at least 48 hours, not 24, between each test day. Similarly update section 4.2 to indicate that there will be two days (not one) between test days.

11) The section on hazards to human subjects, section 2.10, page 24, currently discusses four types of potential hazards. To be comprehensive in the protocol and consent form, Johnson and i2LResearch should add the hazard of, "Fatigue and/or physical discomfort from length of test day" and actions being taken to reduce this discomfort, including the provision of breaks for lunch and dinner, subjects being encouraged to stretch as needed, and a 2 day break between test days.

12) The "hazards to human subjects" section 2.10.10, page 26 also states, "Subjects will be told that if anyone experiences any skin reaction, experiences an injury, or simply feels unwell, he or she should inform i2L 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." EPA recommends that Johnson and i2LResearch add language that the closest hospital and directions will be identified prior to the test date, and discussing reimbursement for medical care costs as applicable.

13) Johnson and i2LResearch should try to reduce the length of the 2 hour preparation time which occurs prior to the exposure period and limit it to essential activities which must occur during that timeframe. (If the preparation time is reduced in length, please reflect the new length in the consent form.)

14) Given the potential length of the test day, Johnson and i2LResearch should provide breaks and breakfast, lunch and dinner to the subjects.

15) Section 7.6 on repellency observations explains that subjects will hold their forearm at approximately a 45 degree angle from the horizontal. EPA recommends that support material be provided to help bolster the subject's arm and for comfort while it's being held at a 45 degree angle. Please provide a photograph illustrating this support for EPA and the HSRB.

16) Regarding medical monitoring and reporting unanticipated problems in section 9.2, please add that subjects will be informed "in a timely manner", both "orally" and in writing, of any significant new findings or new information. Please expand the title for section 9.2. to include "Stop Rule" given the proposed expanded content for that section.

17) In section 9.3 on study termination, individual participation, and withdrawal, in 9.3.2, after the reference to medical management, please add: "This is discussed in detail in section 2.10.10." Please update sections 9.3.6 – 9.3.9 to reflect the new compensation figures agreed to and the 8 hour timeframe (as opposed to 9 hours), in follow-up to EPA's comments.

18) EPA recommends the following changes to the telephone scripts for initial and follow-up contact with potential subjects who respond to recruitment advertisements; the original scripts are included on pages 319-325 of the draft protocol.

Initial contact script

Please add:

- the length of the test day will depend on the length of time that the repellent effectively repels ticks;
- training session will be about 2 hours;
- for privacy reasons, names of subjects will not appear anywhere on the data sheets or in the study reports;
- subjects will be paid according to the updated compensation figures; please use the updated figures in the script; and
- subjects are free to quit or withdraw from the study at any point of time and they will be paid for hours worked.

Follow-up contact script

Please add:

- the length of the test day will depend on the length of time that the repellent effectively repels ticks;
- training session will take place prior to participating in each study and will be about 2 hours;
- subjects will be asked for identification/proof of age during the training session;
- for privacy reasons, names of subjects will not appear anywhere on the data sheets or in the study reports;
- subjects will be paid according to the updated compensation figures; please use the updated figures in the script;
- subjects are free to quit or withdraw from the study at any point of time and they will be paid for hours worked;
- subjects will be provided breakfast, lunch and dinner if they are still participating in the study during these meal times;
- breaks will be provided at specified times;
- an expanded question that asks about allergies to tick bites, in addition to sensitivity;
- pregnancy test will be performed in private; and
- encouragement to read the consent form in advance of the training.

Johnson and i2LResearch submitted revised scripts, in Attachment 4, in response to EPA's comments.

19) Please update Appendix A, checklist of elements, with regard to page numbers and other pertinent information, after the protocol is revised in response to EPA and HSRB comments. Throughout the protocol, after it is revised in response to comments, whenever the protocol refers to other pertinent information as being "above" or "below," please replace such references with a specific section number.

Attachment 2 includes responses and revised language proposed by Johnson and i2LResearch in reaction to EPA's comments.

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

> *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. on human subjects in a laboratory setting against three species of ticks (Pathogen free Amblyomma americanum, Dermacentor variabilis, and *Ixodes scapularis). Testing will take place in a series of up to 18 individual studies (one study per test substance), possibly over several weeks, months, over a year, with each study individually conducted according to this protocol. This data will be used to allow these products to use EPA's new Repellency Awareness Graphic for the labels." (p. 12 of 353, §1.1).*

The Repellency Awareness Graphic system assigns duration of protection (in hours) on the EPA label, coupled with a graphic symbol for the target pest(s), which in this case is for ticks. The First Confirmed Crossing (FCC), defined as a tick crossing into the treated area followed by another crossing (confirming the first) within two 15 minute test periods (or within 30 minutes), will determine repellent failure for each tick species (p. 37 of 353, *§* 7.6.14). A CPT will be calculated for each tick species. The CPT for "ticks" to be used on the insect repellency graphic will be from the tick species with the lowest CPT value (p. 40 of 353, *§10.2.5).* 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 study.

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). *"I2LResearch USA, Inc.'s independent Quality Assurance Unit (QAU) in the person of Jennifer Hostetler will perform all QA duties." (p. 12 of 353 §1.2.1)*

Johnson and i2LResearch agreed to incorporate all of EPA's comments on their draft protocol dated July 28, 2015; their responses to comments and proposed revisions are in

Attachment 2. This section of EPA's review takes into account their revised procedures and design.

1. **Study procedures and design:**

Study site location and testing facility: i2LResearch USA, Inc., Baltimore, Maryland, USA.

Study Director: Timothy Foard

Study Sponsor: S.C. Johnson & Son, Inc., Racine, Wisconsin, USA

Subject selection: §2.1.-§2.7 on pages 14-23 of 353 describe the process of subject recruitment, qualification, compensation, training, and selection**.** §2.1.3-4, §2.2, §2.3.3--10, §2.6, and §2.7 on pages 14-18 and 21-23 of 353, respectively, are most relevant to the science review because they discuss the number of test subjects and alternates, test subject withdrawal from the study and study conduct thereafter, subject inclusion/exclusion criteria, and restrictions. Twelve subjects (ten test subjects and two alternates) will be selected from a pool of subjects to be recruited in the Baltimore Metro area. As described in revisions to §2.3.4 and §2.3.6, it's intended that the pool of subjects to be recruited will generally represent the demographics of U.S. repellent users. The approach to be used to determine the subject pool from which test subjects and alternates will be selected is explained in §2.3.6, revised to address EPA's comments, and includes target % demographic levels of U.S. insect repellent users categorized by sex, age, race, ethnic background, and ability to speak a second language. An individual must be an insect repellent user to be included in the study (§2.6.8). From a science perspective this approach is acceptable because of the absence of data showing that any of these factors make an individual more or less attractive to ticks.

Johnson and i2LResearch propose to revise section 2.3.8 to include the following;

"For each testing period, twelve test subjects (six female and six male) will be selected from the pool of subjects that fulfill the inclusion/exclusion criteria and have signed the ICD for the study, by a subject allocation table via appropriate software (such as Excel or Minitab). This selection will be achieved by randomly selecting the test subjects' assigned code number. The first five females and five males will be assigned as the test subjects. The sixth female and the sixth male will be assigned to act as alternates.

Using a number generating statistical software (such as Excel or Minitab), a second random selection will be made from the ten test subjects to determine the testing day on which each subject will participate. The first five selected will participate in the first test day, and the remaining five subjects will participate in the second test day. Alternates will be asked to be available for both days.

For logistical ease for each test day, SC Johnson and i2L prefer to keep the decision as to which limb (left or right) will be treated based on a coin toss (§4.1)."

Five subjects will participate on Day 1 while the other five will participate on Day 2. Alternates are to be available on both days of testing (§2.3.8 and §2.3.9). If a subject withdraws from a study once it has started, the study will continue with the remaining subjects. The study director may also exclude a subject from a study in the rare event that they are not attractive to ticks, that is, none of the ticks placed on the skin of an untreated subject's arm crawl a minimum qualifying distance up the subject's arm (§2.6.13). Any subjects wishing to participate in more than one day of testing will not be allowed to participate on two consecutive days. Based on comments from EPA, a minimum of 48 hours (two calendar days) is needed between test days to avoid the possibility of any repellent carrying over from an earlier test day to the following one (Revised §2.7.3).

