Science Assessment: Field Testing of S.C. Johnson Personal Mosquito Repellent Mark-2 Product to Support the Use of the EPA Repellency Awareness Graphic

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Mark-2 Study

- Conducted on August 3, 2015 in Wisconsin and August 18-19, 2015 in Florida.
- 30% DEET aerosol spray
- EPA Reg. No. 4822-397

Mark-2 Application Rate

- Applied at 1 g/600 cm^2 $\pm$ 10%
- Mean = 100% of the target amount.
- Range was 94-111% of the target amount.
- One subject received 111% of target amount but no protocol deviation was reported.
- SCJ should report this deviation consistent with SAIRB reporting procedures.

Mosquito Landings on Controls -Wisconsin

- In five of the six exposure periods five mosquito landings were recorded by the untreated control subjects in 1 minute or less.
- Time to five mosquito landings ranged from 12 seconds to 2½ minutes across both untreated control subjects through 16 exposure periods.

Mosquito Landings on Controls - Florida

- August 18 – Five mosquito landings occurred on an untreated control subject in less than one minute in 10 of the exposure periods; in greater than one minute but less than two minutes in six exposure periods; and at 3½ minutes in the last exposure period.

- August 19 – Five mosquito landings occurred in less than one minute in 14 of 15 exposure periods.

Wisconsin - August 3, 2015

- 10 subjects plus 4 alternates
- 5 treated males and 5 treated females
- 2 untreated control subjects (1 M & 1 F)
- 4 female alternates and 1 male alternate
- Protocol Deviation #1 described changes to the number and sex ratio of alternates.

Florida – August 18 and 19, 2015

- Protocol Deviations 2, 3, 4, 5, and 6 were reported.

- Protocol Deviation 6 reported that the study started at two hours post-treatment instead of at three hours post-treatment.

Florida – August 18, 2015

- Protocol Deviations 2, 3, and 4 addressed changes to number, sex ratio, and alternate subjects.
  - 4 females and 1 male treated.
  - 0 alternates.
  - 1 untreated control (male)
  - Untreated control paired with treated subject.

Florida – August 18, 2015

- Protocol Deviation 5 reported missed exposure period #5 due to rain on August 18.
- No landings in either exposure periods 4 or 6.
- No impact on study outcome.

Florida – August 19, 2015

- 3 females and 2 males treated.
- 1 female untreated control.
- Untreated male control from August 18 was an alternate.
- Treated subject paired with untreated subject.

Results -Wisconsin August 3, 2015

- Nine of ten subjects reported a First Confirmed Landing (FCL) through 9.5 hours post-treatment.
- The Study Director stopped the study at 9.5 hours because only one subject remained without a FCL.
- All subjects completed the study.

Results – Florida August 18, 2015

- Four of five subjects reported a FCL through 10 hours post-treatment.
- The Study Director stopped the study at 10 hours post-treatment because only one subject remained without a FCL.

Results – Florida August 19, 2015

- Four of the five subjects reported a FCL through nine hours post-treatment.
- Subject (#158) withdrew after 8.5 hours and his CPT was recorded as 8.5 hours (censored).
- The Study Director stopped the study at nine hours post-treatment because all subjects report a FCL.

Data Analysis

- Kaplan-Meier Survival Analysis was used to calculate Median CPT.
- In this experiment only two subjects did not receive a FCL.
- This resulted in 10% of the data points being "right-censored".
- For those subjects who did not experience a FCL by the end of the study, their CPT values are conservatively assumed to be the post-treatment duration of the study in a given site.

Complete Protection Times

Measure	Wisconsin	Florida
Median	7.5	8.5
95% LCL	4.0	4.5
95% UCL	8.0	10
Range	4.0 to 9.5	4.5 - 10

Conclusions

- The study is acceptable and the data support a Median CPT for the Repellency Awareness Graphic = 7.0 hours.

Ethics Assessment: Mark 2 Product

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Study Specific Data for Mark-2

- 54 subjects were enrolled for the Mark-2 study
- 20 no-shows for training
- 24 subjects assigned to participate in tests with 9 alternates/extras
- 23 subjects completed the testing

Protocol Amendments & Deviations

- No amendments to protocol
- Appendix B to study documents 7 deviations
- From an ethics standpoint, EPA identified follow-up actions associated with deviations 2 and 6 in the Mark-2 study

Deviation 2

- The study documents Deviation 2, which includes the following information in part.
- In Florida, on the training date of 8/17/15, only 5 of 11 males and 8 of 19 females showed up for their scheduled training. One male withdrew before training was complete. As a result, 12 subjects, 4 males and 8 females, were available as test subjects.
- Study director asked 1 male (who was untreated control on 8/18) to come to test session on 8/19 as an alternate.

Follow-up by EPA on Deviation 2

- It's understandable why study director asked untreated control if he could attend next test session as alternate.
- In future draft protocols for repellent studies, EPA should propose the inclusion of alternative recruitment approaches, as feasible, to plan for situations where subjects don't show up or withdraw unexpectedly.

Deviation 6

- As SC Johnson documented in the study, the protocol states that for Deet 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. In this study, there was a two hour delay to the first exposure to the test system. This was an oversight of the study director.

Follow-up by EPA on Deviation 6

- The subjects were exposed to mosquitoes during two extra data collections. This did not negatively impact the subjects' health or safety.
- However, for future studies, EPA will request that the study sponsor ensure adherence to the appropriate start time for first exposures consistent with the protocol.

References in Raw Notes

- Per section 13.5.6 of the completed study, any inadvertent contact of the treated skin reported by test subjects was appropriately documented in the raw data. This is consistent with protocol.
- As a result, the raw data refers to "minor rubs" and "abrasions."
- SCJ confirmed that these terms do not refer to any irritations or injuries. They refer to a treated limb coming in contact with a foreign object which has the potential to transfer repellent off the treated limb.

Protocol Deviations

- SCJ adhered to IRB instructions and protocol in documenting the deviations
- Deviations did not negatively impact subjects' rights, health or safety

Reporting of Incidents

- 2 subjects withdrew, 1 on training day and 1 on the test day.
- There were no adverse events or incidents of concern reported during or after test implementation

Substantive Acceptance Standards

- 40 CFR §26.1703
  - Prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children
- 40 CFR §26.1705
  - Prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 CFR 26. Subparts K & L applicable to third-party research.
- FIFRA §12(a)(2)(P)
  - Makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent

Findings

- Study in compliance with acceptance standards
- All subjects were at least 18; pregnant and nursing women were excluded
- No significant deficiencies in ethical conduct of the research
- Deviations did not compromise health and safety, consent or rights of subjects
- Subjects were fully informed and their consent was fully voluntary, without coercion or undue influence

Conclusion

- Available information indicates that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26

Charge Questions to HSRB

- Is the study sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?
- Does available information support a determination that the research was conducted in substantial compliance with 40 CFR Part 26, subparts K and L?