EPA Review of Five Completed Studies for Field Testing of S.C. Johnson Skin-Applied Mosquito Repellent Products to Support their Use of the Insect Repellency Awareness Graphic

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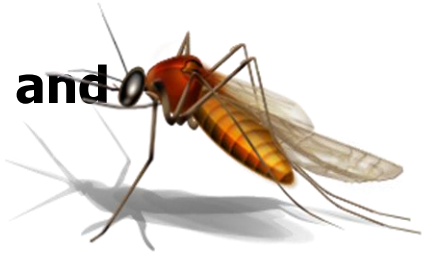
Overview

S.C. Johnson submitted five completed studies, each testing a single insect repellent against mosquitoes in the field to determine, for the EPA Repellency Awareness Graphic, the median Complete Protection Time (CPT) of five of their skin applied repellent products.

What is the Repellency Awareness Program?

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



Purposes:

- 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

Science Assessment: Design of Protocol Applicable to All Five Studies

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Protocol Review

- EPA's science and ethics review of 31 March 2015 found the protocol acceptable with minor changes
- HSRB review on 23 April 2015 concurred with EPA with minor changes
- Amended protocol of 26 June 2015 was approved by IRB on 7 July 2015

Methods Overview

- Testing was conducted at locations in Florida and Wisconsin.
- Testing was conducted against mosquitoes with 20 different treated human subjects per product (10 per site).
- Two untreated control subjects per site

Methods: Uneven Subjects

Several tests were run with uneven numbers of male and female subjects

S.C. Johnson Response: SC Johnson indicated that they conducted a statistical analysis comparing complete protection time (in hours) of men vs. women in studies conducted in Wisconsin for a variety of spray-on personal mosquito repellent products using standard SC Johnson test protocol. The sample size for each individual product was too small (N=10) to warrant a product-by-product comparison of genders, so protection times for all products were combined before statistical testing was done. The Mann-Whitney U test was used to compare females to males, resulting p values of 0.89. This high p value suggests that complete protection time is statistically equivalent for females and males.

Treatment Application Rate

- Aerosol products were tested at (1 g/600cm^2)
- Pump sprays were tested at (0.5 g/600cm^2)
- Method of Application was as follows:
  - Aerosols – spraying, then spreading on skin using fingers
  - Pump sprays – using a pipette, then spreading on skin using fingers

Exposure of Subjects to Mosquitoes

- Subjects were exposed for a 5 minute period every 30 minutes.
- 5 minute exposure periods were delayed until
  - 2 h post app. for products containing 12 – 15.99% DEET
  - 3 h for products containing > 16% DEET
- Exposure periods occurred until product failure or the study director terminated the study

Endpoints and Measures

- Mosquito Landings were used to evaluate repellency.
- Repellent failure was determined by the 'First Confirmed landing'
- Mosquitoes that landed were collected and identified to species for each site

Data Analysis

- Median Complete Protection Time for each product at each site was calculated using Kaplan Meier Survival Analysis using PROC LIFETEST
  (Brookmeyer and Crowley 1982)

HSRB Comments and S.C. Johnson Response

Potential for cross contamination: The protocol should specify steps that will be taken to insure that the treated area on subjects is not impacted by activities that take place before or during the experiment (*i.e.*, rubbing sleeve or pant leg across the treated area).

S.C. Johnson Response: Subjects were not transported using a vehicle after the test substance was applied, and subjects were reminded not to touch or contact the treated skin in any manner. Any inadvertent contact with the treated area was reported to the study staff and documented in the raw data.

HSRB Comments and S.C. Johnson Response (2)

Landing pressure: The protocol includes untreated control subjects with each test to insure that there is sufficient landing pressure to provide valid results. The Board recommends that the Agency and S.C. Johnson consider how a quantitative estimate of landing pressure can be determined without increasing the likelihood of bites if landing pressure is excessive (*e.g.*, recording the time of each landing, the time to reach 5 landings, or the total landings in 5 minutes) and how that information can be used to normalize or interpret CPTs measured under different landing pressure conditions.

S.C. Johnson Response: Study staff recorded the time to reach five landings if less than five minutes. Because all studies were performed at the same two sites, landing pressure appears to be fairly consistent across sites, therefore normalization is not required.

HSRB Comments and S.C. Johnson Response (3)

Delayed start: The Board recognizes the advantages of delaying the exposure to mosquitoes for subjects treated with products that are known from previous experience to last for a long time. However, the protocol needs to provide more information about the criteria used to determine how long to wait before starting the test cycles (5 minute exposure at 30 minute intervals). Regardless of how long the subject's exposure is delayed, the protocol should require a minimum number of completed cycles to insure valid results. For example, following a delayed exposure, the subject should complete at least three exposure cycles before getting a confirmed landing.

