HSRB Report of Review of LNX-001

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CHARGE TO THE BOARD AND BOARD RESPONSE

Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Study LNX-001

Charge to the Board

If the proposed research described in Protocol LNX-001 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes?

Board Response

The active ingredient picaridin in two formulations will be tested in the field by the Carroll-Loye company for picaridin's ability to repel mosquitoes. Picaridin is also known as Icaridin and KBR 3023. Picaridin has a history of use as an insect repellent principally outside the US. The active ingredient will be formulated into a 20% pump spray and into a 20% cream. All experiments will be conducted using Good Laboratory Practices. A dosimetry experiment with 10 individuals will be performed to determine the amount of product that would be utilized by people using the product as directed.

The experiment will be a field study. Two locations in California could be used, either in the Central Valley or in southern California. A mixture of *Culex* and *Aedes* species will be present at these sites.

Legs and/or arms will be tested. There will be two experienced persons serving as negative controls (i.e., without any repellent product) to confirm mosquito biting pressure. Experimental subjects, in pairs, will monitor landings with intent to bite (LIBe's) during a one minute interval each 15 minutes, until the First Confirmed LIBe (FCLIBe) can be determined. Stopping rules will be employed. The Complete Protection Time (CPT) will be determined, expressed as mean and standard deviation plus 95% confidence interval, if data are normally distributed, and methods are described to assess normality.

p. 17 With respect to the science criteria established earlier by the HSRB, the following assessments are made:

<u>General HSRB Scientific Criteria</u>

- The scientific question was stated (i.e., to test the efficacy of picaridin formulated as either a pump spray or a cream in repelling mosquitoes).
- Existing data were not adequate to answer the question of efficacy of these new formulations.
- Because existing data were not adequate to answer the question of efficacy, new studies involving human subjects are necessary.
- The potential benefits of the study are clear, i.e., that an effective repellent would be available that would have either greater efficacy and/or fewer drawbacks than what was currently approved.
- It is likely that the benefits would be realized because repellent efficacy will be determined in carefully designed field experiments.
- The risks are minimal because the active ingredient is of very low toxicity, the other formulation ingredients are of very low toxicity, the mosquitoes will be aspirated before they have an opportunity to bite, and the regions selected will not have evidence of West Nile Virus.
- The most likely relevant risk would be irritation from mosquito bites, but participants will be instructed to remove mosquitoes before they are bitten, or the possibility of infection with West Nile Virus, but the regions selected will have no evidence of the virus. Serology tests will be performed on captured mosquitoes.

Study Design Criteria

- The purpose of the study is clearly defined (i.e., efficacy testing).
- There are specific objectives (i.e., to determine the Complete Protection Time that picaridin in two formulations displays as a mosquito repellent).
- There was a formally stated hypothesis; however, it is broad and untestable. This does not detract from the value of the study because a hypothesis is not really necessary for an efficacy study such as this.
- The sample size will be 10 individuals per product along with 2 experienced individuals to confirm mosquito biting pressure. A dosimetry experiment prior to the field experiment will quantify the amount of repellent being used.
- There is a plan allocating individuals to treatments.
- It is anticipated that the findings from this study can be generalized beyond the study sample.

Participation Criteria

- There is justification for the selection of the target population (i.e., selection primarily or completely from the existing Volunteer Data Base, comprised of individuals previously participating in similar studies or interested in doing so, who routinely are active outdoors, and are routinely exposed to mosquitoes).
- The participants will be representative of some of the population of concern. However, there are others in the population unlike these participants who are likely to use these products, but it would either be unethical to test them or would be less appropriate to test them. The participating population, while not completely representative, is considered appropriate and reasonable.

- The inclusion/exclusion criteria are appropriate.
- The sample will not be a vulnerable group.

Measurement Criteria

- The measurements will be accurate and reliable as defined. The endpoint will be the First Confirmed Landing with Intent to Bite (FCLIBe). While this was viewed as an appropriate endpoint by many of the Board members, there was some concern that the confirming LIBe criterion was not a sufficiently protective/conservative, and that the first unconfirmed LIBE should be the endpoint.
- The measurements will be appropriate to the question being asked.
- Quality assurance will be a part of the experimental plan.

Statistical Analysis Criteria

- The data were designed to be analyzed to calculate Complete Protection Time with a range of variability. There was concern that specific criteria from the standpoint of statistics for the selection of 10 subjects were not provided or available. There was also concern about the handling of censored data.
- Measures of uncertainty were addressed.

