12/16/2009 Final Report of October 2009 HSRB Meeting
Excerpts Concerning CLBR Protocol LNX-003

Assessment of Proposed Carroll-Loye Biological Research Study LNX-003: Efficacy Test of KBR 3023 (Picaridin; Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks Under Laboratory Conditions.

Overview of the Study

The protocol describes a study to measure the effectiveness of picaridin as a tick repellent when used in one of two compound formulations (20% picardin KBR 3032 All-Family Insect Repellent Cream and 20% picaridin KBR 3023 All-Family Insect Repellent Spray). Dosimetry data accumulated in previous Carroll-Loye studies (LNX-001 and LNX-002) would be used for dose selection. The efficacy of picaridin as a tick repellent will be determined in a controlled laboratory setting by placing both Western black-legged ticks (*Ixodes pacificus)* and American dog ticks (*Dermacentor variabilis)* on picaridin-treated and untreated forearms and measuring the speed and distance that moving ticks would penetrate into the treated area at 15-minute intervals. A total of 20 subjects will be enrolled.

Science

Charge to the Board

If the proposed laboratory tick repellency study protocol LNX-003 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested materials in repelling ticks?

Board Response to the Charge

The Board concluded that the protocol submitted for review, if modified in accordance with Agency recommendations and conducted accordingly, will likely yield scientifically valid results on the efficacy of these two picaridin-based insect repellent formulations against ticks.

HSRB Detailed Recommendations and Rationale

Protocol LNX-003 from Carroll-Loye Biological Research (Carroll 2009a, 2009b) will be conducted using methods similar to those presented to and commented on by the Board in the past. Although the study protocol was overly long and includes redundant or unnecessary text, it was relatively clear and addressed adequately a number of key scientific issues, including: scientific justification, objectives, and data collection and compilation methods.

The proposed methods largely follow EPA's guidelines, with the one notable exception being the use of ten volunteers per study aim [sic, vice 'arm'], rather than the Agency's existing recommendation
p. 17 of 26 of six volunteers per study aim [sic]. The greater number of study subjects should yield more useful information than might otherwise be obtained. The protocol also incorporated the use of dosimetry-generated data, which will likely generate data representative of real-world use by consumers.

As has been pointed out previously in Board reviews of other repellency protocols, the proposed statistical approach fails to account for censoring of data and the calculation of complete protection time is not the best end-use of the study data. Calculating the proportion of individuals protected for a given time may be a better way to report this type of data and should be considered by the Agency.

Ethics

Charge to the Board

If the proposed laboratory tick repellency study protocol LNX-003 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

The Board concluded that the proposed laboratory tick repellency study protocol LNX003, if modified in accordance with EPA (Sherman and Sweeney 2009) recommendations, and performed as described, will likely meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendations and Rationale

The submitted documents assert that the study will be conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements of US EPA's GLP Standards described at 40 CFR 160, and the California Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (Carroll 2009a, 2009b). Requirements of FIFRA §12(a)(2)(P) also apply. The protocol was reviewed and approved by an independent human subjects review committee, Independent Investigational Review Board, Inc. (IIRB, Inc.), of Plantation, FL, prior to submission. Minutes of IIRB, Inc. meetings and a copy of IIRB, Inc. policies and procedures were provided to the EPA as a separate document (IIRB, Inc. 2009). These documents indicate that IIRB, Inc. reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

1. The Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Sherman and Sweeney 2009). The proposed study is likely to meet the applicable

ethical requirements for research involving human subjects, in accordance with the following criteria:

a. *Acceptable risk-benefit ratio*. The risks as noted in the study protocol are fivefold: 1) allergic reaction to test materials themselves; 2) exposure to biting arthropods; 3) possible

exposure to arthropod-borne diseases; 4) physical stress from the test conditions; and 5) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are justified by the potential societal benefits, particularly data on the efficacy of these new formulations as personal tick repellents.

- Based on toxicological data currently available for picaridin, coupled with appropriate exclusion criteria, study subjects are unlikely to be at risk of adverse side effects with exposure.

- The risk of bites is negligible and minimized by the study design; tick questing and biting behavior is slow, and study subjects are trained to remove ticks from their forearms prior to biting. Study subjects will be trained in proper tick observation and handling techniques.

- The ticks used for the study are bred and raised in a laboratory environment and are considered to be pathogen-free, minimizing the risk of vector-borne disease. Tick colonies and their rabbit hosts are also screened regularly for known tick-borne diseases, including the rickettsial illness Rocky Mountain Spotted Fever that has been observed in the past to be transmitted within laboratory tick colonies through a trans-ovarian mechanism.

- The potential risks to subjects from physical stress are minimized. Although the 12-hour duration of the study protocol raises some concerns about physical stress and exhaustion, the study investigators attest that similar protocols of equivalent length have never been seen as unduly stressful by study subjects. Appropriate stopping rules and medical management procedures are in place. Subjects are also given frequent breaks and can withdraw from the study at any time should the investigational procedures prove too strenuous.

- Minors and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential stigma resulting from study exclusion due to pregnancy is also appropriately minimized.

b. *Voluntary and informed consent of all*

- The study protocol includes several mechanisms designed to minimize coercive recruitment and enrollment. For example, although many of the

research subjects will be recruited from the University of California at Davis student population, where Dr. Carroll holds an adjunct appointment, student and employees of the Study Director are excluded from participation. Additional mechanisms designed to minimize coercive recruitment, developed in response to earlier HSRB concerns and recommendations (c.f. EPA HSRB 2006a; 2006b) are also in place.

- Monetary compensation is not so high as to unduly influence study subjects.

p. 19 of 26 *c. Equitable selection of study [subjects]*

- The majority of research subjects will be recruited from the University of California at Davis student population. Study subjects are likely to reflect the ethnic and racial diversity of individuals in the City of Davis, but the use of this convenience sample may limit the broad applicability of the study results to the general population. The investigators have noted this fact in the protocol.