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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

December 15, 2015

MEMORANDUM

SUBJECT: Ethics Review of Completed Study entitled, "Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support their Use of the EPA Repellency Awareness Graphic" for MARK-8 OFF! Deep Woods Insect Repellent V

FROM: Maureen Lydon, Human Research Ethics Review Officer
Office of the Director
Office of Pesticide Programs

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

REF: C. Talbert (2015) Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support their Use of the EPA Repellency Awareness Graphic, October 21, 2015. 154 pages, Test Substance MARK-8 OFF! Deep Woods Insect Repellent V (OFF! Insect Repellent Formula, EPA Reg. No. 4822-167) GLP Study No. 873E1 (MRID 49761601)

I have reviewed available information concerning the ethical conduct of the referenced research study, "Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support their Use of the EPA Repellency Awareness Graphic" for test substance MARK-8 OFF! Deep Woods Insect Repellent V (OFF! Insect Repellent Formula, EPA Reg. No. 4822-167). If the research is determined to be scientifically acceptable, I find no barrier in regulation to the U.S. Environmental Protection Agency's (EPA's) reliance on this study in actions under the Federal Insecticide, Fungicide, or Rodenticide Act (FIFRA) or the Federal Food, Drug, and Cosmetic Act (FFDCA). The Human Studies Review Board (HSRB) will be asked to comment on this study.

Completeness of Submission

All requirements of §26.1303 were satisfactorily addressed in the completion of this study as noted in the checklist in Attachment 1.

Purpose and summary of study

The purpose of this study was to establish the complete protection time (CPT) of MARK-8 OFF! Deep Woods Insect Repellent V, which was previously registered and assessed by EPA, in the field against populations of wild mosquitoes, using human subjects. Testing took place at two geographically and ecologically distinct field sites (Wisconsin and Florida). The protocol called for 10 volunteer subjects at each test site with two untreated control subjects at each site. Table 7 summarizing test subject participation was included in each study; an updated version of this table, supplied by S.C. Johnson, is included in Attachment 2. As noted in the updated table 7, 24 human subjects were assigned to the tests and 23 completed the testing at the Wisconsin and Florida sites. Human subjects were used because no reliable models or surrogates have been found to adequately predict the duration of efficacy of topically-applied insect repellents. Because the repellent test products have all been registered by EPA, they have already been found to present little or no risk when used as directed on their labels. The precautions taken to mitigate hazards associated with the study are discussed on pages 17-19 (of 154) of the completed study and were consistent with the approved protocol.

Testing was completed in Wisconsin on a single day and then in Florida on a single day. The Study Director assembled all test subjects in an area within walking distance of the test site for testing preparation (limb preparation, suiting up and test substance application, etc.). Tent enclosure was provided to protect all personnel during this process from mosquitoes present at this location. Each subject was given and instructed to put on a bug suit pants and jacket. This suit is made of tightly woven nylon which allows air exchange but is impenetrable to mosquito bites. The bottoms of the pant legs and ends of the sleeves fit snuggly around the wearer's shoe or wrist respectively; this keeps mosquitoes out. There is also mesh on the sides of the jacket (under arm) for better breathability. The suit has drawstring band around the waist and a mesh area around the face (a zipper allows removal of this mesh around the face). Gloves were provided to protect the hands from mosquito bites. After washing their limbs, subjects put on the bug suit prior to treatment to help reduce any occurrence of abrading or contacting the area of the skin that will be treated. Each subject rolled up the sleeve of their bug suit for their forearm treatment.

The test substance was applied to human forearms. Starting two hours after test substance application, subjects exposed their treated forearms to mosquitoes in the field for 5 minute periods at 30 minute intervals until repellent break-down occurred, or the study director ended the test. Duration of repellency was measured as the time between application of a test substance and the first confirmed landing. A “landing” occurred when a mosquito alighted on the treated test skin of a subject. A “First Confirmed Landing” is when two or more landings occurred in any five minute exposure period or, when one landing occurred in such an exposure period and another landing occurred in the next exposure period.

The median duration for Wisconsin was 8.25 hours and for Florida was 8.0 hours. The duration of CPT for the repellency awareness graphic will be based on the EPA Repellency Awareness Guidance for Skin-Applied Insect Repellent Products, EPA Document No. 730-C-13-001, which states, "The mosquito claim should be calculated using the most conservative (i.e., lowest) CPT from all available field studies" and "The number of hours of protection appearing on the repellency awareness graphic should be expressed as a whole number. If the most conservative calculated CPT is not a whole number, EPA recommends rounding down to the nearest whole number." The data support an 8 hour CPT for use on the repellency awareness graphic.

Institutional Review Board Approval of Revised Final Protocol

The protocol for this study was approved by the overseeing institutional review board, the Schulman Associates Institutional Review Board (SAIRB), and submitted to EPA in draft form for review. The protocol and EPA's review, dated March 31, 2015, were discussed in a public meeting by the Human Studies Review Board (HSRB) on April 22-23, 2015. Per the final HSRB meeting report, dated June 23, 2014, the HSRB concluded that "the amended protocol, when approved by the SAIRB, should meet all applicable ethical standards for the protection of human subjects of research, and all requirements for documentation of ethical conduct of the research. If this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA's reliance on it in actions under FIFRA or Section 408 of FFDAC."

