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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 29, 2009

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

FROM: Kevin J. Sweeney
Science Reviewer

TO: Marion Johnson, Chief
Insecticides Branch, RD

RE: Gaynor, W. (2009) Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin) Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory. Unpublished study dated April 3, 2009, with supporting materials, prepared by ICR, Inc., under Protocol No. G4330108001A382 and Sponsor Project No. 0108-433-0161. 268 p. (MRID 47732701)

Gaynor, W. (2009) Chronology of Lanxess Stable Fly Repellent Protocol Approvals by the Essex Institutional Review Board (MRID 47734901). Unpublished supplemental report to MRID 47732701 dated April 22, 2009.

ACTION REQUESTED

Conduct a science review of a completed stable fly laboratory study. Determine the adequacy of the methods employed and the scientific validity of the reported data. The study determined the repellent efficacy of two conditionally registered products containing picaridin against the stable fly, *Stomoxys calcitrans* L., in the laboratory. The study established the mean and median times to the first bite for each formulation to support label claims of repellency against stable flies. These data were required by the EPA as a registration condition for the following products: 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 47732701 was conducted in accordance with Good Laboratory Practices as described in 40 CFR §160, and provides scientific data that are acceptable. Based on the experimental results, KBR 3023 Insect Repellent Cream repelled stable flies for 4.5 hours while KBR 3023 All-Family Insect Repellent Spray repelled stable flies for 6.3 hours. 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 stable flies under laboratory conditions and to establish a typical consumer dose for each product, to be used as the standard dose in the efficacy phase. The study shall establish the mean and median times to first bite for each formulation under laboratory conditions.

Materials & Methods:

Study locations: The study was conducted in the laboratory of Insect Control and Research, Inc. located at 1330 Dillon Heights Avenue in Baltimore, Maryland.

Repellents Tested: The repellents tested were EPA registered products consisting of 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). The amount of each product applied to the arms of the test subjects was based on the mean dose for each product as determined by the dosimetry phase. The repellency test phase took place on December 9, 2008.

Dosimetry Phase: The dosimetry phase was conducted on September 18, 19, 23, 24, 26, 29, and 30, 2008 and on October 2, 2008. Thirteen test subjects applied the test product to a 250 cm^2 area of their arm. A 50 cm^2 piece of tape was attached to the center of the forearm before treatment. The tape was waterproof but had an absorbent top layer. The tape was weighed before and after treatment to determine the application rate in cm^2. The cream was applied to one arm and the pump-spray to the other. This dosimetry test was repeated three times to yield a total of 33 replicates for each product. The mean application amount was calculated for each subject for each product. A grand mean of the dose for each product was calculated by averaging the thirteen subject means. The application of picaridin products, when expressed in terms of µl per cm^2 of skin surface, was greater for the pump-spray product when compared to the cream product. The dosimetry results are summarized in study Table 3 on page 12 of MRID 47732701.

Tested positive control/comparison repellent: None

Number of Test Subjects/Treatment Regime: A total of 13 subjects participated in this study. There were twelve test subjects (seven male and five female) in the dosimetry phase. In the test phase, twelve subjects participated in each product treatment test while one served as the untreated negative control.

Untreated Control: One subject was selected to be the negative control by a drawing of numbers. One untreated arm of the control subject was used to establish the aggressiveness of each cage of 50 stable flies.

Protocol used including amendments: Protocol No. G4330108001A382 was used as amended on November 10, 2008. The amended protocol can be found in Appendix II of the study MRID 47732701.

Protocol Deviations: None

Experimental design: In the repellency phase, the products were applied at the dose resulting from the dosimetry phase. This treatment regime was adequate to produce reliable data. Repellency evaluations were based on the Time to First Bite test. This procedure required require both of the subject's forearms be exposed in a cage containing 50 adult stable flies for 5 minutes every 30 minutes for 10 hours, or until the first bite occurred on both arms, which came first.

Protocol Amendments: The protocol reviewed by the HSRB dated February 1, 2008, was amended three times and each amendment was approved by the Essex IRB. The science related amendments were: 1) stable fly density increased from 25 to 50 flies; 2) the interval for stable landings on a subject's arm when determining subject acceptability was increased from one minute to two minutes; 3) stable flies were only replaced in the cages where the negative control did not receive an acceptable landing rate instead of replacing all six cages every 30 minutes; 4) stable flies were reared on sugar cubes instead of 10% sucrose solution to avoid overfeeding; and 5) water and sucrose were withdrawn for 24 hours before testing to ensure that the flies would be hungry and likely to bite in repellent tests.

Data analysis: The time at which the repellent failed (Time to First Bite) 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 when calculable. The study director made a concise but sound argument for the duration and sample size justification in this. It should be noted that the data reviewed and analyzed by Rutledge and Gupta (1999) were mosquito repellency studies. As a result, ICR reviewed their own database of stable fly repellent studies from 1990-99. An ICR analysis of nine stable fly tests conducted in their laboratory from 1990 to 1999

indicated that use of landings would significantly underestimate protection time when compared to bites. Based on these data, they also concluded that a sample size as small as seven subjects could be used. However, they opted for the more conservative approach to reduce uncertainty and insure statistical reliability by using a sample size of 12. If the repellent lasted for 10 hours on all subjects, the researchers would have concluded that the product was effective for eight hours ±2 hours. An ICR analysis of 9 stable fly tests conducted in their laboratory from 1990 to 1999 indicated that use of landings would significantly underestimate protection time when compared to bites. The statistical analyses are fully described in Appendix IV of MRID 47732701.

Results:

Results were reported in table form. As presented in Table 1 below lists the mean CPT values for both products with their associated standard deviations. The Median CPT value was nearly the same as the mean CPT value for the 20% spray but there was a one hour difference between the mean and median values for the 20% cream.

Table 1
Repellent Laboratory Test Results with Stable Flies
(See Table 4 on page 14 and Appendix IV of MRID 47732701)

	EPA Reg. No 39967-53 (20% picaridin cream) (3.551 µl/cm^2)	EPA Reg. No. 39967-50 (20% picaridin spray) (4.125 µl/cm^2)
Mean CPT $\pm$ SD (hrs)	4.5 +2.0 (2.5.-7.0)	6.3 $\pm$ 2.0 (4.3 – 8.3)
Median CPT (hrs)	5.5	6.5

Based on the dosimetry data the application of picaridin, when expressed in terms of µl/cm^2 of skin surface, the dose of the spray product was approximately 15% higher than the cream product in this study. There was considerable variability in the amount applied by the test subjects during the dosimetry phase. Compared to the other ICR studies for mosquitoes, the application volume was higher. Subjects in ICR tests appear to apply more product than those in the studies conducted by Carroll-Loye Biological Research. The explanation for this difference is unclear but it is probably associated with variation in perception among the US population of what a typical or adequate dose of a skin applied repellent is.

Discussion

The methods employed in these studies were adequate to produce scientifically reliable data. They were based on study Protocol No. G4330108001A382 as amended on November 10, August 21, and June 12, 2008, in accordance with EPA and HSRB recommendations before testing began.

Conclusions

The data collected from this experiment show that 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) provided a mean CPT of 4.5 hrs. and 6.3 hrs, respectively, against stable flies under laboratory conditions.

Recommendation: The study is scientifically sound and acceptable.