S.C. Johnson Response: Exposures were delayed until two hours after application for products contained 12-15.99% DEET and three hours for products containing more than 16% DEET. All subjects were exposed to mosquitoes for at least three exposure cycles before a confirmed landing was recorded. In addition, delaying exposure periods reduced the exposure of the subjects to potential bites from mosquitoes.

HSRB Comments and S.C. Johnson Response (4)

Randomization: The randomization mechanism should be described in more detail and rationale should be given for any given choice of randomization within the protocol. For example, it is not clear whether/how cross-substance relations are to be evaluated in the data analysis and why randomization among test substances is needed. An explanation of this would be helpful. In addition, when the conditions support use of arm rather than leg for exposure, then it may be more important to consider handedness when selecting what arm to treat, rather than randomly assigning to left or right hand, so the subject can have their dominant hand to remove landing mosquitoes before they bite.

S.C. Johnson Response: One test substance was tested on each day, therefore randomizing the treatment was not necessary. The mechanism for randomizing the arm was not provided in the studies; however, after discussions with S.C. Johnson, they indicated that the mechanism for randomizing the arm to be treated was based on the random selection of test ID numbers. Subjects assigned odd numbers had their left arm treated, and subjects with even numbers had their right arms treated. In addition, the protocol notes that aspirating mosquitoes is not difficult even with a non-dominant hand. The untreated control subjects were allowed to choose which arm to expose.

HSRB Comments and S.C. Johnson Response (5)

Sample size determination: A sample size calculation would be useful here to inform the power of testing and the width of confidence intervals. Power and sample size calculation can be implemented using existing SAS procedures. Information about appropriate sample size calculations is included in the EPA document "Product performance Test Guidelines OPPTS810.3700: Insect Repellents to be Applied to Human Skin."

S.C. Johnson Response: After discussions with S.C. Johnson, they indicated that they did not conduct a sample size calculation or power analysis but the table which summarizes the effect of sample size on the confidence interval for median CPT presented in the protocol for testing repellents against ticks to the Human Studies Review board at the October meeting would apply to these studies because both studies use 10 subjects. In the past, HSRB had positive reviews about the sample size of 10. EPA also believed that a sample size of 10 will provide a reasonable width of the confidence interval for the median based on past studies testing repellents.

HSRB Comments and S.C. Johnson Response (6)

Sources of variation: The protocol does not currently specify the conditions that might cause the CPT data from the two sites to differ; however, the researchers should consider collecting information to explain any large and potentially significant differences in the CPT values between otherwise matched studies conducted at two different sites.

S.C. Johnson Response: The researchers identified mosquitoes to species, recorded habitat characteristics, climatic conditions, and the time to five landings on the untreated control subjects, information which could explain large and significant differences in median CPT.

EPA Comments and S.C. Johnson Response

EPA Comment: Product application is not fully described.

S.C. Johnson Response: The exact method of determining the amount applied to each subject in this study is described in §14.0 and 7.1.8.2.

EPA Comments and S.C. Johnson Response (2)

EPA Comment: 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?

S.C. Johnson Response: For subjects that withdrew before receiving their first confirmed landing, their CPT was considered to be the time at which they withdrew. These "right censored" subjects are indicated by a + on the survival curve graphs. Subjects that withdrew were not replaced with alternates.

EPA Comments and S.C. Johnson Response (3)

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

S.C. Johnson Response: When the minimum landing pressure was not achieved in an exposure period, those exposure periods were used in the study report.

Ethics Assessment: Slides Applicable to All Five Studies

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Overview

- Recruitment
- Informed Consent Process
- Pregnancy Testing
- Training
- Mitigation of Hazards
- Compensation
- Responsiveness to EPA and HSRB Comments
- Independent Ethics Review
- Completeness of Documentation

Recruitment

- S.C. Johnson (SCJ) contracted with two recruitment firms to recruit candidates
- Using approved phone script for the initial call, recruitment firms screened 392 subjects
- Using approved inclusion/exclusion criteria, and taking into account subjects' availability and interest, firms scheduled 170 subjects for SCJ to contact
- Using the approved follow-up screening script, the interested subjects who met the inclusion/exclusion criteria and were available for both the training and test dates were enrolled for each study

Recruitment 2

- Pool generally represented demographics of U.S. repellent users. Not all targets were met due to:
  - availability of subjects for training/test days
  - subjects withdrawing or not showing up on scheduled training or test days

Recruitment 3

- Table 5 in each completed study provides the **demographics** of subjects who were enrolled versus those who actually participated in each study
- Table 6 in attachment 2 to the ethics review memos summarizes data on subject recruitment
- Table 7, also in attachment 2, summarizes data on subject participation