In follow-up to the April 22-23, 2015 HSRB meeting, S.C. Johnson revised the protocol, telephone screening script for initial contact, script for follow-up contact, and consent form to address comments, including the EPA and HSRB comments described in Attachment 3, and submitted the revised documents to the Institutional Review Board (IRB) for review and approval prior to initiating the study.

The SAIRB approvals relevant to this study and associated approval dates are listed below.

<u>Chronology of SAIRB Final Approvals after April 2015 HSRB Meeting</u>

a) 7/10/15 – The SAIRB notified S.C. Johnson that the protocol and informed consent forms were approved by the SAIRB on the dates noted below.

b) 7/9/15 – The SAIRB approved, via expedited review, the updated recruitment/phone script for screening candidates via an initial and follow-up call.

c) 7/7/15 – The SAIRB full board approved the protocol dated 6/26/15 and informed consent form which took into account EPA and HSRB comments.

The June 26, 2015 protocol, which includes the SAIRB-approved changes, is in Appendix A to the completed study. The consent form approved by the SAIRB is date-stamped 7/10/15 and included in the IRB correspondence file (beginning on page 84 of 398.)

The emails and/or forms requesting changes and the IRB's review and approval notifications are provided in the file entitled, "IRB Correspondence for Completed Research Submissions of Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic." The aforementioned SAIRB approval dates are based on page 5 (of 398) of the IRB correspondence file.

Subject Recruitment

Two recruitment firms, J. Reckner Associates, Inc. in Wisconsin and Herron Associates, Inc. in Florida were contracted to recruit potential candidates for these studies. J. Reckner Associates compiled and maintained a list of subjects for Wisconsin and Herron Associates did the same for Florida. A total of 6950-6953 potential candidates served as the initial pool. Using the approved script for the initial phone call, the recruitment firms screened 392 - 395 subjects. Using the approved inclusion/exclusion criteria, and taking into account subjects' availability and interest, the recruitment firms identified and scheduled 170-173 subjects for S.C. Johnson to contact and further screen. There were three additional subjects recruited between 9/10/15 and 9/15/15, so the studies with test days of 9/15/15 and later had a slightly larger pool than those studies whose latest test dates were 9/10/15 and before. 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 studies. This approach was used for all five studies shared with the Human Studies Review Board (HSRB).

For the Mark-8 study, 57 subjects were enrolled. As described on page 13 of the study, the pool of enrolled subjects generally represented the demographics of U.S. repellent users. S.C. Johnson indicated that they made every effort to recruit and schedule subjects to fit the targeted demographics per the protocol. Not all targets were met due to: 1) availability of subjects for the training and test dates; and 2) subjects withdrawing on the training and test day; and 3) subjects not showing up to their scheduled training and/or test dates. A broad range of demographics was still represented in the study looking at the combined demographic data for the human subjects participating in the Florida and Wisconsin testing. Table 5 in the completed study provides the demographics. Table 6, included in Attachment 2 to this memo, summarizes figures on subject recruitment, while Table 7 (also in Attachment 2) summarizes subject participation.

Subject Inclusion/Exclusion Criteria

Consistent with the approved protocol, the following inclusion/exclusion criteria were used for subject selection:

1. Subjects were within the ages of 18-55 and provided proof of age by a driver's license, passport, or other valid identification.

2. Subjects could read and speak English fluently. A percentage of bilingual subjects (English plus another language) were recruited for each study.

3. Subjects were not employees of S.C. Johnson or immediate family members of SC Johnson employees.

4. Subjects had a reliable form of transportation to get to and from the test and training locations.

5. Subjects were willing to be exposed to and potentially bitten by mosquitoes and were not known to be hypersensitive to mosquito bites.

6. Subjects felt they were healthy enough and did not have any health conditions that would make them unable to sit in a chair for long periods, with breaks for limb stretching and movement at reasonable intervals, able to stand continuously for five minutes and be outdoors for several hours where high temperatures, high humidity and sweating were possible

7. Subjects were willing to participate in testing outdoors where high temperatures, high humidity and sweating were possible.

8. Subjects did not have a known sensitivity or allergy to mosquito bites, Elastikon (or equivalent) tape, latex, insect repellents, or skin care products.

9. Subjects were free of skin disease, skin problems, such as eczema, psoriasis, or atopic dermatitis.

10. Subject were willing to refrain from using alcohol 12 hours before the test, and refrain from nicotine, and fragrance products (e.g., soap, perfume, cologne, hair spray, lotion, etc.) during the test.

11. Female Subjects were not pregnant or breast-feeding.

12. Mosquitoes were attracted to subjects' untreated skin.

13. Subjects were users of insect repellent products.

Consent Process

Each potential subject who expressed interest in participating in the study and met the inclusion/exclusion criteria met with the Study Director or Principle Investigator at the scheduled training session. At this session, the subjects were provided with copies of the informed consent document (ICD) and asked to read the entire document. In cases where S.C. Johnson had an email address for eligible subjects, S.C. Johnson emailed the consent form to the subjects in advance of the training session. During the training, after the subjects completed reading the consent form, the Study Director or Investigator asked the

subjects if they had any questions regarding the information in the consent form, the study, and their role in the study. S.C. Johnson answered any questions. If a subject still wished to enroll in the study, he or she was asked to sign their copy of the ICD and the Study Director or Sub Investigator witnessed the signature. S.C. Johnson gave each subject a copy of his or her signed ICD.

