Science Assessment: Field Testing of S.C. Johnson Personal Mosquito Repellent Mark-4 Product to Support the Use of the EPA Repellency Awareness Graphic

Kevin Sweeney
Registration Division
Office of Pesticide Programs

Mark-4 Study

- Conducted on August 5, 2015 in Wisconsin and September 22, 2015 in Florida.
- 15% DEET aerosol spray
- EPA Reg. No. 4822-380

Mark-4 Application Rate

- Applied at 1 g/600 cm^2 $\pm$ 10%
- Mean = 102% of the target amount.
- Range was 95-114% of the target amount.
- One subject received 114% of target amount but no protocol deviation was reported.
- S.C. Johnson should report this to the SAIRB consistent with their reporting procedures.

Mosquito Landings on Controls - Wisconsin

- Five mosquito landings occurred in less than one minute on untreated control subjects in all exposure periods except one.
- Time to five mosquito landings ranged from 15 seconds to 1¼ minutes across both untreated control subjects through 17 exposure periods.

Mosquito Landings on Controls - Florida

- Five mosquitoes landed on an untreated control subject in less than one minute in five out of six exposure periods.
- Time to five mosquito landings ranged from 21 seconds to nearly 2 minutes across both untreated control subjects through eight exposure periods.

Wisconsin - August 5, 2015

- 10 subjects plus 2 alternates
- 5 treated males and 5 treated females
- 2 untreated control subjects (1 M & 1 F)
- 1 female alternate and 1 male alternate
- No protocol deviations reported.

Results -Wisconsin August 5, 2015

- Eight of ten subjects reported a First Confirmed Landing (FCL) through 10 hours post-treatment.
- The Study Director stopped the study at 10 hours with two subjects remaining. One received a landing at 10 hours while the other did not.
- All subjects completed the study.

Florida – September 22, 2015

- 0 alternates (Protocol Deviation 1)
- Only 8 treated subjects in the study (Protocol Deviation 2).
- 6 females and 2 males treated (Protocol Deviation 2).
- 2 untreated control subjects – 1 M and 1 F.

Florida – September 22, 2015

- Protocol Deviation 3 reported missed exposure period #4 due to rain and that the 5th exposure period began 5 minutes early due to oncoming weather.
- Two landings occurred in exposure period 3. Subject #333 received an unconfirmed landing and continued in the study. Subject #334 received a FCL and was removed from the study.

Florida – September 22, 2015

- In exposure period 5 a FCL was received by one subject (#329) and an unconfirmed landing by another subject (#321).
- Subject #333 did not receive a FCL in exposure period 5 and continued in the study through exposure period 7.

Florida – September 22, 2015

- Protocol Deviation 3 - corrective actions:
  - For the subjects receiving the FCL and landing in exposure period 5, respectively, the CPT was determined to be exposure period 3, which was 3.5 hours post-treatment.
  - Subject ID #329 was removed from the study but Subject ID #321 remained in the study until a FCL occurred at 5.0 hours post-treatment. However, a CPT of 3.5 hours was the value reported.

Results – Florida September 22, 2015

- Seven of eight subjects reported a FCL through 5.5 hours post-treatment.
- The Study Director stopped the study at 5.5 hours post-treatment because only one subject remained without a FCL.
- All subjects completed the study.

Data Analysis

- Kaplan-Meier Survival Analysis used to calculate Median CPT.
- In this experiment only three subjects in the experiment did not receive a FCL. This resulted in 16% 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 CPT	7.5	5.0
95% LCL	4.0	2.5
95% UCL	9.0	5.5
Range	4.0 - 10	2.5 - 5.5

Conclusions

- The study is acceptable and the data support a Median CPT for the Repellency Awareness Graphic = 5.0 hours.

Ethics Assessment: Mark 4 Product

Maureen Lydon
Office of the Director
Office of Pesticide Programs

Study Specific Data for Mark-4

- 41 subjects were enrolled for the Mark-4 study
- 14 no-shows (12 for training and 2 for testing in WI)
- 22 subjects assigned to participate in tests
- 7 alternates/extras at WI test location
- 22 subjects completed the testing. No one withdrew

Study Specific Data 2

- Within the two week period following the test date of August 5, 2015, there were two cases of birds that tested positive for West Nile Virus
- The birds were collected in Kenosha County, WI on August 14, 2015 and August 17, 2015 at locations at least 10 miles away from the WI test location
- The Wisconsin State Health Department released the positive test results for West Nile virus on August 24, 2015

Study Specific Data 3

- Consistent with the protocol, notification letters, approved by the SAIRB, were sent to the test subjects.
- S.C. Johnson sent the letters "return receipt requested" and included post cards for the subjects to send back to confirm receipt. (Draft letter is Attachment 4 to ethics review.)

