EPA Review of Protocol for Field Testing of S.C. Johnson Skin-Applied Mosquito Repellent Products

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Overview

- Johnson submitted a insect repellent field testing protocol to determine the Complete Protection Time (CPT) of their 18 skin applied repellent products to support the use of the EPA Repellency Awareness Graphic.

Overview (2)

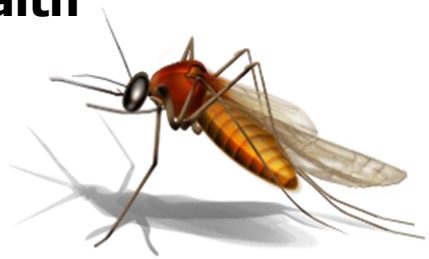
- Testing will be conducted in Florida and Wisconsin.
- Testing will be conducted against mosquitoes with 20 human subjects per product (10 per site).

Comparisons to Skin-Applied Repellent Protocols Reviewed by the HSRB

- In this protocol, all product types are proposed to be tested at the same dose, 1 g/600cm^2, and a dosimetry phase is not proposed. This is a departure from the design of repellent efficacy studies that that have been reviewed and approved by EPA and the HSRB in recent years, which have experimentally determined the dose.

What is the Repellency Awareness Program?

A program to raise public awareness of the health protectiveness of mosquito and tick repellents applied to the skin.



Purposes:

- Raise consumer awareness of the efficacy of skin-applied insect repellents.
- Increase EPA and consumer confidence in the efficacy claims on labels.
- Improve consumer protection against vector borne diseases, such as West Nile virus and Lyme disease.

EPA Repellency Awareness Graphic

Shows that mosquitoes are repelled

Typical length of time product repels mosquitoes

Shows that ticks are repelled

Typical length of time product repels ticks

Repellency Awareness Graphic

- 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.

Science Assessment

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Study Objectives

- This study is designed to determine the complete protection time (CPT) of up to eighteen EPA registered skin applied repellent products from S.C. Johnson & Son, Inc. in the field against wild adult mosquito populations using volunteer human subjects to support their use of the EPA Repellency Awareness Graphic.

Study Objectives (2)

- The data provided from this research can be used by the EPA to add the Repellency Awareness Graphic to skin applied insect repellent labels, thereby allowing for better protection of consumers from nuisance bites and bites that lead to arthropod-borne diseases.

Acute Toxicity of the Test Materials

- All test materials are Johnson Products registered by the EPA as skin applied insect repellents.
- Acute Dermal LD_{50} >2,000 mg/kg body. weight
- Minimally irritating to the skin and eyes.
- Not a skin sensitizer.

Margin of Exposure (MOE) Estimate

- Johnson prepared an estimate of the Margin of Exposure via the dermal route for each of the 18 products to be tested.
- The proposed exposures to the subjects in these tests are not of concern for the three active ingredients to be tested.

Calculated Margins of Exposure for DEET Products

Table 1:

Product	Dose (mg)	Acute Product LD_{50} (mg/kg)	MOE	Adj. Acute Product LD_{50} (mg/kg)	Adj. MOE	Acute Active Ingredient LD_{50} (mg/kg)	MOE
5% DEET Spritz (4822-415)	1133	>2,000	**141**	5000	**353**	4280	**4083**
5.6% DEET Towelette (4822-552)	1133	>2,000	**141**	5000	**353**	4280	**3645**
7% DEET Spritz (4822-395)	1133	>2,000	**141**	5000	**353**	4280	**2916**
15% DEET Aerosol (4822-380)	1133	>2,000	**141**	5000	**353**	4280	**1361**
15% DEET Aerosol (4822-543)	1133	>2,000	**141**	5000	**353**	4280	**1361**
25% DEET Aerosol (4822-167)	1133	>2,000	**141**	5000	**353**	4280	**817**
25% DEET Towelette (4822-258)	1133	>5,000	**353**			4280	**817**
25% DEET Spritz (4822-399)	1133	>5,000	**353**			4280	**817**
25% DEET Aerosol (4822-572)	1133	>5,000	**353**			4280	**817**
30% DEET Aerosol (4822-397)	1133	>5,000	**353**			4280	**680**
98.25% DEET Spritz (4822-276)	1133					4280	**307**