Training

The subjects were trained in the skill of aspirating blood-seeking mosquitoes prior to participating in the study. In Wisconsin, training took place in the lab at the S.C. Johnson and Son Inc. Entomology Research Center in Racine, Wisconsin. In Florida, training occurred in the field at Collier Seminole State Park in Naples, Florida.

In Wisconsin, lab-reared female Aedes aegypti (yellow fever mosquitoes) were used. These mosquitoes were from colonies which have been fed only on animal hosts, never on humans, for many years. These mosquitoes were free of any disease-causing organisms which can afflict humans. Ten mosquitoes were released in a 2' x 2' x 2' screened cage with two entry ports. The study staffer demonstrated how to aspirate mosquitoes from their own bare forearm by inserting both arms into the cage, a battery-powered aspirator held in one hand (this forearm was protected by a long sleeve). When a mosquito landed on the staffer's bare forearm, it was observed for the distinctive posture it adopts when preparing to bite. The mosquito was aspirated before it could bite. The same procedure was followed with additional mosquitos.

After the subjects watched at least eight mosquitoes captured in this way by the study staffer, they were asked to try it themselves in the same manner. The study staffer observed these attempts closely and provided guidance as needed. The subjects were given additional mosquitoes to aspirate until the staffer felt that they were sufficiently proficient to participate in the field test. All mosquitoes from this training session were killed by exposure to compressed carbon dioxide and disposed in the trash.

In Florida, an appropriate laboratory site for training was not available. Instead, the subjects underwent training in the field at Collier Seminole State Park in Naples, Florida. This possibility and approach was described in section 8.2 of the approved protocol. The Study Director located an outdoor area where the mosquito landing rate was adequate to supply wild mosquitoes for practice, but not so heavy that trainee subjects were overwhelmed with mosquitoes while learning to aspirate. Both the staff members and test subjects wore bug suits to protect the entire body from mosquitoes and gloves over the hands. A study staffer demonstrated how to aspirate mosquitoes from their suit protected forearm with the battery powered aspirator. When a mosquito landed on the staffer's forearm, it was observed for the distinctive posture it adopts when preparing to bite and the mosquito was aspirated. The same procedure was followed with additional mosquitoes. After the subjects watched at least eight mosquitoes captured in this way by the study staffer, they were asked to try it themselves in the same manner. The study staffer observed these attempts closely and provided guidance as needed. The subjects practiced aspiration

until the staffer felt that they were sufficiently proficient to participate in the field test. No skin was exposed to biting mosquitoes during the training.

Exclusion of Pregnant Women

The pregnancy test was performed by the potential subject alone in a private bathroom. The results were verified by the subject only. After completion of the pregnancy test, a female member of the study staff asked in a private setting if the potential subject is still interested in participating in the study. If they were no longer interested, they did not need to explain why. If the test subject was interested in participating, the results were verified by a female of the study staff in a private manner. The results were kept confidential, were not recorded, and were not disclosed to anyone. The female staff member only notified the Study Director which females were and were not participating in the study. S.C. Johnson confirmed for EPA that pregnancy testing for each study was conducted on the training day in all cases. If the test day occurred more than 48 hours after the training day, the pregnancy test was repeated on the morning of the test day. This was consistent with section 2.3.12 of the approved protocol. No pregnant or nursing female subjects participated in the study.

Mitigation of Hazards

As described in the approved protocol and completed study, there were five types of hazards associated with the study, including: adverse reaction to the test substances; exposure to biting mosquitoes; exposure to mosquito-vectored diseases; general risks of being in the field; and unanticipated loss of confidentiality. Pages 17 – 20 of the completed study describes the precautions taken to mitigate those hazards. Some examples of these precautions are included in this memo and are consistent with the protocol approved in advance of the study.

No subjects with known allergies to mosquito bites were allowed to participate as a test subject. Subjects received specific training on how to remove mosquitoes from their skin before they could be bitten. In addition, test subjects only exposed one forearm for mosquitoes to land. For untreated control subjects who were at greater risk of being bitten, when they received five lands within the 5-minute exposure (the minimum necessary to ensure adequate mosquito landing rate), they covered their exposed limbs by rolling down their sleeve.

In the U.S., mosquitoes can transmit various disease-causing organisms to humans, notably the West Nile virus. All subjects were instructed as to what symptoms of these diseases may look like, so they could seek informed medical care in the very unlikely event they contracted any of these diseases and became symptomatic. To reduce the risk of contracting any mosquito-borne diseases, the study was conducted in areas where the 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 the test date. The Study Director continually monitored for emerging reports of mosquito borne diseases in the area of the test locations prior to the test date and within two weeks following the test date. The

Study Director consulted the USGS, CDC and State Health Department websites to monitor reported mosquito borne disease in areas for the county where the test location resided. Study staff provided food and non-alcoholic beverages on site, and encouraged subjects to drink regularly to keep hydrated. A tent enclosure was provided to keep subjects away from mosquitoes between test exposure periods and shade was also provided to protect them from direct sun. In addition, ample seating was provided to subjects participating in testing. (For the information of the HSRB, the protocol did not explicitly state that seating would be provided to subjects. However, the seating was a positive difference which provided some comfort to subjects and it was implied in protocol section 10.5.2.6 which states that "test subjects will be instructed and reminded on how to properly **sit and stand** during study to not lean on or rest against the treated skin." Furthermore, the approved inclusion/exclusion criteria referenced, in part, that a subject should be able to "sit in a chair for long periods, with breaks for limb stretching and movement at reasonable intervals, able to stand continuously for five minutes...". In the future, EPA will suggest that such information be included in the section on mitigating risk if discomfort from testing will likely occur and the study sponsor offers a solution as S.C. Johnson did in each of their mosquito repellent studies.)