Treatments and replication: Ten subjects will be treated with the test substance for each tick species repellency evaluation. Each subject will serve as their own treatment and untreated control (using opposite arms) to allow for comparison of tick behavior in the presence and absence of the test substance. The decision as to which arm to treat will be based on a coin toss on the day of the treatment. A positive control substance will not be used (§4.0, pp. 30-31 of 353).

Justification for sample size is discussed in §10.2 on pp. 41-43 of 353 of the protocol, specifically in §10.2.2 and §10.2.3 where literature is referenced to support the need for more than five subjects per test but retaining ten subjects. These sections will be revised to include Johnson's and i2L's response to EPA comments as follows (see Attachment 2 of this review):

"*The number of test subjects for a tick repellency efficacy study should strike a balance among three critical and competing criteria:*

a) Minimization of potential hazard to test subjects, where fewer subjects is better.

b) Statistical robustness, where more subjects results in greater precision of numeric estimates.

c) Consistency with previous repellent efficacy studies. Current and recent practice is to utilize <u>ten</u> subjects for each test site/test product.

The standard data analysis method for tick repellency efficacy studies involves the Kaplan-Meier estimator, and the measure of interest is the Kaplan-Meier median. The confidence limits associated with the Kaplan-Meier median are positional values in the distribution, rather than calculated values as in the case of a confidence interval around the mean. The table below indicates which positions in the distribution of values constitute the lower confidence limit (LCL) and upper confidence limit (UCL) of the median for various sample sizes. The assumption is that the values are sorted in increasing order, so value "1" in the distribution refers to the smallest value (i.e., the minimum).

Kaplan Meier median confidence limits were calculated using SAS, which employs a generalization of the Brookmeyer and Crowley (1982) sign test under a log-log transformation.

► **Table 1: Kaplan-Meier Median Confidence Limits for a Range of Sample Sizes.**

Sample size	Distributional position for 95% LCL	Distributional position for 95% UCL	Percent of values above LCL
10	**1**	**8**	**90%**
12	2	10	83%
15	3	11	80%
20	5	15	75%

As evidenced by the table, sample sizes larger than ten would provide only marginal increases in precision relative to the increase in the number of exposed test subjects. Given that a sample size of ten meets criteria a) and c), and a sample size greater than ten has limited impact in criterion b), I recommend the continued use of ten as the sample size for tick repellency efficacy studies."

Doubling the number of subjects would also increase the cost of the study significantly. The test as designed uses the lowest CPT from the three tick species tested to avoid an overestimate of CPT for the Insect Repellency Graphic.

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 353 of the protocol. The footnotes are listed once but apply to all three tables.

Table 1. Study Design –DEET Products

Repellent Product		Number of Tick Species[1]	Number of Human Subjects per Tick Species (Replicates)	Total Replicates per Product[2]	Maximum Number of Tick Exposures per Species /Product Test (18 hours)[3]
EPA Reg. No.	Product Type				
4822-415	5% DEET Spritz	3	10	30	72/206
4822-552	5.6% DEET Towelette	3	10	30	72/206
4822-395	7% DEET Spritz	3	10	30	72/206
4822-380	15% DEET Aerosol	3	10	30	72/206
4822-543	15% DEET Aerosol	3	10	30	72/206
4822-167	25% DEET Aerosol	3	10	30	72/206
4822-258	25% DEET Towelette	3	10	30	72/206
4822-399	25% DEET Spritz	3	10	30	72/206
4822-572	25% DEET Aerosol	3	10	30	72/206
4822-397	30% DEET Aerosol	3	10	30	72/206
4822-276	98.25% DEET Spritz	3	10	30	72/206

[1] Adult American dog tick, adult Lone Star tick, and adult or nymphal blacklegged (deer) tick.

[2] Ten replicates per tick species for a total of 30 replicates. A CPT will be calculated for each species based on ten treatment replicates. The lowest CPT will be used for the Insect Repellency Graphic.

[3] Based on four tick exposures to the treatment per hour (One every 15 minutes.). This value doubles to 412 when untreated control exposures are included.

Table 3. Study Design – Picaridin Products

Repellent Product		Number of Tick Species[1]	Number of Human Subjects per Tick Species (Replicates)	Total Replicates per Product[2]	Maximum Number of Tick Exposures per Species /Product Test (18 hours)[3]
EPA Reg. No.	Product Type				
4822-536	5% Picaridin Spritz	3	10	30	72/206
4822-535	5% Picaridin Lotion	3	10	30	72/206
4822-556	20% Picaridin Spritz	3	10	30	72/206
4822-564	20% Picaridin Aerosol	3	10	30	72/206

Table 4. Study Design –p-Methane-3, 8-Diol (PMD) Products

Repellent Product		Number of Tick Species[1]	Number of Human Subjects per Tick Species (Replicates)	Total Replicates per Product[2]	Maximum Number of Tick Exposures Per Species/Product Test (18 hours)[3]
EPA Reg. No.	Product Type				
4822-526	8% PMD Towelette	3	10	30	72/206
4822-515	10% PMD Lotion	3	10	30	72/206
4822-528	10% PMD Spritz	3	10	30	72/206

Product application: Each subject will have one forearm treated with the repellent product to be tested. The choice of forearm treatment will be made by the study director or designated staff on the day of the test based on a coin toss. As a result, the surface area of both forearms will be measured for every subject. Surface area calculation is described in §5.2 on page 31 of 353 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 from 6 cm above the wrist bone to 12 cm above that point towards the elbow (18 cm above the wrist bone) and 'D' equals the distance between the wrist and the elbow measurements. An example is provided in Appendix I of the protocol.

A set (fixed) application rate of 1 gram of product per 600 cm^2 (1.67 mg/cm^2) is proposed for aerosol and lotion products while 0.5g of product per 600 cm^2 (0.835 mg/cm^2) will be applied for spritz/pump spray products. Test substances will be applied by i2L Research staff. A dosimetry phase to determine a 'typical consumer application rate' by dose titration, which would be based on the grand mean of triplicate applications made/cm^2 by the test subjects will not be performed. Five reasons for using a set (fixed) application rate rather than a titrated application rate are stated (p. 32 of 353, §6.1.2 – §6.1.2.5):

"(1) Influence of outliers: A single outlier data point can unduly influence the mean of 10 application rates applied by subjects. A set application rate avoids this risk;

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

(3) Product (test substance) effect: Varying application rates between studies make it impossible to determine if performance difference is driven by the application rate or the test products;

(4) Time and cost: Subject-derived application rates introduce additional time and cost to a study compared to a set rate; and

(5) Relation to actual consumer use: A set application rate can be related to known consumer behavior. Subject-derived application rates allow the possibility of an atypical result. The application rates proposed in this protocol are based on dosimetry data from previously EPA/HSRB reviewed repellent studies."

To apply the target application rate of 1.67 mg/cm^2 for lotions and aerosols the following formula will be used:

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

To apply the target application rate of 0.835 mg/cm^2 for spritz/pump sprays the following formula will be used:

[Area of the Limb/600 cm^2] * 0.5 gram = weight (amount) of product to apply

The application of repellent product to the skin of each subject will depend on the product type (§6.7 on pages 33-34 of 353):

- For pump sprays the test substance container is placed on a balance, weighed, 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. A gloved i2L

Research staff member will spread the substance evenly throughout the treatment area.

- 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. The acceptable range will be within 10% of the target weight.
- 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.
- For towelettes a 250 ml beaker is placed on a top loader balance. The balance is tared. A single towelette is placed in the beaker and the balance is re-tared to determine the weight. The towelette is removed from the beaker and squeezed gently over the treatment area. The procedure is repeated until the target quantity of product has been delivered.