Calculated Margins of Exposure for Picaridin Products

Table 2:

Product	Dose (mg)	Acute Product LD_{50} (mg/kg)	MOE	Acute Active LD_{50} (mg/kg)	MOE
5% Picaridin Spritz (4822-536)	1133	>5,020	**354**	>2000	**12494**
5% Picaridin Lotion (4822-535)	1133	>5,040	**356**	>2000	**2824**
20% Picaridin Spritz(4822-556)	1133	>5,020	**354**	>2000	**3124**
20% Picaridin Aerosol (4822-564)	1133	>5,020	**354**	>2000	**3124**

Calculated Margins of Exposure for p-Methane-3, 8-Diol (PMD) Products

Table 3:

Product	Dose (mg)	Acute Product LD_{50} (mg/kg)	MOE	Acute Active LD_{50} (mg/kg)	MOE
8% PMD Towelette(4822-526)	**1133**	>5,000	**353**	>5000	**4412**
10% PMD Lotion (4822-515)	**1133**	>5,000	**353**	>5000	**3529**
10% PMD Spritz(4822-528)	**1133**	>5,000	**353**	>5000	**3529**

Dosage and Product Application

- Johnson will not include a dosimetry phase to determine "typical consumer dose."
- Instead, Johnson proposes a standardized dose of 1.67mg product/cm^2, equivalent to 1g/600 cm^2, will be applied to each subject.

Dosage and Product Application (2)

- A set dose can be related to known consumer behavior based on past tests reviewed by the HSRB where dosimetry was employed for skin applied insect repellent products.

Dosage and Product Application (3)

- Based on an analysis of the dosimetry results from repellent studies reviewed by EPA and the HSRB since 2006, EPA considers the following to be the appropriate product doses for studies conducted under this protocol: lotion – 0.9g/600cm^2, pump spray 0.4g/600cm^2, and aerosol 0.8g/600cm^2.

Dosage and Product Application (4)

Dosimetry Results from Skin Applied Repellent Mosquito Studies presented to the HSRB

Formulation Type	Total No. of Subjects in Dosimetry Phase for Mosquito Tests	Mean Dose (g/600 cm^2) $\pm$ 1 SD	Dose range (g/600 cm^2)	Recommended Dose (g/600 cm^2)
Lotion	112	0.933 $\pm$ 0.299	0.63-1.23	0.9
Pump spray	92	0.434 $\pm$ 0.113	0.32-0.55	0.4
Aerosol	25	0.815 $\pm$ 0.262	0.55-1.08	0.8

Dosage and Product Application (5)

- Formulation types to be tested include pump sprays (Spritz), aerosols, lotions (creams), and towelettes.
- Data may be bridged from a pump spray to a towelette because pump spray and towelette formulations are usually similar and the pump spray is applied at a lower dose.

Field Sites

- Studies will be conducted at two locations in the United States.
  - Wisconsin – temperate forest
  - Florida – swamp and marshland
- When unable to complete testing at U.S. sites, Johnson proposes to conduct testing at established sites in Cairns, Australia.

Field Sites (2)

- Use of field testing sites in Australia.
  - The protocol did not adequately address other science parameters that need to be considered.
  - Protocol will need to be amended to include a more robust discussion of mosquito species, disease vectors, and argument to bridge to U.S. species and conditions.

Experimental Design

- At each test site ten subjects (5 males and 5 females) will be treated with the test substance. Two additional subjects (one male and one female) will serve as the negative control for each test set.
- Each subject will have one forearm or lower leg (calf) treated with the repellent product to be tested.