Staff were cognizant of the types of wildlife they may find in the areas where testing was conducted, and moved subjects away from areas where they found potentially harmful organisms, such as fire ants and wasps. Staff also encouraged subjects to perform frequent tick checks to remove any acquired ticks before they had opportunity to bite. No reports of any tick activity occurred during the test. Subjects were told that if anyone experienced any skin reaction, experienced an injury, or simply felt unwell, he or she was to inform study staff right away. Such subjects would immediately be given appropriate care, and could withdraw from testing. As of December 10, 2015, S.C. Johnson had not received any reports of adverse reactions after the test.

Subjects were advised on several occasions that they could withdraw from the study for any reason, without penalty. However, if they chose to withdraw early due to a non-health related reason, they would only be paid for the hours in which they have participated. Page 19 of this study notes that, "In Wisconsin, one control subject withdrew from the test after the fifth exposure interval (4.5 hours post treatment) feeling ill. In Florida, one test subject withdrew from the test prior to treatment of test subjects and an alternate was substituted." S.C. Johnson will amend the latter statement in the report to clarify that one test subject withdrew on training day. Regarding the subject who felt ill, S.C. Johnson provided the following additional information. The test subject contacted the study director after the test day regarding other testing. When the study director asked about his ailments on the test day, "the test subject commented that he just felt ill and that he had helped a friend do work the night before until late and that he was probably over tired. He took some aspirin and went to sleep and felt better afterward."

Follow-up Action by EPA

S.C. Johnson adhered to the protocol with regard to the subject who felt ill. In future draft protocols, EPA will ensure that the protocol indicates that if a subject

feels ill and withdraws from a study, the study sponsor will contact the subject the next day to determine his/her health status.

Confidentiality

The identity of each subject was protected in the following ways consistent with the approved protocol:

- Each subject was assigned a code number;
- Only subjects' code numbers appear on data sheets and in the reports;
- Study records were maintained in locked cabinets and electronic files kept on a password-protected computer server; and
- No one outside of the study sponsor, study staff, the recruitment firm, the IRB, or certain governmental agencies (such as U.S. EPA) will have access to subjects' personal information.

Compensation

Subjects were paid $60 for participating in an approximately 3-4 hour training session conducted prior to the field testing. Test subjects that chose to withdraw or were asked to withdraw from the training session were still paid $60 for attending all or part of the training session. For each field test day, subjects were paid $15 per hour for the test day. If a test day exceeded 8 hours, subjects were paid $18 for each additional hour beyond the first 8 hours, rounded up to the nearest hour. Test subjects who chose to withdraw or were asked to withdraw on the test day were still paid for the hours they participated. All subjects were paid for the hours in which they participated, from the time they arrived on site until the time they departed. The alternates, if they were not needed on the test day to replace an absent or withdrawn test subject, were paid $50.

Protocol Amendments

There was no amendments to the protocol.

Protocol Deviations

Appendix B to the study documents six protocol deviations on pages 112-117 (of 154). EPA identified follow-up actions associated with deviations 1, 4 and 6.

Deviation 1

Section 2.2.3 of the protocol called for the recruitment firm to make initial contact with the potential subjects. A male subject who was used in the study was not initially contacted by the recruitment firm. He was referred to the Study Director by another test subject used in the study. The male recruit was treated the same as if he were recruited via by the recruitment agency. The subject was interviewed via telephone, and completed the consent form and required pre-test training. The late

addition of the male subject allowed for the appropriate number of male to female test subjects.

Follow-up Action by EPA

It's reasonable to expect that subjects might be referred by other test subjects who participate in studies. For that reason, in future draft protocols for repellent studies, EPA should address this in the recruitment or other appropriate section.

Deviation 4

Page 115 of the completed study describes deviation 4 as follows:

"Test Substance Application Rate Data Sheets:

a. Subject 207: The measurement for the upper left arm is 28.5 cm, and subsequent calculated dose was 0.83g. The measured value from original raw data sheet looks like 23.5 cm and not 28.5. Using this value (23.5) in the dose calculation, the target dose amount would have calculated out to be 0.78g.

b. Subject 219: The measurement for the lower arm is 16 cm. and subsequent calculated dose was 1.05g. The measured value from original raw data sheet is 18 cm. Using this value (18) in the dose calculation, the target dose amount would have calculated out to be 1.07g."

Follow-up Action by EPA

OPP scientists confirmed that the incorrect dose would not have affected the health and safety of the subjects. However, EPA will follow-up with the study sponsor to reiterate the importance of ensuring that correct arm measurements are clearly and accurately documented in future studies so that correct doses are calculated and administered to subjects. EPA will ask the study sponsor to identify safeguards that can be put in place to address this.