Product treatments will be made by the i2LResearch's staff. The target dose weight and actual weight applied will be recorded on a data sheet (p. 47 of 353, Appendix II). Margin of Exposure (MOE) estimates are based on an assumed 80 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/application rates presented by S.C. Johnson in Appendix VIII (pp. 63-68 of 353), the MOE values for the products and their associated 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.

Test area demarcation and product treatment: ***"****Four lines will be drawn on both of the subjects forearm as follows* (§7.5 on pp. 35-36 of 353)*:*

- *'Release line' 3 cm above the wrist bone towards the elbow;*
- *'Boundary line' 3 cm above the release line towards the elbow (this will be the edge of the treated area);*
- *'Crossing line' 3 cm above the boundary line;*
- *An upper boundary line 12 cm above the boundary line; this will not be used during testing and serves only to denote the boundary of the treated area.*

The treatment will be applied as previously described."

Subject training: Subject training is adequately explained in Johnson's and i2LResearch's revised training description in Attachment 2, in the response to EPA's comment # 1.

Conducting the test and repellency observations (§7.3 and §7.6 on pages 35-38 of 353).

In response to EPA comments, as proposed, the sections on experimental design and repellency observations will be revised to include the following information:

- Each species evaluation will be conducted separately on different days.
- Ticks will be tested one at a time on each test subject, at 15 minute intervals. The test day could last up to 19 hours: 1 hour for preparation time, and up to 18 hours for exposure period, depending on the repellent tested.
- Test subjects will wash their forearms with soap and water and dry them thoroughly with a paper towel.
- Test substances will be applied to the test subject's forearm as described in §7.5 "**Test area demarcation and treatment".**
- *Section 7.6 includes revised language reflecting the following steps:*
- Thirty minutes after the treatment is applied, the first tick exposure will begin.
- For each exposure, the subject will sit in a chair and hold their control (untreated) forearm at an approximately 45 degree angle from the horizontal, fingers pointing down. The subject will hold their forearm so that the inner surface faces away from the body and upwards. Support material will be provided to help bolster the subject's arm and for comfort while it's being held at a 45 degree angle from the horizontal.
- Three timers will be pre-set to help aid in the timing of each exposure interval. One timer will be set to monitor the 15 minute exposure interval, and two timers will be set for three minutes each for the ticks' response on the control and treated arms, respectively.
- The 15 minute timer will be activated. An i2L Research staff member will gently pick up a single tick from the holding vial, using fine forceps or a cotton-tipped applicator stick or equivalent, and place it on the release line on the inner surface of the subject's control forearm, and activate the first three minute timer.
- The tick will be oriented gently towards the elbow using forceps or a cotton-tipped applicator stick or equivalent. A normally active tick will begin to crawl up the forearm towards the elbow. The tick will be allowed three minutes to move across the boundary line.
- If the tick crosses the boundary line within three minutes, it will be considered to be actively questing, and will be immediately removed from the control arm. The tick will be accepted as attracted to the subject's skin and behaving normally and thus acceptable for use in the repellency test. If the tick is not attracted, it will be removed and discarded by immersing it in isopropyl alcohol, and the process will be repeated until a control tick is verified. The 3 minute timer will be stopped and reset accordingly.
- Once an acceptable tick is selected, the subject may relax their control arm. They will then lower their treated forearm to 45 degrees from the horizontal. The confirmed tick will be placed at the release line on the treated arm, and the second 3 minute timer will be activated, and oriented using the same method as for untreated arm.
- The tick will be allowed three minutes to move across the boundary line and 3 cm into the treated area (to the crossing line).
- If the tick does not cross the boundary line to the treated area within three minutes, it will be recorded as being repelled.
- If the tick crosses the boundary line into the treated area, but then does not reach the crossing line within three minutes of being released, it will be also reported as being repelled.
- If the tick crawls to the crossing line within three minutes of being released, it will be reported as not repelled.

- The tick will subsequently be killed by immersion in isopropyl alcohol. No ticks will be re-used.
- The above procedures will be repeated for each exposure period, every 15 minutes. The start time for each will be recorded as the time that the first tick is placed on the subject's untreated forearm.
- The exposure of a single tick every 15 minutes will continue for 18 hours or until the test substance 'breaks down' (i.e. fails to repel, see below). Each exposure may last anywhere from 6 to 15 minutes, depending on control tick behavior.
- Test substance breakdown occurs when one tick is recorded as not being repelled (i.e. crossing or repellent failure) and one of the two following events occur: (i) the first subsequent tick to be exposed is also recorded as not being repelled or (ii) the first subsequent tick is repelled, but the second subsequent tick is recorded as not being repelled. Either (i) or (ii) will be counted as confirming crossings within 30 minutes of the first crossing. The time of breakdown will be recorded as the time of the first confirmed crossing.
- Subjects will be instructed to wash their arms with mild soap and water once the product on their arm has broken down, or at the conclusion of the test day.
- The ticks will not be allowed to bite the subjects for health and safety reasons. Any tick that ceases movement for more than a few seconds will be gently prodded with forceps or a cotton-tipped applicator stick or equivalent. It should be noted that, unlike mosquitoes, most ticks will not bite immediately but will often crawl about on the host for hours before biting.
- Repeat the above procedure every 15 minutes for up to 18 hours or repellent failure.

2. Endpoints and Measures

"Test substance breakdown" occurs when one tick is recorded as not being repelled and one of the following events occur:

(i) The first subsequent tick to be exposed is also recorded as not being repelled or
(ii) The first subsequent tick is repelled, but the second subsequent tick is recorded as not being repelled.

Either one of the above events will be counted as confirming crossings within 30 minutes of the first crossing. The time of breakdown will be recorded as the time of the First Confirmed Crossing (FCC), which defines repellent failure for that replicate. The time of the first crossing is recorded as the CPT for that replicate.

Calculation of Complete Protection Time (CPTs) and Duration of Protection

CPTs will be calculated as the time from test substance application to the time of breakdown (i.e., First Confirmed Crossing). The breakdown times of each test subject will be calculated as the number of hours from treatment time to first confirmed crossing. The time in hours for each individual test subject will be used to calculate the median protection time for each species separately. The breakdown times will be used to

calculate the median CPT (within a 95% confidence interval) for each substance for each species (§10.3.1 and §10.3.2 on pages 43-44 of 353).

The duration of protection for each test substance will be defined as the lowest median CPT from the three tick species tested. This value will be rounded down to the closet full hour and used for the Repellency Awareness Graphic (§10.3.3 on page 44 of 353).

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3. Data Analysis:

The objective of the data analysis is to estimate the Median Complete Protection Time. 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 has an advantage as a non-parametric method for survival analysis; this method does not require or assume the data to follow a particular parametric distribution. This method can also account for censored observation. 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 nonparametric data sets (§10.3.6 on page 44 of 353).

The statistical software may consist of widely used software packages or on-line resources for the Kaplan-Meier Estimator.

Alternate subjects: §*10.2.9 states: "There will be two alternate subjects, one of each gender, in case any of the test subjects withdraw from the study before treatment applications are completed. Once treatments have been applied, subjects cannot be replaced. Therefore, if a subject withdraws after a test has begun, testing will continue with only the remaining subjects."*

E. Compliance with Applicable Scientific Standards

This protocol adequately addresses the following elements according to applicable scientific standards assuming that EPA's comments, outlined below, are addressed:

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

EPA Science Comments

The five elements listed below require revision/amendment before the research goes forward. Johnson and i2LResearch agreed to address all of EPA's comments. Attachment 2 includes their proposed revisions in response to the following comments:

1) Pre-training of subjects is barely described. More information is required. The protocol should be explicit with regard to the training outline and specific topics to be addressed.

2) Please provide more details on the exact timing of the testing. The protocol needs to explicitly describe the amount of time the technician has to do testing and the amount of time in a 15 minute period that requires the subject to be seated and exposed to ticks.

3) Repellent sample size selection: The protocol cites one example of the effect of sample size on confidence interval width when changed from 10 to 20 subjects. Submit a simulation showing the impact of increasing sample size on the width of 95% confidence interval of median CPT where median CPT will be estimated using Kaplan Meier method. This can be presented in table form.