Study Specific Data 4

- Letter explains why the subject is receiving it, informs the subject about the two birds with the West Nile virus that were detected, explains that the location of the detection was at least 10 miles from the test site, describes virus symptoms (provided by the Centers of Disease Control and Prevention) and when they generally appear, asks subjects to contact S.C. Johnson and provides a phone number if subjects experienced symptoms of West Nile disease, and notes that they may seek medical care if they experienced symptoms.

Study Specific Data 5

- Letter also states S.C. Johnson (SCJ) will reimburse subjects for the costs of medical care
- As of December, 2015, SCJ had not been contacted by any subject experiencing symptoms
- S.C. Johnson was following the approved protocol when they learned of the 2 birds with the virus
- Study Investigators monitored the detection of mosquito borne disease cases in the areas where testing occurred before the testing and for two weeks following the last test date

Study Specific Data 6

- The Study Investigators were monitoring detection of mosquito borne diseases by following the Wisconsin State Health Department website on mosquito borne disease detection by county.
- This web site is updated typically on a weekly basis.
- As of August 19, 2015 no cases of mosquito borne disease had been detected in Kenosha County in 2015. When the data was updated the following week (Aug. 25/26), West Nile virus had been detected in Kenosha County.

Study Specific Data 7

- At that time, the Study Investigators called the Kenosha County and Wisconsin State Health Departments to obtain more information on detection of West Nile virus in Kenosha County
- The Study Investigators learned that two birds, from separate locations in Kenosha County, one collected on August 14th and one collected on August 17th tested positive for West Nile virus
- The positive results for West Nile virus were released on August 24th

Study Specific Data 8

- Both locations where the birds were collected were located at least 10 miles away from the test location
- No human or mosquito cases of West Nile virus had been detected during that period
- After obtaining this more detailed information on the West Nile virus cases, the Study Investigators began the process to contact test participants that West Nile virus had been detected in the test area within two weeks following the test date(s)

Study Specific Data 9

- S.C. Johnson (SCJ) confirmed that every subject received their notification letter either through receipt of a confirmation card or via phone call.
- SCJ also told EPA that, "S.C. Johnson confirmed with the IRB that the approach we followed (via letter and confirmation card) was the appropriate route to follow."

Follow-up Action by EPA

- Protocol states "Study staff will monitor and contact test participants if any mosquito borne disease cases are reported in the test area within two weeks following the test date."
- SCJ followed the protocol. The letter sent by S.C. Johnson asked subjects to contact S.C. Johnson if they had experienced symptoms of the West Nile virus.
- In future draft protocols for repellent studies, EPA should ensure that the protocol is clear with regard to what it means to "**monitor**" test participants if any mosquito borne disease cases are reported in the test area within two weeks following the test date.

Follow-up Action by EPA 2

- A separate but related topic is coverage of medical costs.
- In future protocols and consent forms, EPA will recommend that language be included that the study sponsor will cover the costs of medical care resulting from a subject's participation in the study as opposed to reimbursing the subject for medical costs.
- This takes into account comments made by the HSRB at their last meeting.

Protocol Amendments & Deviations

- One amendment to protocol reflected change in study director. Original director took 10 week sabbatical.
- Appendix B to study documents 4 deviations
- From an ethics standpoint, EPA identified a follow-up action related to deviation 3

Deviation 3

- Deviation 3 noted that the fourth exposure period was cancelled due to heavy rain and the fifth exposure began 5 minutes early due to oncoming weather. As described on page 23 of the study, "the protocol did not address how to determine repellent break down point in the event of rain delay, so conservative logic was developed and used for all MARK studies where a rain delay occurred. If a land occurred during an exposure period immediately following a rain delay, the break down period was determined to be (the) period when the rain delay began."

Follow-up by EPA on Deviation 3

- In future draft protocols for repellent studies, EPA should ensure that the protocol addresses how to determine repellent break down points in the event of a rain delay
- Related to this, the protocol should discuss where the subjects will go for coverage in the event of a rain delay

Protocol Deviations

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

Reporting of Incidents

- No subjects withdrew from the study
- S.C. Johnson (SCJ) followed the protocol in informing subjects, that two birds with West Nile virus were detected at least 10 miles from the test site within two weeks after the testing
- SCJ provided all information required by protocol

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?