Deviation 6

Page 117 of the study describes deviation 6 as follows:

"Section 10.6.6 called for the first exposure to be 3 hours post treatment for DEET formulas with an active ingredient amount of 16.0% and above. There was only a 2 hour post treatment delay before the first exposure for this study." Subsequent to their study submittal to EPA, S.C. Johnson corrected their section on "impact on the study/results" to read: "There was no negative impact on the results of the study by having two extra data collections added to the start of the exposures."

Follow-up Action by EPA

The subjects were exposed to mosquitos 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.

The deviations listed in the report did not negatively affect participants' rights or their health or safety. However, EPA has identified follow-up actions in response to each deviation. S.C. Johnson adhered to the IRB instructions and protocol regarding documentation of deviations. As stated in section 13 of the protocol, "The amendments, deviations, as well as any adverse events will be documented in the Study Director's final report. Documentation will include a description of the change, the reason for the change and the effect of the change on the conduct and outcome of the study."

Regulatory and Statutory Standards

The following provisions of 40 CFR 26 Subpart Q, as amended, define the applicable ethical standards, which read in pertinent part:

> §26.1703: Except as provided in §26.1706, EPA must not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> §26.1705: Except as provided in §26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with all applicable provisions of subparts A through L of this part.

In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) applies. This passage reads:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

Findings

Prior HSRB and EPA Review

Because this study was initiated after April 7, 2006, prior submission of the protocol and supporting materials to EPA was required by 40 CFR §26.1125. The requirements of 40 CFR §26.1125 for prior submission of the protocol to EPA and of

§26.1606 for HSRB review of the protocol were satisfied. The study protocol was approved by the SAIRB prior to submittal to EPA. The HSRB discussed the protocol at its April 22-23, 2014 meeting, and concurred with EPA's assessment that the protocol, if revised as suggested by the Agency and the HSRB, would meet the applicable requirements of 40 CFR part 26, subparts K and L.

Responsiveness to HSRB and EPA reviews

EPA's and the HSRB's ethics comments on the protocol were addressed before the research was conducted. Please see Attachment 3 for details.

Prohibition of research involving intentional exposure of pregnant or nursing women or of children

All enrolled subjects were at least 18 years old and there were no pregnant or nursing female subjects. The prohibition in 40 CFR §26.1703 of research involving intentional exposure of pregnant or nursing women or of children under age 18 was satisfied.

Substantial compliance with 40 CFR 26 subparts A through L

40 CFR §26.1705 requires that EPA not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with all applicable provisions of subparts A through L of this part. Within this range, only subparts K and L are directly applicable to the conduct of third-party research such as this. The study documents substantial compliance with subparts K and L.

Compliance with 40 CFR 26 subpart M

As documented in Attachment 1 to this review, the central requirements of 40 CFR 26 subpart M, §26.1303 to document the ethical conduct of the research were satisfactorily addressed.

Compliance with FIFRA §12(a)(2)(P)

The requirement of FIFRA §12(a)(2)(P) that human subjects of research be "fully informed of the nature and purposes of the test and of any physical and mental health consequences reasonably foreseeable therefrom," and "freely volunteer to participate in the test," was met for this study.

EPA Conclusion

The study entitled, "Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support their Use of the EPA Repellency Awareness Graphic" for test substance MARK-8 describes research conducted in substantial compliance with the applicable requirements of 40 CFR 26, subparts K and L. The conduct of the study met all

applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied.

With regard to lessons learned, in future draft protocols, EPA will ensure that the protocol indicates that if a subject feels ill and withdraws from a study, the study sponsor will contact the subject the next day to determine his/her health status. Also, it's reasonable to expect that subjects might be referred by other test subjects who participate in studies. For that reason, in future draft protocols for repellent studies, EPA should address this possibility in the recruitment or other appropriate section. EPA will also follow-up with the study sponsor to reiterate the importance of ensuring that correct measurements of forearms are clearly and accurately documented in future studies so that correct doses are calculated and administered to subjects. EPA will ask the study sponsor to identify safeguards that can be put in place to address this in future studies. Finally, for future studies, EPA will request that the study sponsor ensure adherence to the appropriate start time for first exposures consistent with the protocol.

If this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA reliance on it in actions under FIFRA or §408 of FFDCA.

Attachment 1: §26.1303 Completeness Checklist
Attachment 2: Tables 6 and 7 from Completed Study
Attachment 3: Responsiveness to EPA and HSRB Ethics Comments on Draft Protocol

Attachment 1
§ 26.1303 Checklist for Completeness of Reports of Human Research Submitted for EPA Review

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

	Requirement	Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.	Y n/a Y n/a	The IRB-approved protocol and consent form were previously reviewed and commented on by the Human Studies Review Board (HSRB).
	§1115(a)(2): Minutes of IRB meetings which shall be 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	Minutes were previously provided to EPA and HSRB members when the protocol was submitted for review. Minutes for IRB meetings on 2/3/15 and 7/7/15 are provided in Volume 2- IRB Correspondence for Completed Research Submissions of Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic, D. Hollas, Sept. 28, 2015, 398 pages.
	§1115(a)(3): Records of continuing review (CR) activities.	n/a	According to the SAIRB, the CR will occur in February 2016.
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	Y	WIRB correspondence provided in a separate file to the HSRB. Please see Volume 2 –IRB Correspondence for Completed Research Submissions of Field Testing of S.C. Johnson (SCJ) Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic, D. Hollas, Sept. 28, 2015, 398 pages. Note that this Volume 2 was submitted along with the completed study for Test Substance MARK-2, GLP study 864E1. However, Volume 2 applies to all SCJ studies which followed protocol no. 90017040. Relevant pages in Volume 2: 5, 102-105, 117-121, 124-137, 161-180, 373-398.
	§1115(a)(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	Y Y	Previously provided to HSRB members with the protocol. Updated information was included in a separate file provided to HSRB members with the completed study. See Volume 2 (with title identified in cell above). Please see pages 373-374.
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).	Y	Previously provided to EPA.
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).	n/a	