4) A randomization mechanism needs to be inserted into sections 2.3.8 and 2.3.9.

5) Amend the protocol to require subjects to wait at least two calendar days (48 hours) between experiments if they participate in multiple experiments.

Attachments:

1. EPA Protocol Review
2. Revised Language from S.C. Johnson and i2LResearch in Response to EPA's Science and Ethics Comments
3. Proposed Revised Consent Form Addressing EPA's Comments
4. Revised Scripts for Initial and Follow-up Telephone Contact with Potential Subjects who Respond during Recruitment
5. §26.1111 Criteria for IRB approval of research
6. §26.1116 General requirements for informed consent
7. §26.1117 Documentation of informed consent
8. §26.1125 Criteria for Completeness of Proposals for Human Research
9. Additional information submitted by SAIRB directly to EPA
10. SAIB Board Roster
11. Proposed Recruitment Materials submitted by Recruitment Firm

Attachment 1

EPA Protocol Review

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

Date on Draft Protocol: July 28, 2015

Principal Investigator and any sub-investigators: Timothy Foard

Participating Laboratory:
I2LResearch USA, Inc.
1330 Dillon Heights Avenue
Baltimore, MD 21228

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

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

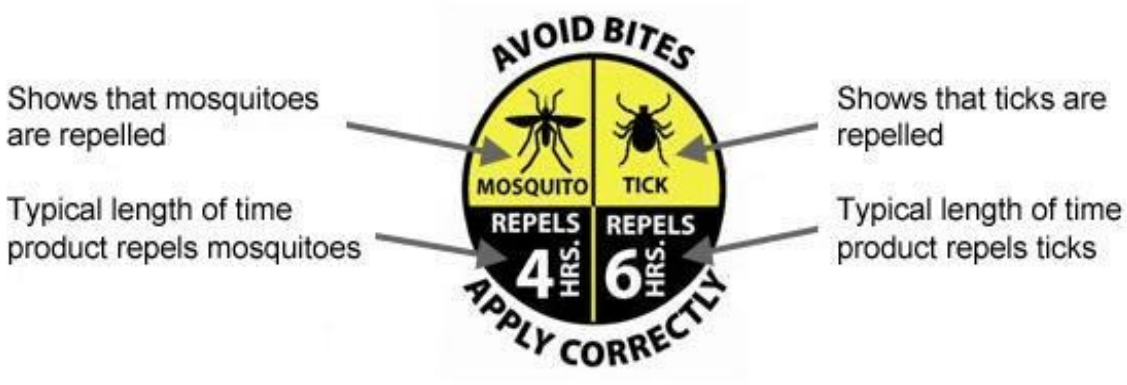
1. Societal Value of Proposed Research

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

"*This data will be used to support these products' use EPA's new Repellency Awareness Graphic for labels. This system assigns duration of protection (in hours) by the repellent on the EPA label, coupled with a graphic symbol for the target pest(s), in this case Ticks*" (pp. 13, §1.4.2).

This study is designed to determine the complete protection time (CPT) against adults of three species of ticks (pathogen free *Amblyomma americanum*, *Dermacentor variabilis*, and *Ixodes scapularis*) on human subjects in a laboratory setting for up to eighteen EPA registered repellent products from S.C. Johnson & Son, Inc. Direct testing of the duration of efficacy is important because consumers, who rely on repellents to avoid tick 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 ticks on their product labels. This graphic is intended

to help consumers easily identify the repellency time (based on the tick species with the lowest CPT) for ticks (and mosquitoes 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 Complete Protection Times of eighteen S.C. Johnson & Son, Inc. personal tick repellent products. This information does not currently exist.

(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 tests of these products against ticks 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 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?

"To establish the duration of protection of up to eighteen EPA-registered repellent products ('test substances') from S.C. Johnson & Son, Inc. ('Johnson') on human subjects, in a laboratory setting, against three species of tick (Amblyomma americanum, Dermacentor variabilis, and Ixodes scapularis). Testing will take place in a series of up to 18 individual studies (one study per test substance), possibly over several weeks, months, or a year with each study conducted individually according to this protocol" to be revised based on comments from EPA and the HSRB. (pp. 12, §1.1). *"The rationale is to provide data on the duration of protection from ticks crossing onto human skin that has been treated with one of Johnson's eighteen EPA-registered test substances (personal tick repellent products.)"* (p.13, §1.4.2).

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

The objective may be achieved by the study as proposed if the protocol is revised and amended to explain, in more detail, the items noted in the EPA science comments 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. 41-43 of 353 (§10.2). The researcher's justification for sample size is based on EPA accepted repellent protocols recommended by the HSRB including: Carroll-Loye Biological Research SPC-002, HSRB review of February 2009; and LNX-003, HSRB review September 2010.

In addition, the registrant provided the following rationale regarding sample size: "*The number of test subjects for a tick repellency efficacy study should strike a balance among three critical and competing criteria:*

a) Minimization of potential hazard to test subjects, where fewer subjects is better.

b) Statistical robustness, where more subjects results in greater precision of numeric estimates.

c) Consistency with previous repellent efficacy studies. Current and recent practice is to utilize <u>ten</u> subjects for each test site/test product.

The confidence limits associated with the Kaplan-Meier median are positional values in the distribution, rather than calculated values as in the case of a confidence interval

around the mean. The table below indicates which positions in the distribution of values constitute the lower confidence limit (LCL) and upper confidence limit (UCL) of the median for various sample sizes. The assumption is that the values are sorted in increasing order, so value "1" in the distribution refers to the smallest value (i.e., the minimum).

► **Table 1: Kaplan-Meier Median Confidence Limits for a Range of Sample Sizes.**

Sample size	Distributional position for 95% LCL	Distributional position for 95% UCL	Percent of values above LCL
10	**1**	**8**	**90%**
12	2	10	83%
15	3	11	80%
20	5	15	75%

As evidenced by the table, sample sizes larger than ten would provide only marginal increases in precision relative to the increase in the number of exposed test subjects. Given that a sample size of ten meets criteria a) and c), and a sample size greater than ten has limited impact in criterion b), I recommend the continued use of ten as the sample size for tick repellency efficacy studies."

(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. One arm from each subject will remain untreated and serve as the untreated control, and the other arm will be treated with the test product and serve as the treatment group. A positive control will not be used (pp. 30-31 § 4.0).

(c) How is the study blinded?

Based on revised material submitted in response to EPA comments, the study is not blinded.

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

The test subjects (5 male and 5 female) will be randomly selected from a pool of potential subjects (pp. 17-18 of 353, §2.3) to be developed, based on revised information submitted to EPA in response to comments. One arm from each subject will remain untreated and serve as the untreated control, and the other arm will be treated with the test product and serve as the treatment group. The arm serving as part of the treatment group will be selected randomly by flipping a coin on the day of treatment. Based on revised information submitted to EPA in response to comments, if a subject is used on more than one test day, there will be two days between them, and the test arm for the second day

will be opposite of the one used in the earlier test day to minimize any risk of repellent carryover (pp. 30-31 § 4.0).

(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 Complete Protection Time. Complete Protection Time (CPT) will be calculated as time from application of each test substance to a subject and the first confirmed tick crossing 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 has an advantage as a non-parametric method for survival analysis; this method does not require or assume the data to follow a particular parametric distribution. This method can also account for censored observation. 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 median CPT from the tick species with the shortest median CPT. This value will be rounded down to the closest full hour (pp. 43-44 of 353, §10.3).

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

The analysis will provide the lowest 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 precision and cost.

The number of test subjects for a tick repellency efficacy study should strike a balance among three critical and competing criteria:

a) Minimization of potential hazard to test subjects, where fewer subjects is better.

b) Statistical robustness, where more subjects results in greater precision of numeric estimates.

c) Consistency with previous repellent efficacy studies. Current and recent practice is to utilize <u>ten</u> subjects for each test site/test product.