Experimental Design (2)

- The controls are appropriate to monitor the mosquito landing rate (biting pressure) of mosquito populations at the test site. The data collected from these subjects will not be used in the calculation of the Median Complete Protection Time.

Experimental Design (3)

- For each product treatment there will be a total of 20 treated subjects and 4 negative control subjects.
- The subjects will be blinded to the test substances with which they are treated.
- A positive control substance will not be used.
- A second product treatment group may be added to some of the field tests.

Experimental Design (4)

- The test subjects will be selected at random from a pool of potential subjects. Assignment of the test substance to the subjects will be also be randomized.
- The decision to use arms or legs will be based on the behavior of the species of mosquitoes present in the field.
- If two test substances are tested on one test day, assignments of these treatments will also be randomized amongst the test subjects. Different subjects will be used for each product treatment.

Experimental Design (5) – DEET Products

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

Experimental Design (6) – Picaridin Products

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

Experimental Design (7) – PMD Products

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

Endpoints and Measures

- Unit of measure for determination of the repellent effects is Complete Protection Time (CPT).

- *"Subject specific Complete Protection Time (CPT) will calculated as time from application of each test substance to a subject and the 'First Confirmed Landing' on that subject."*

Endpoints and Measures (2)

- *A 'Landing' occurs when a mosquito alights on the treated skin of a subject.*
- *A 'First Confirmed landing' is that which is followed by another Landing within a 5 minute exposure period or, when one Land occurs in such an exposure period and another Land occurs in the next exposure period (30 minutes later)."*

Statistical Analysis Plan

- 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 Survival Analysis, which is advantageous since CPTs may not be normally distributed.

Statistical Analysis Plan (2)

- The Kaplan Meier Survival Analysis 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 data sets.

Statistical Analysis Plan (3)

- The proposed sample size of 10 subjects per field site represents a reasonable compromise between decreasing confidence interval width and limiting costs based on past analyses by the EPA.

Measures to Ensure Reliability

- Standard Operating Procedures (SOPs) will be in place that must meet Good Laboratory Practices requirements.
- Subjects' attractiveness to mosquitoes will be determined prior to testing
- Subjects will be trained on how to aspirate mosquitoes and will be paired up.
- Study Director and technicians will monitor on-site activities.
- Aspirated mosquitoes will be collected and identified.

Compliance with Scientific Standards

The following elements are adequately addressed:

- Available toxicity studies with DEET, picaridin, and PMD.
  - Adequately characterize toxicological profile of the formulations.
  - Data to support estimate of acceptable Margin of Exposure (MOE).

Compliance with Scientific Standards

- The following elements are generally acceptable but require refinement and clarification:
  - Experimental design
  - Data analysis

Science Comments and Recommendations

- Inclusion of field testing sites in Australia.
  - The protocol does not specify those possible sites or identify the endemic mosquito species at those sites.
  - **Johnson response:** Made reference to some details on established sites in Cairns, Australia.
  - **EPA**: provide complete science details.

Science Comments and Recommendations 2

- Field site qualification should describe in more detail how the study director will know if the selected site did not have mosquito-borne disease transmission activity for at least one month prior to the start of the test.
- **Johnson response**: Consult USGS, CDC, and State Health Department websites for updates.

Science Comments and Recommendations 3

- Change "mosquito biting pressure" to "mosquito landing rate" as subject bites are not counted or recorded in this study.
- **Johnson response:** Provided revised protocol sections with changes.

Science Comments and Recommendations 4

- The justification for sample size requires further elaboration and explanation.
- **Johnson response:** Sample size is adequate and is unlikely to overestimate CPT due to selection of the lowest CPT value, known subject attractiveness to mosquitoes, and historical precedent.

Science Comments and Recommendations 5

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

Science Comments and Recommendations 5 continued

- **Johnson response**: Kaplan-Meier Survival Analysis takes into account censored data and thereby accounts for missing observations. Subjects will not be replaced if they withdraw before their CPT is determined.

