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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

May 24, 2010

SUBJECT: Science Review of Human Study of Black Fly Repellent Performance

FROM: Kevin J. Sweeney, Senior Entomologist
Insecticides Branch
Registration Division (7505P)

TO: Marion Johnson, Chief
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RE: Carroll, S. (2010) Efficacy Test of KBR 3023 (Picaridin; Icaridin)-based Personal Insect Repellents (20% Cream and 20% Spray) with Black Flies under Field Conditions. Unpublished study prepared by Carroll-Loye Biological Research under Project No. LNX-002. 331 p. (MRID 48053802)

ACTION REQUESTED

Conduct a science review of a completed black fly field study. Determine the adequacy of the methods employed and the scientific validity of the reported data. These data were required by the EPA as a condition of registration for EPA Reg. No. 39967-50 KBR 3023 All-Family Insect Repellent Cream (20% picaridin cream) and EPA Reg. No. 39967-53 KBR 3023 All-Family Insect Repellent Spray (20% picaridin pump-spray).

CONCLUSIONS

Scientific aspects of the research were assessed in terms of the recommendations of the draft EPA Guidelines §810.3700 and of the EPA Human Studies Review Board. Study MRID 48053802 was conducted in accordance with Good Laboratory Practices as described in 40 CFR §160, and provides scientific data that are acceptable. The Human Studies Review Board will be asked to comment on this study.

SCIENCE REVIEW

Study Objectives: To determine the Complete Protection Time (CPT) of two registered insect repellent formulations containing picaridin against adult black flies under field conditions. The study shall establish the mean time to first confirmed landing for each formulation under field conditions.

Materials & Methods:

Study locations: One field study in Southeastern California was used in this study. The site was an open landscape of Mojave Desert shrub and herbaceous plants as well as irrigated hedgerow plantings.

Study Dates: Dosimetry testing was conducted on September 26-30, 2009 in the Arthropod Behavior Laboratory at Carroll-Loye Biological Research. Repellent product tests were conducted on March 20, 2010.

Repellents Tested: The repellents tested were conditionally registered products EPA Reg. No. 39967-50, KBR 3023 All-Family Insect Repellent Cream (20% picaridin cream – Repellent 'A'), and EPA Reg. No 39967-53, KBR 3023 All-Family Insect Repellent Spray (20% picaridin pump-spray –Repellent 'B').

Tested positive control/comparison repellent: There was no positive control in this study.

Untreated Control: Two experienced negative control subjects (one male and one female) established and monitored the ambient Landing with Intent to Bite (LIBe) pressure at the same intervals as for repellent exposure; one minute every 15 minutes. There were no statistical comparisons to the untreated controls.

Black fly species and life stage: Repellents were evaluated against the adult life stage of the black fly, *Simulium vittatum*. Black fly collections were identified by the Study Director.

Number of Test Subjects/Treatment Regime: A total of 25 subjects (selected from a pool of 119 subjects diverse in age and ethnicity) participated in this study. All subjects were found to be attractive to black flies. There were 15 test subjects (8 female and 7 male) in the dosimetry phase. Twenty treated subjects and two untreated subject participated in the test phase with three more subjects serving as alternates. In the test phase, ten subjects participated in each product treatment test on each day.

Protocol used including amendments: Protocol LNX-002 (amended), dated August 13, 2009 begins on p.162. Amendment 1, dated August 13, 2009, begins on p. 225. This amendment fully addressed the EPA's comments in its review of the protocol, and responded to HSRB comments at the meeting in June 2009.

Protocol Deviations: One protocol deviation, dated April 1, 2010 is reported beginning on p. 260. The deviation resulted from the use of an older version of a data capture form instead of the intended version. This deviation had no effect on data quality or subject safety.

Dosimetry: The standard dose used for the spray product was based on dosimetry testing with the same materials reported in study LNX-001. The standard dose used for the cream product was determined by pooling data from study LNX-001 with additional dosimetry data collected as described below. These data were collected at the request of the sponsor to improve the accuracy of the dosing rate for the cream product. Data for the cream product

collected from 10 subjects in LNX-001 were supplemented by dosimetry data collected from the arms and legs of 15 unique subjects in this study. The mean arm and leg dosimetry data for each of the 15 subjects were pooled with the mean arm and leg data for each of the 10 subjects from LNX-001. The dose rate for this study was based on the grand mean calculated from those values expressed in weight per unit area then converted to volumetric doses.