The confidence limits associated with the Kaplan-Meier median are positional values in the distribution, rather than calculated values as in the case of a confidence interval

around the mean. The table below indicates which positions in the distribution of values constitute the lower confidence limit (LCL) and upper confidence limit (UCL) of the median for various sample sizes. The assumption is that the values are sorted in increasing order, so value "1" in the distribution refers to the smallest value (i.e., the minimum).

► **Table 1: Kaplan-Meier Median Confidence Limits for a Range of Sample Sizes.**

Sample size	Distributional position for 95% LCL	Distributional position for 95% UCL	Percent of values above LCL
10	**1**	**8**	**90%**
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15	3	11	80%
20	5	15	75%

As evidenced by the table, sample sizes larger than ten would provide only marginal increases in precision relative to the increase in the number of exposed test subjects. Given that a sample size of ten meets criteria a) and c), and a sample size greater than ten has limited impact in criterion b), I recommend the continued use of ten as the sample size for tick repellency efficacy studies.

2.2 How and to what will human subjects be exposed?

Subjects will be exposed to 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 the requirements are fulfilled for EPA registration of repellent products for contact skin use (pp. 27-29 of 353, §3.3). Additional information on each product is provided in Appendix VI and VII of the protocol on pages 56-62 of 353 and in Tables 1, 2, and 3 in this review.

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

Johnson must submit efficacy data to EPA to satisfy product performance requirements and support label claims for these products. 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 must 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?

Johnson is proposing a set dosage rate of 1 gram of product per 600 cm^2 (1.67 mg/cm^2) for aerosol and lotion products, and 0.5 g of product per 600 cm^2 (0.835 mg/cm^2) for spritz/pump spray products. 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. 32-33 of 353, §6.1.2):

(1) "Influence of outliers: A single outlier data point can unduly influence the mean of 10 application rates applied by subjects. A set application rate avoids this risk;

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

(3) Product (test substance) effect: Varying application rates between studies make it impossible to determine if performance difference is driven by the application rate or the test products;

(4) Time and cost: Subject-derived application rates introduce additional time and cost to a study compared to a set dose; and

(5) Relation to actual consumer use: A set application rate can be related to known consumer behavior. Subject-derived application rates allow the possibility of an atypical result. The application rates proposed in this protocol are based on dosimetry data from previously EPA/HSRB reviewed repellent studies."

Johnson proposed: "To apply the target dose of 1.67 mg/cm^2 for lotions and aerosols the following formula will be used:

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

Johnson proposed: "To apply the target dose of 0.835 mg/cm^2 for spritz/pump sprays the following formula will be used:

[Area of the Limb/600 cm^2] * 0.5 gm = weight (amount) of product to apply"

The application of repellent product to the skin of each subject will depend on the product type (pp. 33-34, § 6.7.1 – 6.7.4)

- 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 applied is below the required weight, the limb will be sprayed with more test substance targeting the required weight as closely as possible. The acceptable range will be within 10% of the target weight.

- 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 while carefully observing the balance read out.

- For towelettes, a 250 ml beaker is placed on a top loader balance. The balance is tared. A single towelette is placed in the beaker and the balance is re-tared to determine the weight. The towelette is removed from the beaker and squeezed gently over the treatment area. The procedure is repeated until the target quantity of product has been delivered.

- Treatments will be made by study staff. §6.4-6.6 on pages 33 of 353 describe preparations before treatments are made. The target dose weight and actual weight applied will be recorded on a data sheet (p. 47 of 353, Appendix II).

(c) What duration of exposure is proposed?

The exposure is a 3-minute period starting 30 minutes after application where the tick is placed on the untreated arm to determine if it is attracted to the subject's skin. After a tick is deemed to be attracted to the subject, the tick is then placed on the treated arm for 3 minutes. This exposure process is repeated every 15 minutes thereafter for 18 hours or until the test substance fails to repel the tick. (pp. 36-37**,** § 7.6.4 – 7.6.13)

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:
"Complete Protection Times (CPT) will be calculated as time from test substance application to the time of breakdown (i.e., the first confirmed crossing).

To assess crossing, four lines will be drawn on the treated and untreated forearms as follows:
i. "A 'release' line 3 cm above the wrist bone.
ii. A 'boundary' line 3 cm above the release line and is at the edge of the treated area.
iii. A 'crossing' line 3 cm above the boundary line, and
iv. An upper boundary line 12 cm above the boundary line which will denote the upper boundary of the treated area."

"A 'crossing' occurs when a tick crosses the 'crossing' line on the treated skin of a subject. Test substance breakdown occurs when one tick is recorded as being repelled (i.e., crossing or repellent failure) and one of the following events occur: (i) the first subsequent tick to be exposed is also recorded as not being repelled or (ii) the first subsequent tick is repelled, but the second subsequent tick is recorded as not being repelled. Either (i) or (ii) will be counted as confirming crossings within 30 minutes of the first crossing. The time of breakdown will be recorded as the time of the first confirmed crossing."

Using the Kaplan-Meier estimator, the Median CPT will be calculated for all test subjects exposed to each tick species. The lowest median CPT of the three tick species will be used on the label.

Subjects with repellent failures will be removed from the test. The test will be terminated no later than 18 hours after the first tick exposure.

The endpoints are appropriate to the questions being asked and address uncertainty associated with the sample size, values, and the lowest Median Complete Protection Time value.

The data form for each tick exposure is presented in Appendix III on page 48 of 353.

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

- Good Laboratory Practices, as defined by 40 CFR part 160 will be followed throughout all studies.
- Study staff will conduct a training session with the subjects on a day prior to the test date.
- Study staff will treat the skin of the exposed limb with the test substance and the limb will be measured in advance.
- Study staff will place ticks on the untreated and treated arms.
- Study staff will monitor and record tick movement and the start and stop times for each exposure period.
- Study staff and the study director will track test substance samples, closely monitor the testing, and data recording.
- Alternate subjects will be enrolled to ensure adequate sample size.
- A Quality Assurance Unit will be in place to monitor all study activities and data collection.
- Test subjects can only take part once in any two-day testing period. If scheduled to participate in two studies within one week, there will be two calendar days in between test days.

(c) What QA methods are proposed?

"A representative of i2LResearch USA, Inc.'s (i2L) independent quality assurance unit (QAU) in the person of Jennifer Hostetler will perform all QA duties. The QA representative will conduct critical phase inspections at intervals adequate to ensure study integrity, and maintain written and signed records of each inspection. Records shall identify the study and include the date of the inspection, positive and negative findings, actions recommended and taken to resolve negative findings, the scheduled date for re-inspection (if any), and the dates(s) the findings are reported. All inspection findings will be reported to management and the study director. Any problems, amendments or deviations discovered shall be brought to the attention of the sponsor, Study Director and management immediately. The QA will review the final reports for accuracy and compliance with GLPs and the protocol. A signed QA statement will be included in each final report that lists the phase inspections that were conducted, their dates, and the dates their findings were reported to management and the study director." (pp. 12 of 353, §1.2)

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

Complete Protection Time (CPT) will calculated as time from test substance application to the time of breakdown (i.e., the first confirmed crossing). 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 nonparametric data sets. The duration of protection for each test substance will the median CPT for the tick species with the lowest median CPT. This value will be rounded down to the closest full hour (pp. 43-44 of 353, §10.3).

3.1 Representativeness of Sample

(a) What is the population of concern?

The population of concern consists of people who would purchase and use tick repellents and who best represent U.S. repellent users. Information to characterize this population is available from Neilson information, including the 2015 Neilson survey, which shows that the majority of repellent users are caucasians between the ages of 35-55. Additionally, about 13% of repellent buyers are Hispanic. Based on revised information submitted to EPA, the recruitment pool to be developed, from which subjects will be recruited, is expected to be in line with the indices above and described in revised section 2.3.6. (pp. 16-17 of 353, §2.3.6).

(b) From what populations will subjects be recruited?