Informed Consent

- S.C. Johnson (SCJ) adhered to the inclusion/exclusion criteria from the approved protocol
- Interested subjects who met the inclusion/exclusion criteria met with Study Director or Principle Investigator at training session
- Subjects were provided the informed consent document (ICD) and asked to read it
- SCJ emailed consent forms to subjects in advance of training if they were provided an email address
- SCJ asked subjects if they had questions and answered them
- If subjects wished to enroll, they signed ICD and were given a copy

Pregnancy Testing

- Pregnancy testing was carried out consistent with the approved protocol, section 2.3.12, reviewed by the HSRB
- S.C. Johnson (SCJ) confirmed that that testing for each study was conducted on the training day
- If the test day occurred more than 48 hours after the training, the pregnancy test was repeated on the morning of the test day
- No pregnant or nursing female subjects participated in the study
- HSRB reviewed this approach without comment at the April 22-23, 2015 HSRB meeting

Training

- The subjects were trained to aspirate blood-seeking mosquitoes prior to participating in the study
- In WI, training took place in a lab and in FL, a field. Training was consistent with approved protocol
- Study staffer demonstrated how to aspirate mosquitoes
- After subjects watched at least 8 mosquitoes captured and aspirated properly, they tried it themselves. Subjects did this until the study staffer felt they were proficient and could participate in the field test
- For the FL training in the field, subjects wore bug suits and gloves for protection during the training, consistent with protocol

Mitigation of Hazards

- Protocol and completed study identifies five hazards associated with these studies and precautions taken to mitigate the hazards

- Hazards include:

    1. adverse reaction to test substances
    2. exposure to biting mosquitoes
    3. exposure to mosquito-vectored diseases
    4. general risks of being in field
    5. unanticipated loss of confidentiality.

Mitigation of Hazards 2

- Pages 18 – 19 of each study describe the precautions taken to mitigate hazards
- A few examples of precautions include:
  - Excluding participants with known allergies to mosquito bites
  - Training subjects to remove mosquitoes from skin before subjects could be bitten
  - Limiting exposure to one forearm (cont.)

Mitigation of Hazards 3

- A few examples of precautions include:
  - Conducting studies in areas where presence of mosquito-borne disease had not been detected by county or state health staff or mosquito abatement district staff within one month prior to test date
  - Providing food and beverage on site
  - Providing tent enclosure to keep mosquitoes away from subjects between exposures (cont.)

Mitigation of Hazards 4

- A few examples of precautions include:

  - Directing subjects to inform study staff right away if they experienced skin reactions, injury or simply felt unwell
  - Telling subjects they could withdraw from study for any reason without penalty
  - Other precautions to mitigate hazards on pages 18-19 of each study

Compensation

- Subjects were compensated consistent with protocol. Compensation included:
  - $60 for participating in training, even if subject withdrew from training
  - $15 per hour of participation on test day
  - $18 per hour for each additional hour on test day beyond first 8 hours
  - $50 provided to alternate if not needed on test day

Responsiveness to Comments

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

Responsiveness to Comments 2

- SCJ should consider whether additional stopping rules should be added to the protocol
  - *SCJ: Expanded stopping rules √*
- Demographics of recruiting pool should be representative of US repellent users. Add details to protocol.
  - *SCJ: Revised protocol accordingly √*

Responsiveness to Comments 3

- Prospective subjects should have option to read consent form themselves
  - *SCJ: Revised protocol. SCJ made ICD available prior to training. Subjects asked to read ICD. SCJ answered questions. √*
- 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 √*

Responsiveness to Comments 4

- Explain how compensation handled if participate in training but not study
  - *SCJ: Revised protocol and ICD to provide details of compensation √*
- Discuss whether repeat tests limited. Include plan for follow-up w/subjects after study.
  - *SCJ: Included details on when and how SCJ would follow up in section 11.2.4 & 11.2.8 √*

Responsiveness to Comments 5

- Provide process to contact subjects in event new information is discovered
  - *SCJ: Expanded protocol sections 11.2.4 and 11.2.8 , as well as 2.8.2.5 √*
- Provide justification for excluding non-English speakers or amend protocol. Provide information on demographics of pool at each site and recruitment strategies.
  - *SCJ: Provided justification and demographics √*

Responsiveness to Comments 6

- Concern over plan to handle claims similar to workmen compensation claims.
  - *SCJ: Revised ICD to change language√*
- Question raised about statement in ICD that study is confidential
  - *SCJ: Revised ICD to clarify this√*

Independent Ethics Review

- The Schulman Associates IRB (SAIRB) approved the revised protocol, ICD and phone script for initial and follow-up calls
- SAIRB has AAHRPP accreditation, is registered with OHRP, and is independent of the investigators

Completeness of Documentation

- SAIRB correspondence was provided
- Requirements of §26.1303 are satisfied