Laboratory and Field Conditions

- Laboratory experiments are not proposed, except for the dosimetry
- Field experiments will be appropriate.
- The study will include a stop rule plan, medical management plan, and a safety monitor.

EPA's science analysis identified a deficiency in the lack of a stated hypothesis, and one was subsequently added. However, the objective of this study, i.e, length of time of efficacy in repelling mosquitoes in the field, is clear and the lack of a formally stated hypothesis, or a vague and broad hypothesis, does not detract from the scientific value of the study. EPA also identified a deficiency in a lack of an explanation for the negative control in the dosimetry experiment; however, it is a necessary control to determine whether any factors besides the formulated product (e.g., sweat) might alter the weight of the dosimeters. EPA also noted that the method of measuring the treatment area was not described. The Board concurred with this deficiency and urged that it be addressed. There were also two statistical deficiencies identified, and the Board urged greater consideration of statistical issues with respect to determination of sample size and analysis of the data.

HSRB Consensus and Rationale

The protocol LNX-001 to study the efficacy of a cream formulation and a pump spray formulation of picaridin for repelling mosquitoes is sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of these formulations against mosquitoes.

Charge to the Board

p. 19 b. If the proposed research described in Protocol LNX-001 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response

Background on Study

The proposed study would evaluate the efficacy of two different skin-applied formulations of an already registered and marketed insect repellent, Icaridin (registered by the Agency as Picaridin). Icaridin is also known under the registered trade name Bayrepel^{TM} and marketed under the brand name Autan.

The research is to be conducted by Carroll-Loye Biological Research, a private laboratory in Davis, CA. The sponsor of this study is LANXESS, Inc. of Pittsburg, PA. 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 FIFRA §12(a)(2)(P), the U.S. EPA's Good Laboratory Practice (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). Finally, the protocol was reviewed and approved by an independent human subjects review committee, Independent Investigational Review Board (IIRB), Inc., of Plantation, FL prior to submission to the Agency.

The revised research protocol submitted consists of two interdependent studies: 1) a dosimetry study, performed under controlled laboratory conditions, designed to determine the amount of an insect-repelling compound, known as KBR 3023 (picaridin; Icaridin), that normal subjects would typically apply when provided with one of two compound formulations (lotion or pump-spray); and 2) an efficacy study, performed at field sites in Central California and/or Southern California, designed to measure the effectiveness of 20% KBR 3023 (Picaridin; Icaridin), as a mosquito repellent. Dosimetry will be determined either by passive dosimetry using self-adhesive roll-gauze (spray and aerosol formulations) or by direct measurement of compound application (lotion formulation). The efficacy of 20% KBR 3023 (picaridin; Icaridin) as a mosquito repellent will be determined by measuring the ability of the two formulations to prevent mosquito landings (defined as "Lite with Intent to Bite"; LIBe) under field conditions. Mosquitoes will be aspirated mechanically after landing but prior to biting; prior to initiation of the efficacy study, all volunteers will be trained, using laboratory-raised, pathogen-free mosquitoes in a controlled laboratory setting, both to recognize a mosquito landing with the intent to bite (LIBe) and to remove such mosquitoes with an aspirator. The strengths and weaknesses of each study design are described above.

The dosimetry study will enroll 10 healthy volunteers, each of whom will apply both formulations. These same subjects may or may not participate in the efficacy study. The

efficacy study will be conducted at two field sites located in Central and/or Southern California, depending on the season. A total of twenty study participants will take place in the two field trials; ten volunteers will test the lotion formation and ten will test the pump spray formulation. For each field trial, two additional untreated control subjects (experienced field-workers or

p. 20 frequent participants of Carroll-Loye-conducted repellency studies) will be enrolled to determine ambient LIBe pressure under field conditions; such measurements are necessary to determine 20% KBR 3023 (picaridin; Icaridin) efficacy as a mosquito repellent. Each control subject may or may not participate in both field trials, thus a total of two to four control subjects may be enrolled. The test compounds would be administered to a standardized skin surface area, with a comparison to the two control participants. Each untreated subject will be attended by two assistants who will aspirate mosquitoes prior to biting, thus minimizing risk of exposure to vector-borne illnesses. In addition, three alternate subjects will be enrolled to: 1) replace any subject who withdraws from participating; and 2) protect the confidentiality of any subject excluded from the study as a result of pregnancy or other potentially stigmatizing condition, as described below. The number of participants enrolled in this study thus will total a minimum of 25 volunteers and a maximum of 37 volunteers, a number that appears to be adequately justified (Carroll 2007a; Carroll 2007b).