Subjects will be recruited by a recruiting firm. Using advertisements in digital, and social media mediums in both English and Spanish languages, the firm will recruit a pool of people from the Baltimore, MD area who are generally interested in participating in research studies. Test subjects will be recruited for each study following demographics included in section 2.3.6 in order to best represent U.S. repellent users. The firm will contact individuals, in the recruitment pool to be developed, by email or telephone to compile a list of potentially interested and eligible subjects.

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

The table in section (p. 17 of 353, §2.3.6) outlines the intended demographics of the initial group of potential volunteers who will be recruited by the recruiting firm. If the recruited pool follows the outlined demographics, the pool should be representative of the population of concern.

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

Yes. Each test substance tested will be evaluated with three species of ticks which are the most common species that occur throughout the United States.

3.2 Equitable Selection of Subjects

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

The inclusion/exclusion criteria, *with EPA's comments highlighted below*, are complete and appropriate. The sponsor agreed to address EPA's comments.

"2.6.1 The subject must be between 18-55 years old and provide proof of age with a driver's license, passport or other valid identification.

2.6.2 The subject must be able to read and speak English fluently.

2.6.3 The subject must not be an immediate employee of Johnson or of i2L, or be immediately related to employees or owners of either company.

2.6.4 The subjects must have a reliable form of transportation to get to and from the i2L laboratory.

2.6.5 Subjects must feel they are healthy enough to participate in the study and do not have any heath conditions that may affect the study or be worsened by the application of repellent products.

2.6.6 The subjects must be willing to be exposed to crawling ticks with the understanding all measures possible will be taken to prevent bites.

2.6.7 The subjects must have no known allergies or sensitivities to tick bites.

2.6.8 Subject must be a user of insect repellent products.

2.6.9 The subjects must not be hypersensitive to repellent or latex or ~~other~~ skin care products. The subject must be free from skin disease, skin problems such as eczema, psoriasis, or atopic dermatitis.

2.6.10 The subjects must be willing to wear short sleeves on their scheduled test day(s) (other clothing choices will be optional).

2.6.11 The subjects must agree to inform the Study Director or other staff if they have violated any study-related restrictions in the previous 12 hours (see 'Restrictions', below) as soon as possible, so a decision can be made whether to continue inclusion of the subject in that day's testing.

2.6.12 The subjects must be able to sit in a chair for long periods (with breaks for limb stretching and movement given at reasonable intervals).

2.6.13 Confirmation will be needed that the ticks in the study are attracted to the subjects' untreated skin (this confirmation will occur during the test, when each subject acts as their own negative control—see 'Methodology for Testing Tick Repellency' below). If a subject is found to be unattractive to ticks at the first exposure, they will be replaced with an alternate subject. In the unlikely event that a subject is determined not be attractive to the ticks, when the study is underway, they will not be allowed to continue to participate in the study. The study will continue with the remaining subjects.

2.6.14 The subjects must be willing to follow the study procedures as explained and be willing to sign an ICD.

2.6.15 The subjects must not be pregnant or be breast-feeding. To confirm that participating test subjects are not pregnant, within 48 hours prior to their scheduled test day, female subjects will be required to perform an over-the-counter pregnancy test that will be supplied by i2L. This can be done on the same day as the training session, on a separate visit to i2L at a later day or on the day of the test. If the test is done on separate day, the subject will be paid $25.00 for their time.

The test will be performed by each test subject alone, in a private bathroom, at the i2L facility. The results will be initially seen by the test subject only. After completion of the pregnancy test, a female i2L employee will ask, in a private setting, if the potential subject still wants to participate in the study. If they do, the negative test result will be verified by that i2L employee and relayed to the Study Director (if the Study Director is not the verifying employee). The results will be kept confidential, will not be recorded, and will not be

disclosed to anyone other than the test subject, the verifying employee, and/or the Study Director. Test subjects will not be required to disclose the results of the test, with the understanding that if they do not, they will not be allowed to participate in the test. Test results will be disposed by the test subject.

2.6.16 This procedure will be repeated for each test day that any female subject participates in, that will take place more than 48 hours after the most recent negative, pregnancy test."

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

The protocol excludes people who are employees of S.C. Johnson or i2LResearch or immediately related to employees or owners of either company.

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

No.

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

Recruitment

Based on updated information submitted to EPA, the recruitment process will use the approach described below:

Test subjects will be recruited for each study following the demographics table in section 2.3.6 to best represent US repellent users. Subjects will be recruited from the Baltimore, Maryland area, via advertising through digital and social media. Advertisements will be posted in digital and social media mediums, such as Facebook, Yahoo/Bing, Google and Craigslist. A Spanish language advertisement will also be posted on line using the same media, plus an online Spanish language newspaper that advertises within the recruitment area. The advertisements will contain a link to a study-specific secure website where interested respondents can learn more about the study as well as complete a pre-screening qualification form. The forms that are filled out on the website will be automatically uploaded into a secure and encrypted portal, to which i2L employees will have access. Every effort will be made to achieve the demographic composition, via a stratified random sample of the pool of recruited subjects. The qualifying subjects will be stratified into smaller subgroups according to their race/ethnicity, age, and gender to help ensure that the sample demographic composition of the test subjects will be approximately similar to that of the table below for each test day. The final report will specify the demographic composition goals, and the demographics of test subjects who participated in the study, due to availability of test subjects on each test day.

Individuals from the pool will be contacted by telephone or e-mail (in which case a follow up telephone call will be made) to determine whether they meet the basic inclusion criteria. They will be given a brief outline of the study. If they are interested in enrolling

in the study, they will be given a time, date and location to meet with i2L staff for a training session to learn more about the study and their potential role in it, go over the inclusion/exclusion criteria, and receive answers to any questions they may have. Contact information is included on the consent form for any individual who has additional questions or if further clarification is desired after they have attended the training session.

Informing Potential Subjects and Informed Consent

Several mechanisms will be used to inform potential subjects. The revised phone scripts included in Attachment 4 describe the information to be shared, in initial and follow-up phone conversations, with potential subjects who respond to recruitment advertisements. All interested and eligible participants must attend a 2 hour training session prior to participating in each study. The details of the training program are explained in Attachment 2 in response to EPA comment # 1 and will be inserted in section 2.2.5 of the protocol. One of several aspects of this training will include review of the Informed Consent Document (ICD). The trainer will also provide test subjects with the study director's contact information (name, email, and phone number) to answer any follow up questions. This information will be on the first page of the provided ICD. Prior to each study, all subjects must provide informed consent by signing the proposed revised Informed Consent Document included in Attachment 3.

(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 S.C. Johnson and i2LResearch and their families, are excluded from participation.

3.3 Remuneration of Subjects

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

In response to EPA comments, SC Johnson and i2LResearch propose the following compensation in revised Section 2.5:

2.5.1 Each subject will be paid $30 for taking part in each training session.
2.5.2 For each test day, test subjects will be paid $104.00 ($13 per hour) for any length of participation up to 8 hours (see 'Study termination, individual participation, and withdrawal' in Section 9 for exceptions). If a test day exceeds 8 hours, subjects will be paid $19.50 (time and a half) for each additional hour, rounded up to the nearest hour.
2.5.3 An alternate who is not needed to replace a test subject will be able to leave and will be paid $50. The decision as to whether an alternate is needed will occur within the first two hours of the test, before all the treatments have been finished. If an alternate is

asked to replace a subject, he or she will be paid at the same rate as other test subjects, as described above.

2.5.4 Subjects who have participated in the training session, but then choose to withdraw or are asked to withdraw from or during the training session, will still be paid $30.00 for attending all or part of this session.

2.5.5 Any female subject who has to visit i2L solely for the purpose of taking a pregnancy test (which will occur within 48 hours prior to the test day), will be paid $25.00.

2.5.6 Subjects may decline to participate at any time during the training session or test day without penalty.

2.5.7 If the Study Director or other i2L USA staff ask a subject to withdraw from the test and they have complied with all of their requests, or if a test subject needs to withdraw early because of a health or emergency reason, full payment will still be made even if the test subject has participated for less than eight hours. This will not affect payment for any previous test days that had been completed.