Science Comments and Recommendations 6

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

Science Comments and Recommendations 6 continued

- Describe treatment allocation when, and if, testing is conducted on consecutive days with different products and when more than one test substance is tested per day.

Science Comments and Recommendations 6 continued

- **Johnson response:** Subjects will be treated with only one test substance. Different subjects will be recruited if a second substance is tested on the same day. Testing is unlikely on consecutive days but a one-day in-between participation in testing will be followed.

Science Comments and Recommendations 7

- The protocol states that up to 10% of the exposure periods in a test may have less than the minimum landing (biting in the protocol) pressure of five mosquitoes landing in five minutes or less.
- Will treatment exposures occur during periods of insufficient landing pressure?

Science Comments and Recommendations 7 continued

- If treatment data are collected during these periods, how will they be used in CPT calculation?
- If they are not used, how will the lack of data points be considered in the K-M survival analysis and calculation of Median CPT?

Science Comments and Recommendations 7 continued

- **Johnson response**: Prescribed limit on exposure periods with insufficient pressure is set to 10%. Gaps will be reported.

- **EPA**: However, the response does not mention how first confirmed landings will be addressed if there is a missing exposure period between landings.

Science Comments and Recommendations 8

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

Science Comments and Recommendations 8 continued

- **Johnson response**: Based on Johnson's experience with active ingredient levels that result in duration times of typically 6 hours or longer, we will delay the first exposure period as follows:
  - For Deet and Picaridin formulas with active ingredient amounts of 12.0-15.99% the first exposure to the test system will be delayed to 2 hours post treatment.

Science Comments and Recommendations 8 continued

- **Johnson response**: For Deet and Picaridin formulas with active ingredient amounts of 16.0% and above, the first exposure to the test system will be delayed to 3 hours post treatment.

Science Comments and Recommendations 9

- State/justify why no positive control substance is to be used.
- **Johnson response:** Due to this lack of information on how the positive control data would be used to normalize the data, the exposure of additional test subjects to repellent products and mosquitoes is not justified.

Science Comments and Recommendations 10

- Based on an analysis of the dosimetry results from repellent studies reviewed by EPA and the HSRB since 2006, EPA considers the following to be the appropriate product doses for studies conducted under this protocol: lotion – 0.9g/600cm^2, pump spray 0.4g/600cm^2, and aerosol 0.8g/600cm^2.

Science Comments and Recommendations 10 continued

- **Johnson response**: Support the use of one dose regardless of formulation type to reduce variability in the study. Retain product dose of 1g/600 cm^2.

Science Comments and Recommendations 10 continued

Dosimetry Results from Skin Applied Repellent Mosquito Studies presented to the HSRB

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Science Comments and Recommendations 11

- Product application is not fully described. After weighing the set dose, how is the product applied to the limb for pump sprays and lotions?
- **Johnson Response**: Provided revised protocol sections.

Science Comments and Recommendations 12

- All raw data must accompany all study submissions.
- Appendix III – Land Data Form. Identification of which limb was treated needs to be added to this data sheet.
- Provide more detail on data compilation and processing.
- **Johnson response**: agreed and will make revisions.

Compliance with Scientific Standards

- If amended to address the concerns raised in the EPA review, the Johnson protocol entitled "Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support the Use of the EPA Repellency Awareness Graphic" is likely to yield scientifically reliable information, satisfying the following scientific criteria from the framework recommended by the HSRB:
  - It would produce important information that cannot be obtained except from research with human subjects.
  - It has clear scientific objectives.
  - The study design should produce adequate data to achieve those objectives.