Dose rates: Volumetric dose rates were expressed in micro-liters per square centimeter of treated skin (µl/cm^2). The dose applied to each subject was calculated based on the measured skin area of the treated limb, and was reported in milliliters (ml). Volumetric doses were converted to mass doses expressed in milligrams using the specific gravity of formulations—0.98 for lotion, and 0.96 for spray. For the spray product each subject received 0.97µl/cm^2 of product, equivalent to 0.9312 mg product/µl. For the cream product, the volumetric dose rate was 1.94µl/cm^2, equivalent to 1.9012 mg product/µl. Because both products contain 20% picaridin, the average picaridin dose was 1/5 the average product dose. For the spray product the mean picaridin dose was 98 mg per subject and 202 mg/subject for the cream product. MOE calculations were based on an assumed 70 kg subject and the acute dermal LD_{50} value for picaridin at the limit dose of greater than 2,000 mg/kg. For the cream product the MOE = 690 and for the spray product the MOE = 1429, both values exceed the target MOE = 100.

Experimental design: The experimental design was very similar to recent Carroll-Loye Biological Research studies. Ten subjects each were randomly assigned to one of two repellent treatments at the site for a total of ten subjects per treatment. Each treatment was applied to an equal number of males and females. The sample size of ten treated subjects per test material per field trial is larger than is required by EPA guidelines —large enough to ensure robust averages across subjects.

Repellent doses were prepared for each subject based on the surface area of the limb to be treated. In each case, half the subjects on the test date were treated on the right arm and the other half on the left arm. Subjects were treated approximately 2.5 hours before field exposure. Untreated control subjects and subjects treated with repellent were exposed to black flies for one minute every 15 minutes until the repellent failed. Subjects were protected from black flies between exposure periods in a screened enclosure. Treated subjects were partnered in groups of two and each partner monitored the front of their own exposed forearm and the back of their partner's forearm. Black flies landing with intent to bite (LIIBe) were recorded, aspirated into containers, and identified in the laboratory. No other flying insects were detected in the field trial. Abiotic factors were recorded hourly and included temperature, wind speed, relative humidity and light intensity data.

Black fly disease pathogen detection: Assays for pathogens were not conducted because black fly transmitted diseases are not endemic to the United States.

Data analysis: Subjects remained in the test until the repellent failed as determined by the First Confirmed Landing with Intent to Bite (FCLIBe), or until the end of the test period, whichever came first. The time at which the repellent failed equaled the Complete Protection Time (CPT), and a CPT was recorded for each subject. The CPT for treated subjects where

product failure did not occur equaled the test period length. Collected data were analyzed by Kaplan-Meier survival analysis. Mean CPT for each repellent was reported as mean CPT $\pm$ sd with the respective 95% confidence interval; and the Kaplan-Meier median CPT values were reported. An estimate of time to 25% failure for each test product was also calculated. The mean number of landings with intent to bite (LIBe) was also reported for each product treatment. Kaplan-Meier survival plots are presented in Figures 1 and 2 of the study.

Results:

Eleven of the 20 subjects experienced a Confirmed Landing with Intent to Bite (CLIBe). Mean CPT values were reported because the 1999 repellent guideline calls for them, but the K-M medians and the reported time to 25% failure provided undistorted summary statistics, which better characterize the duration of protection provided.

Table 1 below summarizes the results of the field test. The mean CPT values were not significantly different for both products equaling 9.9 h. Median CPT values were calculable for both products and were nearly the same, 10.1 h for the cream product and 9.8 h for the spray product. The mean LIBes per subject was 1.4 for the cream and 1.9 for the spray. Despite a trial lasting nearly 12 hours, six subjects in this test did not experience any Landings with Intent to bite (LIBe).

Table 1: Repellent Field Trial Results
(See Tables 6, 7, 8, 9 and Figures 1 and 2 in MRID 48053802)

	Reg No. 39967-50 Cream 20%	Reg No. 39967-53 Spray 20%
Mean CPT ± sd (95% CI)	9.9 ± 2.0 h. (8.5 – 11.4 h)	9.9 ± 1.5 h. (8.8 – 11.0 h)
Kaplan-Meier Median CPT	10.1 h	9.8 h.
Time to 25% failure	9.1 h	9.1 h.
Mean LIBes per subject	1.4	1.9

Conclusions:

The methods employed in these studies were adequate to produce scientifically reliable data. They were based on study protocol LNX-002 as amended in accordance with EPA and HSRB recommendations before testing began. Both products provided a high degree of repellency against adult black flies. The reported protocol deviation was non-substantive in nature and did not affect the design or conduct of the research, or the resulting data.

Recommendation: The study is scientifically sound and acceptable.

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