2.5.8 The Study Director or other designated i2L USA staff may end a particular subject's participation in a training session or on a test day, at any time, for any reason. If a test subject is asked to withdraw from the test because they have not followed all their directions or if they choose to withdraw from testing early on a test day for a non-health related or non-emergency reason, full payment will not be made if the test subject participates in less than eight hours. Instead, they will be paid for the number of hours worked (rounded to the nearest hour) at a rate of $13.00 per hour. This will not affect payment for any previous test days that had been completed."

(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 paid by checks sent in the mail, or hand delivered while they are on site at the i2L facility. I2L issues checks on the 15th and on the last day of the month."

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 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 (pp. 27-29 of 353, §3.1). Additional information on each product is provided in Appendix VI and VII of the protocol on pages 56-62 of 353 and in Tables 1, 2, and 3 in this review. Margin of Exposure (MOE) estimates are based on an assumed 80 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 (Appendix VIII pp. 63-68 of 353). 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:

1) Adverse reaction to the test substances
2) Exposure to ticks
3) Exposure to tick-vectored diseases
4) Unanticipated loss of confidential information.
5) Fatigue and/or physical discomfort from length of test day

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

The test materials are EPA-registered tick repellent products and they will be used consistent with the Directions for Use on the product labels. Therefore, EPA considers the exposure of the subjects to the tested levels of the test substance 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 by excluding candidates known to be sensitive to the test material; excluding candidates known to be sensitive or allergic to ticks bites; conducting the research with disease free ticks; technician removal of ticks before they bite; using subject identification codes to help ensure privacy; and incorporating procedures to keep the results of pregnancy testing private and permit discrete withdrawal. To try to address fatigue and physical discomfort, the study sponsor will provide breakfast, lunch and dinner to participating subjects as described in the revised protocol, breaks and opportunities to stretch during the test day, and support for the subject's arm as it's held at an angle during the exposure period. Also, there will be a two-day break between test days. Practical steps to minimize subject risks have been taken, and the remaining risks have a low probability of occurrence.

4.2 Risk minimization

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

1) Adverse reaction to the test substances
2) Exposure to ticks
3) Exposure to tick-vectored diseases
4) Unanticipated loss of confidential information.
5) Fatigue and/or physical discomfort from length of test day

Risk of adverse reaction to test substances

Participating subjects must be users of insect repellent products. The subjects must not be hypersensitive to repellent or latex or skin care products. The subject must be free from skin disease, skin problems such as eczema, psoriasis, or atopic dermatitis.

As discussed in section 2.8 of the protocol, i2L will have at least two First-Aid qualified staff members and supplies on site to monitor subjects for medical problems. In the case of medical emergency, i2L staff will call 911, ask for emergency assistance, and follow instructions given by the emergency dispatcher.

As discussed in the revised language for section 2.10.2.10, subjects will be told that if anyone experiences any skin reaction, experiences an injury, or simply feels unwell, he or she should inform i2L 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 laboratory test site and directions will be identified prior to the test date. At least one study staff member will remain with the other subjects if other staff members have to depart with an injured or ill subject. The study sponsor will reimburse test subjects for the costs of medical care. All adverse effects will be followed until resolution is reached.

Subjects may also ask for standard first aid items, such as bandages, antiseptics, and mild topical antihistamines as 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 first aid assistance at any time.

Risk of exposure to ticks

The participating subjects must have no known allergies or sensitivities to tick bites. Staff members will be trained to move or remove ticks from subjects before they have the opportunity to bite. Tick exposure will be limited to one tick at a time, and only on the area of the forearm.

Risk of exposure to tick-vectored diseases

To greatly reduce, if not eliminate, the risk of contracting any tick-borne diseases, the study will be conducted with laboratory-reared ticks, which are not known to harbor any

pathogens. This will be documented with confirmation from the supplier lab. Staff members will be trained to move or remove ticks from subjects before they have the opportunity to bite. Tick exposure will be limited to one tick at a time, and only on the area of the forearm.

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 bathroom at the i2L facility. 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 that female i2LResearch employee and relayed to the Study Director (if the Study Director is not the verifying employee.) The results will be kept confidential, will not be recorded, and will not be disclosed to anyone other than the test subject, the verifying employee, and/or the Study Director.

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 testing facility in locked cabinets and electronic files kept on a password-protected computer server. No one outside the recruitment firm, i2L, Johnson, the IRB, or certain governmental agencies (such as USEPA) will have access to subjects' personal information.

Fatigue and/or physical discomfort from length of test day

To try to address fatigue and physical discomfort, the study sponsor will provide breakfast, lunch and dinner to participating subjects assuming the test day extends to those meal times, as described in section 7.3.6 of the revised protocol. The study director will provide up to three 15 minute breaks to each test subject per test day and opportunities to stretch throughout the test day, as well as support for the subject's arm as it's held at an angle during the exposure period. Also, there will be a two-day break between test days.

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

As described in section 2.10.2.10, subjects will be told that if anyone experiences any skin reaction, experiences an injury, or simply feels unwell, he or she should inform i2L 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. Also, please see the revised language for sections 9.2.5 – 9.2.6:

"9.2.5 The nearest local hospital to i2L's laboratory will be located and directions identified prior to any study-related procedures taking place.

9.2.6 Should a Type 1 allergic reaction (i.e. anaphylaxis) occur on the test day or if any other serious injury or medical issue occurs, the i2L staff will call 911and follow the instructions given by the emergency dispatchers. If instructed to transport the subject to a hospital, one study staff member and one other i2L staff member (one to drive and one to observe and take care of subject) will perform this task. If there are not sufficient Study staff present to both carry on the study and transport the affected subject(s), the Study Director or Principle Investigator will abort the test day."

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

As discussed in section 2.8 of the protocol, i2L will have at least two First-Aid qualified staff members and supplies on site to monitor subjects for medical problems.

Based on the revised language for section 2.10.2.10, subjects will be told that if anyone experiences any skin reaction, experiences an injury, or simply feels unwell, he or she should inform i2L 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 laboratory test site and directions will be identified prior to the test date. At least one study staff member will remain with the other subjects if other staff members have to depart with an injured or ill subject. The study sponsor will reimburse test subjects for the costs of medical care. All adverse effects will be followed until resolution is reached.

Subjects may also ask for standard first aid items, such as bandages, antiseptics, and mild topical antihistamines as 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 first aid assistance at any time.

Also, as proposed, section 9.2, on **Medical monitoring and reporting unanticipated problems,** will be revised as follows (as per EPA's recommendations):

"9.2.1 The i2L staff will watch for unanticipated problems or adverse effects to the subjects. Subjects will be told that if anyone experiences any skin reaction, experiences an injury, or simply feels unwell, he or she should inform i2L 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.
9.2.2 Any problems or adverse effects will be promptly reported to Johnson, and the IRB.
9.2.3 Subjects will be informed in a timely manner both orally and in writing of any significant new findings discovered during the course of this study which may

influence their continued participation. The Study Director and recruitment firm will keep on file the phone numbers and addresses for each study participant as a means to contact them if needed.
9.2.4 New findings will also be reported, in writing, to Johnson and the IRB in a timely manner.
9.2.5 The nearest local hospital to i2L's laboratory will be located and directions identified prior to any study-related procedures taking place.
9.2.6 Should a Type 1 allergic reaction (i.e. anaphylaxis) occur on the test day or if any other serious injury or medical issue occurs, the i2L staff will call 911and follow the instructions given by the emergency dispatchers. If instructed to transport the subject to a hospital, one study staff member and one other i2L staff member (one to drive and one to observe and take care of subject) will perform this task. If there are not sufficient Study staff present to both carry on the study and transport the affected subject(s), the Study Director or Principle Investigator will abort the test day.
9.2.7 Subjects will be instructed that if they develop a rash or other irritation on their treated forearm within 48 hours of the end of the most recent test day, they should inform i2L staff and seek medical advice. All adverse effects will be reported to Johnson and the IRB within five business day of their being noted, or within the same day in the case of serious adverse effects.
9.2.8 If i2L or Johnson learns of new findings or new information relating to the safety or hazard of any of the test substances, i2L will contact the subjects and advise them accordingly both orally and in writing in a timely manner. The IRB will also be advised."

