Excerpts Relevant to Carroll-Loye Protocol LNX-002 Review
June 24-25, 2009 EPA Human Studies Review Board Meeting Report
October 26, 2009

p. 28 of 40 **Assessment of Proposed Carroll-Loye Biological Research Study LNX-002: Efficacy Test of KBR 3023 (Picaridin; Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) with Biting Flies Under Field Conditions.**

Overview of the Study

The protocol describes a study to test the efficacy of two formulations (lotion and spray) of 20% picaridin in the field against at least one of 4 species of biting flies. Dosimetry data recently accumulated in a previous study (LNX-001) would be used for dose selection. One habitat is proposed. Ten test subjects and two untreated controls would be tested in a suitable environment that had adequate biting pressure of biting flies but relatively few mosquitoes.

p. 29 of 40 Repellent-treated skin would be exposed for 5 minutes in each 30-minute interval until repellent failure. The endpoint would be the "Lite with Intent to Bite" (LIBe), and the criterion for data to calculate complete protection time would be first confirmed LIBe.

Science

Charge to the Board

If the proposed field repellency study protocol LNX-002 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 biting flies in the field?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Carley and Sweeney 2009) that this protocol will provide scientifically valid results on the efficacy of two picaridin formulations against biting flies, with modification as noted below. Additional Board review of the protocol is not required prior to study implementation.

HSRB Detailed Recommendations and Rationale

The protocol submitted for review had many similarities to previously reviewed CLBR protocols and completed studies involving mosquitoes. The format of the protocol description was revised to provide greater clarity. The study protocol and associated documents incorporated many of the Board's previous comments and recommendations. The endpoint was LIBe, which

the Board has previously expressed preference for because of the lesser risk to study participants than bites.

Agency reviewers identified two concerns: 1) the standard of biting of one LIBe in five minutes was not well justified and may be insufficiently high to yield valid results and could lead to inappropriately right censored data; and 2) a change of the previously-used paradigm of one minute exposure of treated limbs to insects out of each 15 minute period to five minutes in each 30 minute period was not explained or justified (Carley and Sweeney 2009). The Board concurred with both of these concerns, and recommended that they be addressed in the revised protocol as possible.

Additional Board recommendations concerned two issues: 1) the particular species on which data would be accumulated; and 2) the calculation of complete protection time.

With respect to the species tested, although four types of biting flies were proposed as possible insects to be monitored, it was pointed out that these four species display varied behaviors and aggressiveness. When questioned, the Agency indicated that it already had some useful data on some species of biting flies – such as stable flies – accumulated in the laboratory.

The Agency thus expressed interest in obtaining data from other species that cannot be readily studied in laboratory tests. The Board thus recommended that the study be conducted only if black flies (preferably) and/or biting midges were present in sufficient numbers at the field site. Accumulated data should be acquired on one or both of these species, as well as any other species of biting flies that may also be present. If black flies or biting midges are not available in sufficient numbers and with sufficient biting pressure at the field site, other types of biting flies should not be considered acceptable substitutes.

Echoing earlier concerns about the types of calculations and statistical analyses that will be conducted on these insect repellency data, the Board recommended that the protocol be amended to explain better how mean complete protection time will be calculated accurately using the appropriate types of statistical analyses. Mean protection time versus the duration of the study should be clarified, particularly as it affects the prevalence of censored data. The study's duration should be sufficiently long to ensure that the repellent will fail for a substantial portion of study participants, thereby limiting the occurrence of right-censored data. The protocol should also be revised to clarify how the analysis will proceed in the presence of censored data (using Maximum-likelihood or Kaplan-Meier methods).

In the context of this and other insect repellency studies, the Agency is again urged to update its guidance to sponsors so that they can conduct tests and analyze the resultant data in a useful and accurate manner.

Ethics

Charge to the Board

If the proposed field repellency study protocol LNX-002 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

HSRB recommendation

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Carley and Sweeney 2009) and HSRB recommendations, is likely to 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 the US EPA's GLP Standards described at 40 CFR 160, and the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (Carroll 2009). The 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.

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 (Carley and Sweeney 2009). The proposed study is likely to meet the applicable ethical requirements for research involving human participants, in accordance with the following criteria:

a. *Acceptable risk-benefit ratio*. The risks as noted in the study protocol are five-fold: 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 formations as personal insect repellents.

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

The study is designed to minimize the likelihood of biting fly and mosquito bites, through the use of: LIBes rather than actual confirmed bites as a study endpoint; pre-bite removal and joint observation; clear stopping rules; limited exposure periods. Study participants will be trained in proper insect observation and handling techniques.

Biting fly and mosquito bites, should they occur, are usually mild and easily treated with over-the-counter steroidal creams. The study will also exclude participants who have a history of severe skin reactions to such bites.

To minimize the risk that study participants will be exposed to pathogens like West Nile Virus – not transmitted by the biting flies in question but via other arthropods that may be present at the field sites – the study will be conducted only in areas where known vector-borne diseases have not been detected by county and state health or vector/mosquito control agencies for at least two weeks. The study is also planned for a location where mosquitoes are not abundant and at a time of year in which most arthropod-borne pathogens are not usually detected. Finally, mosquitoes that land with the intent to bite will be collected and subjected to multiplex RT-PCR assays for several known arthropod-borne pathogens—including West Nile Virus, Western Equine Encephalitis Virus, and St. Louis Encephalitis Virus—with clear plans to contact study participants and alert them if a transmissible pathogen is detected.

The potential risks to participants from environmental stress are minimized by the provision of a climate controlled rest area, food, water and medical supplies, and by careful monitoring for signs of dehydration, heat stress and hypothermia. Appropriate stopping rules and medical management procedures are in place.

p. 32 of 40 Minor[s] 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 participants*

The study protocol includes several mechanisms designed to minimize coercive recruitment and enrollment.

Monetary compensation is not so high as to unduly influence participants.

c. *Equitable selection of study participants*

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

2. The Board recommended that the study protocol be modified to address the few concerns noted in the EPA's Ethics Review (Carley and Sweeney 2009). In addition, the Board recommended that the investigators clarify of [sic] what "3rd party" medical coverage means, as listed in the current informed consent document.