Requirement			Y/N	Comments/Page References
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	Discussed in consent form and section 2.8 of revised protocol. Please note that the revised protocol is attached to and submitted with each completed study.
		(2) The measures proposed to minimize risks to the human subjects;	Y	Discussed in consent form and section 2.8 of revised protocol.
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	Discussed in consent form and section 2.9 of revised protocol.
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Discussed in consent form and section 2.1 of revised protocol discusses rationale for human subjects.
		(5) The balance of risks and benefits of the proposed research.	Y	Discussed in revised protocol including section 2.9.
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Provided in separate file to EPA and HSRB.
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	Section 2 of revised protocol.
	§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	Revised consent form, and section 2.4 of revised protocol.
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	Separate file provided to HSRB with requests sent to IRB and responses.
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.		Y	See Volume 2 provided to HSRB.
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	Revised consent form approved by IRB was provided to HSRB.
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.			n/a	

Attachment 2 – Table 6 –Subject Recruitment Summary (as of 9/18/15)

Number of subjects initially contacted by recruitment firms	6950
Number of subjects interviewed by recruitment firms	392
Number of subjects screened by SCJ study staff	170

Table 7 Summary of Test Participation in GLP Study 873E1

At EPA's request, S.C. Johnson provided an updated Table 7 including the state-specific information and any corrections to total figures. New information is provided in red type.

GLP 873E1 - 4822-167	Wisconsin	Florida	Total
Number of Subjects Enrolled	22	35	57
Number of No-Shows to training and/or testing	No-shows for training: 2 No-shows for testing: 0	No-shows for training: 18 No-shows for testing: 0	20
Number Assigned as Test Subjects	12	12	24
Number Assigned as Alternates or Extras	4 alternates 4 extras	4 alternates 0 extras	12 (Note to HSRB: In the study, the table cited 11.)
Number of Test Subjects Withdrawn Voluntarily	1 on test day (post-treatment)	1 on training day	2 ** (Note to HSRB: In the study, the table cited 1 as a typo. However, it should be 2, 1 on training day and 1 post-treatment on test day.)
Number of Test Subjects Withdrawn Involuntarily	0	0	0
Number of Test Subjects Completed Research	11	12	23 ** (Note to HSRB: In the study, the table cited 24**.)
	In Wisconsin: 12 test subjects (10 treated and 2 controls) and 4 alternates were randomly selected as described in the report out of the pool of 20 trained participants.	In Florida: Only 16 trained participants were available on this test day. 12 test subjects (10 treated and 2 controls) and 4 alternates were selected as described in the report out of the pool of 16 trained participants.	

**post-treatment withdrawal was previously considered as 'completing research' instead of 'withdrawn'

Notes for HSRB:

Table 6

The numbers listed in Table 6 in each of the ethics and science review memos are accurate for each of the studies.
S.C. Johnson highlighted for EPA that there were 3 additional test subjects recruited between 9/10 and 9/15, so the studies with test days of 9/15 and later had a slightly larger pool than those studies whose test dates were 9/10 and before.

Test Subject who Withdrew Voluntarily

As discussed on page 19 of the study, one test subject withdrew 4.5 hours post treatment. S.C. Johnson provided additional explanation regarding this as follows: "This test subject did contact the study director after the test day regarding other testing. The study director did ask about his ailments on the test day. The test subject commented that he just felt ill and that he had helped a friend do work the night before until late and that he was probably over tired. He took some aspirin and went to sleep and felt better afterward."

Table 7

Table 7 includes a reference to "number assigned as alternates or extras."

At EPA's request, S.C. Johnson provided the following explanation of "extras."

> "'Extras' was the term we used for individuals who attended training but were not randomly selected as a treated subject, untreated control, or alternate. If we had more than 16 people complete training, there would be extra individuals not needed for the test. The extras would have signed the consent form and would have been paid for their attendance at the training session, the same as all other participants attending training. Extras were not requested to show up on test day."

Error on page 19 of MARK-8 Study that's corrected in Table 7

Also, there is a statement on page 19 of the report that “In Florida, one test subject withdrew from the test prior to treatment of test subjects and an alternate was substituted.”

S.C. Johnson noted that this was a “transcription error.” The test had four alternates and all were female. The participant in question withdrew from training before being assigned as a treatment, control, or Alternate subject. S.C. Johnson will amend the report to state that in Florida one test subject withdrew on training day. This is noted in table 7.