(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 these studies or suffer a research-related reaction, call the Study Director listed on the front page of this consent form at 410-747-4500, or Safety Call at (866) 344-3932 available 24-hours."* There is no time limit given.

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

The revised consent form, in Attachment 3, 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 that is not paid for by any insurance policy that covers you in case of illness. All adverse effects will be followed until resolution is reached. 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

Director, the study staff, or study site from liability for mistakes or intentional misconduct by signing this consent document."

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 these studies. The benefit to society is the knowledge gained regarding the efficacy of personal tick repellents."*

(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 knowledge gained regarding the efficacy of personal tick repellents."*

(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, revised to address EPA's comments, 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, the IRB provided records of their review to EPA.

(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, based on the revised language submitted in response to EPA's comments.

(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?

Initial information on the study will be shared, via telephone, with prospective subjects who respond during the recruitment process. Prior to participating in any aspect of the study, each potential subject who has expressed interest in participating in the study and has met the inclusion/exclusion criteria will be required to complete a 2 hour training program.

If a subject chooses to participate in multiple studies, as discussed in revised section 2.2.7, the subject will be required to attend a training session prior to their participation in each study.

During the training session, the following aspects of the study will be discussed and the following activities completed:

1. Upon arrival, subjects will be asked to provide proof of age with a driver's license, passport, or other valid identification.
2. Test subjects will be given the Informed Consent Document (ICD), time to read the ICD, and the opportunity to ask questions about it.
   The trainer will provide a brief outline of the study, the test subjects' potential role in the study, the potential length of the study on any given test day, and discuss the inclusion/exclusion criteria.
3. Any questions or concerns about the study will be discussed and answered.
4. The employee conducting the training session with test subjects will let all training attendees know that if a test subject needs to speak to the study director in private about any aspect of the study, time will be made for this discussion once the general training session is over.

5. To confirm understanding of the consent form, the following questions will be asked:
    a. Do you understand that you will be exposed to live ticks and that individual ticks will be placed on your arm, monitored, taken off, and discarded in order to collect study data?
    b. Do you understand that a repellent product will be applied to your arm and ~~left~~ remain on your arm for a potential exposure period of 18 hours maximum?
    c. Do you understand that one test day has the potential to last up to 19 hours, including up to 18 hours of testing and 1 hour of preparation?
    d. Do you understand that you have the freedom to quit or withdraw from the study at any time, and that you will be paid for the hours worked?
    e. Do you understand that your participation in this study is voluntary and that you may leave the study at any time?
6. All subjects who meet the requirements for participation and agree to participate in the study will sign the ICD and will receive a copy of the signed ICD. They will also receive a copy of the testing schedule.
7. The trainer will provide test subjects with the study director's contact information (name, email, and phone number) to field any follow up questions. This information will be on the first page of the provided ICD.
8. The subjects will then have their forearms measured for the future testing as per section 5 of the protocol, and will be shown how to position their arm for testing. The procedures of each 15 minute exposure interval will be briefly explained.
9. Female subjects will take the pregnancy test within 48 hours prior to the first testing day. If the time until this day is more than 48 hours, these subjects will be asked to come to i2L on a separate occasion to take this test.
10. If the subject is eligible to participate in a subsequent study and chooses to do so within 3 months of having completed full training, they will have the option of completing a shorter training session prior to the next study; the shorter training session would be the same as that described above but would exclude the measurement of the forearm, discussed in step # 8 above, given that their measurements would have already been taken and recorded during the first training session.

(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 or their family members. 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?

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 bathroom at the i2L facility. 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 that female i2LResearch employee and relayed to the Study Director (if the Study Director is not the verifying employee.) The results will be kept confidential, will not be recorded, and will not be disclosed to anyone other than the test subject, the verifying employee, and/or the Study Director.

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 testing facility in locked cabinets and electronic files kept on a password-protected computer server. No one outside the recruitment firm, i2L, Johnson, the IRB, or certain governmental agencies (such as USEPA) will have access to subjects' personal information.

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

The revised informed consent form states: *"Participation in any of these studies is voluntary. You may refuse to take part or quit at any time without penalty or loss of benefits to which you may be otherwise entitled."*

Subjects are informed about their right to withdraw during both the initial and follow-up telephone conversations which occur after potential subjects apply for participation in the study during the recruitment process. Subjects are again informed of their right to withdraw during the training program and when questions are asked during the training program to confirm their understanding of the consent form.

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

Please see the revised language proposed for the sections cited below.

2.5.4 Subjects who have participated in the training session, but then choose to withdraw or are asked to withdraw from or during the training session, will still be paid $30.00 for attending all or part of this session.

2.5.7 If the Study Director or other i2L USA staff ask a subject to withdraw from the test and they have complied with all of their requests, or if a test subject needs to withdraw early because of a health or emergency reason, full payment will still be made even if the test subject has participated for less than eight hours. This will not affect payment for any previous test days that had been completed.

2.5.8 The Study Director or other designated i2L USA staff may end a particular subject's participation in a training session or on a test day, at any time, for any reason. If a test subject is asked to withdraw from the test because they have not followed all their directions or if they choose to withdraw from testing early on a test day for a non-health related or non-emergency reason, full payment will not be made if the test subject participates in less than eight hours. Instead, they will be paid for the number of hours worked (rounded to the nearest hour) at a rate of $13.00 per hour. This will not affect payment for any previous test days that had been completed.

Attachments 2 - 4

Note: Attachments 2 through 4 contain sensitive information and, as a result, were not included in the public version of EPA's science and ethics review of the S.C. Johnson and i2LResearch tick protocol. Attachment 2 – 4 were provided to the HSRB.

Attachment 5

§ 26.1111 Criteria for IRB approval of research
Field Testing of SC Johnson Tick 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	

Attachment 6

§26.1116 General requirements for informed consent
Field Testing of SC Johnson Tick 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	No benefits to subject. Benefits to society.
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	N/A	Alternative is not to participate.
	(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	N/A	No additional cost to subject.
	(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	Y	
	(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	

Attachment 7

§26.1117 Documentation of informed consent
Field Testing of SC Johnson Tick 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. 310-318. Revised consent form addressing EPA comments is in Attachment 3 to EPA's review memo.

(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	
(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.		Not applicable.

Attachment 8

40 CFR 26.1125 Submission of proposed human research for EPA review
Field Testing of SC Johnson Tick 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	Section 2.10. pp. 24-26. EPA comments in Attachment 2.
		(2) The measures proposed to minimize risks to the human subjects;	Y	Section 2.10, to be revised in response to EPA comments.
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	Section 2.11, p. 26.
		(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 1.4 - Page 13 See Rationale for human testing- Section 2.1 – pp. 13-14.
		(5) The balance of risks and benefits of the proposed research.	Y	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	See IRB's conditional approval statement on page 352.
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	See revised language for sections 2.3.3 – 2.3.6.
	§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. 310-318 of draft. See revised language for section 2.4. Revised ICD is in attachment 3 to review memo.
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 343-353. Additional information sent to EPA is in Attachment 9.
	§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 HSRB Review and approval. p. 352.

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	
	(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. 343-353. IRB also provided information directly to EPA. See Attachment 9 for the HSRB.
	(3) Records of continuing review activities.	n/a	
	(4) Copies of all correspondence between the IRB and the investigators.	Y	pp. 343-353
	(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	p. 353 and list of members in Attachment10.
	(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. SAIRB provided the SOPs listed below to EPA.
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).	n/a	n/a for protocols

Attachment 8(a)

<u>Schulman Associates Institutional Review Board (IRB) SOPs Submitted to EPA</u>

Schulman Associates IRB submitted directly to the EPA, the following SOPs, with a watermark indicating that their content is "Confidential Business Information."

Note for website: The HSRB received the list of SOPs, but the list is not publicly available.

Note: Attachments 9 – 11 are provided in separate files for the Human Studies Review Board.