Ethics Assessment

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Office of Pesticide Programs

Value to Society

- Proposed study would test the field repellent efficacy of up to 18 EPA-registered products against mosquitoes
- Product-specific efficacy testing is required to support label claims of repellency against mosquitoes and to obtain the Repellency Awareness Graphic
- Testing is important because consumers cannot readily assess the duration of efficacy

Subject Selection

- Participants will be recruited from among a database of interested volunteers maintained by a recruitment firm
- Inclusion and exclusion factors are well defined and appropriate
- Vulnerable subjects will not be recruited

Proposed Field Test Site Locations

- Primary locations:
  - Wisconsin, Florida
- If testing is to be conducted outside of the U.S. mosquito season:
  - Cairns, Australia
  - Protocol notes that all human testing laws in Australia will be followed, including IRB review

Risks to Participants

- Possible adverse reaction to test material
- Exposure to biting mosquitoes or mosquito-vectored disease
- General risks of being in the field
- Loss of privacy or confidentiality

Benefits

- No direct benefit to subjects
- Primary direct beneficiary is sponsor
- Indirect beneficiaries will include repellent users who may be able to more easily determine the duration of efficacy

Risk:Benefit Balance

- Risks have been effectively minimized
- Risks are reasonable in light of the expected societal benefits of the knowledge likely to be gained

Independent Ethics Review

- The Schulman Associates IRB (SAIRB) reviewed and conditionally approved the protocol and informed consent materials
- Final approval is conditioned on the sponsor obtaining EPA and HSRB review
- SAIRB has AAHRPP accreditation, is registered with OHRP, and is independent of the investigators

Informed Consent

- Description of proposed consent process is satisfactory
  - Potential subjects meet with study director or principle investigator to discuss study, review consent form
  - Pregnancy testing
  - Training session
- Consent form includes all elements required by regulations

Respect for Subjects

- Effective methods for protecting subjects' privacy
- Proposed level of compensation is appropriate
- Subjects will be free to withdraw at any time
- Medical care for research-related injuries will be provided at no cost to subjects

Applicable Ethical Standards

- This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws
- The primary ethical standards applicable to the conduct of this research are 40 CFR 26, Subparts K and L, and FIFRA 12(a)(2)(P)
- Attachment 1 to the EPA Review contains a point-by-point evaluation of how this protocol addresses the requirements of 40 CFR 26 Subparts K and L

EPA Comments

- Revise benefits section of Informed Consent Form; payment not is considered a benefit
  - *SCJ: Will revise accordingly √*
- Amend protocol and consent form to exclude immediate family members of Johnson employees
  - *SCJ: Will revise accordingly √*

EPA Comments (cont.)

- SCJ should consider whether additional stopping rules should be added to the protocol
  - *SCJ: Will incorporate add'l stopping rules √*
- Demographics of recruiting pool should match demographics of repellent users
  - *SCJ: The recruitment firm will build a volunteer pool with demographics that match test areas √*

EPA Comments (cont.)

- Prospective subjects should have option to read consent form themselves
  - *SCJ: Will revise accordingly √*
- Include details about transportation to/from test site and what happens if a subject withdraws
  - *SCJ: Subjects must provide their own transportation to and from test site √*

EPA Comments (cont.)

- Explain compensation if subject participates in the consent meeting, the training meeting, and/or the pregnancy testing, but then ultimately decides not to participate in the research
  - *SCJ: The consent meeting, training session, and pregnancy testing will take place on the same day, within 48 hours prior to the planned field testing - $60 compensation if subject withdraws during/after this session. √*

Findings in EPA Ethics Review

- No deficiencies relative to 40 CFR 26, subparts K and L, or to FIFRA § 12(a)(2)(P)
- Protocol meets the applicable requirements of 40 CFR part 26, subparts K and L

Charge Questions

If the proposed field repellency study protocol is revised as suggested in EPA's and the HSRB's review and if the research is performed as described:

1. Is this protocol likely to generate scientifically reliable data, useful for estimating the complete protection time of various EPA-registered S.C. Johnson skin-applied mosquito repellents in the field against wild adult mosquito populations?

2. Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

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Sincerely,

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