Attachment 3 – S.C. Johnson Mosquito Repellent Completed Studies -

Responsiveness to EPA and HSRB Ethics Comments on Draft Protocol

	Comment from EPA and/or HSRB	Action taken by Study Sponsor
1.	Please revise the benefits section of the Informed Consent Form as follows: *"You will not personally benefit from this study~~, other than the financial compensation~~."* The proposed payment to subjects is considered compensation for lost time and inconvenience, not a benefit of participating in the research. This study provides no direct benefits to subjects.	The study sponsor addressed this comment and deleted the requested language on page 9 of the IRB-approved final consent form (dated July 10, 2015). (Volume 2 to the study for test substance MARK-2 provides the IRB correspondence that impacts all of the completed studies based on the same protocol. The final consent form can be found in Volume 2, on pages 84-94 of 398. Volume 2 is entitled IRB Correspondence for Completed Research Submissions of Field Testing of S.C. Johnson (SCJ) Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic, D. Hollas, Sept. 28, 2015, 398 pages.)
2.	Johnson should inquire with the recruiting firm about the demographics of the volunteer pool from which subjects will be recruited, and provide additional details in the protocol to support the statement that the pool of subjects will be demographically and ethnically representative of the population in the area where the field testing will be conducted. The pool of subjects should also be representative of the overall population of concern, which is repellent users in the United States.	The study sponsor addressed this comment in the expanded section 2.2.3 of the protocol which includes additional details.
3.	The protocol excludes Johnson employees from becoming subjects. Please amend the protocol and consent form to also exclude immediate family members of Johnson employees.	As requested, the study sponsor excluded family members on page 3 of the final IRB-approved consent form (dated July 10, 2015).
4.	Johnson should consider whether additional stopping rules should be added to the protocol. Examples of conditions which	The study sponsor expanded the language in protocol section 11.2.6 to address this comment. The sponsor added the following

	may be appropriate to trigger a stop to the research (either for an individual participant or for the whole study) include: mosquito landing rate falls below threshold needed to challenge test material, wind speeds exceed a certain level, subject asks to withdraw, subject exhibits hypersensitivity to insect bites, subject exhibits sensitivity to the test material, medical management is invoked. The first two examples would apply to the entire study; the other examples would apply to an individual subject.	language: "If the test subjects asks to withdraw, if any adverse reactions or sensitivity such as redness, edema, itching, or pain to the test substance are observed or reported, subjects exhibit hypersensitivity to insect bites and/or any medical management is needed, the test subject will be removed from the test immediately."
5.	The protocol and consent form must explain how compensation will be handled if a potential subject participates in the consent meeting, the training meeting, and/or the pregnancy testing, but then ultimately decides not to participate in the research.	The study sponsor addressed this comment. In section 2.2.6 of the protocol, the sponsor added the following language: "Test subjects that choose to withdraw or asked to withdraw from the training session will still be paid $60.00 for attending all or part of the training session." In section 2.2.7 of the protocol, the sponsor added, "Test subjects that choose to withdraw or are asked to withdraw from the study on the test day will still be paid for the hours which they participated on that test day (however, this will not affect payment for any previous test days in which the subject may have already participated)." The same topics were addressed in the compensation section in the final consent form. Finally, these topics were also addressed in sections 12.2.5 and 12.2.6 of the final study.
6.	The protocol and consent form should be revised to include details about whether subjects will be transported by the researchers to and from the testing site. If the testing site is remote, and if Johnson intends to transport the subjects to the testing site, then Johnson should make arrangements to transport any subjects who withdraw back to the starting location within a short period of time after that subject indicates his or her desire to withdraw. If Johnson cannot make such arrangements, then a subject who withdraws should be paid for all of the time spent at the study site, even if he or she has chosen	The final consent form was updated to state: "You must have a reliable form of transportation to get to and from the test and training locations. You are responsible for your own transportation to the [and] from the training and test site locations." Section 2.3.4 of the final protocol was expanded to state, "Subjects are responsible for their own transportation to and from the training and test site locations."

	to withdraw early. Not compensating a subject for this type of time and inconvenience could unduly influence him or her to continue participating.	
7.	The protocol provides that the entire consent document will be read aloud to potential subjects during the consent meeting. Given that the ability to read English is a requirement to participate, Johnson should offer subjects the option of reading the consent form themselves. If Johnson wishes to confirm understanding of the consent form, Johnson should draft several questions to be asked of each potential subject prior to them signing the consent form, and those questions should be included in the revised materials that are reviewed by SAIRB before the study is initiated.	The study sponsor revised section 2.4.1 of the protocol to include the new language underlined below: "Prior to participating in any aspect of the test, each potential subject who has expressed interest in participating in the study and has met the inclusion/exclusion criteria will meet with the Study Director or Principle Investigator at the scheduled training session. <u>At this session, the subjects will be provided with copies of the Informed Consent Document and will then be asked to read the entire document</u>." In addition to the revision to section 2.4.1 noted above, section 2.4.2 was also revised to state *"After the potential subjects have completed reading the consent, The Study Director or Principle Investigator will ask the subjects if they have any questions regarding the information in the consent form, the study and their role in the study. Any questions will be answered."* In addition, the screening document was revised to make it clear that the subjects could request a copy of the consent document in advance for their review. S.C. Johnson confirmed that, since most of the test subjects asked for a copy of the consent document at this point, their practice was to send the consent form via email to all eligible test subjects. Given the changes above, it was determined that additional questions to confirm understanding of the informed consent document were not necessary; all test subjects could read and speak English, all test subjects were given ample time and opportunity to read the consent form and ask questions about it, and study staff asked each test subject if they

		had any questions about the consent document. Any questions were answered.
8.	The protocol should discuss whether the number of repeat tests per person should be limited. There should be some plan to follow-up with subjects after their participation in the study has ended to check for any delayed consequences of study participation. This could consist of a phone call to check on health status.	The protocol did not limit the number of repeat tests per person. S.C. Johnson provided the following explanations: a. All products which are subject to this protocol are registered by EPA and have been previously evaluated for safety. b. There were and are no anticipated hazards from repeated use. c. Since the protocol dictated that a minimum of two full calendar days would occur between treatments, it was not expected that residual active ingredient would be present in a later study. d. The protocol called for exposure to be controlled by exposing the test subjects to no more than the typical use rate. e. Exposure was further minimized by instructing each participant to wash their treated limb at the conclusion of the study. f. Test subjects were monitored during the study, so if an adverse reaction was noted, they could be removed from the study and avoid subsequent exposure. As of December 10, 2015, S.C. Johnson had not received any reports of adverse reactions after the test. The study sponsor expanded protocol section 11.2.4 to state, "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." This statement follows the pre-existing language that, "Subjects will be informed both verbally and in writing of any significant new findings, such as detection of

		mosquito borne disease in the area or product contamination, discovered during the course of the testing which may influence their continued participation." Section 11.2.8 was expanded to state, "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." Language was already included in protocol section 11.2.9 and in the consent form providing a 24 hour contact number that test subjects could use for any research-related issues or concerns. Follow-up was deemed necessary only if S.C. Johnson came into possession of new information about which the test subjects should be notified consistent with the protocol. On the topic of following up with subjects, prior to S.C. Johnson finalizing the protocol, OPP told S.C. Johnson that the expanded information described above was sufficient.
9.	The protocol team should provide a process to contact subjects in the unlikely event that new information is developed or discovered as a result of the study, for example, if mosquitoes were discovered with vector-borne disease or if a contaminated product was identified.	The study sponsor expanded protocol section 11.2.4 to state, "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." This statement follows the pre-existing language that, "Subjects will be informed both verbally and in writing of any significant new findings, such as detection of mosquito borne disease in the area or product contamination, discovered during the course of the testing which may influence their continued participation." Section 11.2.8 was expanded to state, "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."

		Protocol section 2.8.2.5 was also expanded to further reduce the risk of contracting any mosquito-borne disease and include the following language: "The study director will consult USGS, CDC and State health department websites that provide data on occurrences of mosquito borne disease by state and by county in each state. The study director will contact local State Health Departments to inquire about cases of mosquito borne disease if information cannot be found on the website and will contact Mosquito Control Districts to inquire about cases of mosquito borne disease if available in the county of the test location. In the event that testing occurs outside of the U.S., similar resources for determining the presence of mosquito borne disease, such as the Queensland health Website, will be consulted prior to any international testing."
10.	The protocol team should provide a justification, in the protocol or IRB documents, for excluding non-English speakers, especially at the Florida site where Spanish-speakers are a significant proportion of the population; or if no justification for exclusion is provided, the protocol should be amended to include Spanish speakers. In order to assess the representativeness of the study population, the protocol team should provide to EPA general information on population demographics of subject pool at each site, and some information about recruitment strategies. This is particularly important if alternate sites located outside of the U.S. are used.	The revised protocol addressed this comment. The original section 2.2.3 of the protocol did not provide details on the demographic targets. The revised section 2.2.3 provides details on the demographic targets. With regard to the requested justification language, the protocol was revised to state: "This pool will generally represent the demographics of US repellent users. Current repellent product labels are in English, so to target users familiar with and that understand the product labels, we will be recruiting English speaking subjects. This research does not offer benefits to the subjects, so limiting recruitment to English speakers does not result in equity-of-access issues. In addition, the language that someone speaks does not directly affect attractiveness to mosquitos. SCJ will target recruiting a minimum of 10% bilingual (English and another language) to help not restrict recruitment to only English speakers." After this language, the revised protocol includes 2015 Neilson data related to U.S. repellent users.

11.	The Board discussed two additional aspects of the study that could benefit from clarification. The Board expressed concern regarding the statement in the consent document that care and compensation for injury would be handled similar to a workers compensation claim. It was not clear if this was an appropriate mechanism for care and compensation in a research study. The consent form states "This study is considered confidential." The Board questioned whether this is intended to refer to data collected on individual subjects or whether the details of the study should not be disclosed or discussed with others.	In the consent form, the study sponsor deleted the worker compensation claim language that concerned the HSRB and revised the applicable section to read as follows: "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. If you believe you may have suffered any physical or mental side effects as a result of your participation, please contact the Study Investigator using the phone number on page 1 of this document. 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 doctor, the study staff, or study site from liability for mistakes or intentional misconduct by signing this consent document." Regarding confidentiality, the study sponsor clarified the consent form in response to the comment. The sentence in question stated that, "This study is considered confidential." After this sentence, the study sponsor clarified that "The details of the study should not be discussed or disclosed with others not involved with the study. All data collected on individual subjects is also confidential." (This is included on page 93 of 398 in Volume 2.)