Ethics and Regulatory Compliance Review

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in the EPA's initial Science and Ethics Review, dated May 24, 2007 (Carley and Sweeney 2007a). With the provision of an amended protocol on June 14, 2007 (Carroll 2007b), the proposed research described in Protocol LNX-001 comports with the applicable ethical and regulatory requirements of 40 CFR 26, subparts K and L.

Subpart K of the Agency's final human studies rule requires that the investigator submit to the EPA all information that pertains to the IRB review of proposed research (40 CFR 26.1115a) as well as additional information specified in 40 CFR 26.1125, if not already included in the IRB documentation. The information requested under 40 CFR 26.1125 includes a discussion of the potential risks to human subjects, the measures proposed to minimize these risks, expected benefits if any and to whom, alternative means to obtain comparable information, and the balance of risk and benefits of the research. In addition, subject information sheets and approved written informed consent agreements should be provided, along with any information about recruitment and the presentation of this subject information. Finally, the investigator should provide copies of all correspondence with the IRB, including official notification of IRB review and approval. As submitted to the Agency, the amended protocol (Carroll 2007a; Carroll 2007b) meets the regulatory requirements of 40 CFR § 26.11159 . For example, the original and amended protocols were reviewed and approved by IIRB. Documentation previously provided to the EPA by IIRB indicates that it reviewed this study pursuant to the standards of the Common Rule (45 CFR 46, Subpart A) and determined it to be in compliance with that Rule.

With respect to study design, the risks to participants are minimal and justified by the likely societal benefits, including data on the efficacy of 20% KBR 3023 (picaridin; Icaridin) as a mosquito repellent. The nature and likelihood of any side effects or adverse events are described clearly in the informed consent documents (with separate documents outlining the risks for treated volunteers and experienced, untreated controls). The risks to study participants are three-fold: 1) allergic reaction to test materials themselves; 2) exposure to biting arthropods; and 3) possible exposure to arthropod-borne diseases.

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Reasonable attempts have been taken to minimize any potential harm, and plans for the medical management of any side effects or adverse events have been developed. Although 20% KBR 3023 (picaridin; Icaridin) is not currently used as an insect repellent in the United States, for example, repellent formulations containing 20% KBR 3023 are commercially available in Europe and Australia, and have been used for years with little evidence of toxic effects. Laboratory analyses, as summarized by Dr. Ghoma Sangha of LANXESS at the public meeting of the HSRB, also suggest that participants enrolled in this study are unlikely to be at increased risk of experiencing adverse side effects upon exposure to the test materials.

Reactions to mosquito bites are usually mild and easily treated with over-the-counter steroidal creams. Excluding subjects who have a history of such severe skin reactions will minimize the risk of a subject experiencing a severe physical reaction to a mosquito bite. In addition, the study protocol is designed specifically to minimize the likelihood that a mosquito will bite, through the use of clear stopping rules, limited exposure periods, pre-bite aspiration and joint observation.

To minimize the risk that study subjects will be exposed to illnesses such as West Nile Virus, field tests of repellent efficacy 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 one month. Finally, mosquitoes collected while attempting to bite control and treated subjects during the field tests will be subjected to multiplex RT-PCR assays for several known arthropod-borne diseases—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.

In accordance with the provisions in the EPA's final human studies rule (40 CFR §§ 26.1701-1704), minors and pregnant women are explicitly excluded from participation, the latter being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study. The use of so-called "alternate" subjects ensures that the results of over-the-counter pregnancy tests would be kept private; that study participants may be designated as alternate subjects and automatically excluded from participation allows for potentially pregnant volunteers to withdraw without compromising their confidentiality.

Finally, the study protocol also included several mechanisms designed to minimize coercive subject recruitment and enrollment. For instance, although the study is to be conducted by Carroll-Loye Biological Research, a private research laboratory in Davis, California, the Principal Investigator of the study and Co-Owner of the research laboratory, Dr. Scott P. Carroll, also is an adjunct faculty member of the Department of Entomology at the University of California, Davis. The majority of research participants will be recruited from the University's student population, including from Dr. Carroll's own department, but the protocol specifically excludes any student or employee of the Study Director and includes a substantial waiting period between recruitment and study enrollment and an interview by Dr. Carroll designed to minimize coercive subject recruitment and enrollment. In addition, compensation for study participation is not so high as to unduly influence enrollment. It is important to note, however, that the planned use of a convenience sample of study participants may limit the broad applicability of the study results to the general population; this fact is noted by the study investigators in the protocol.

p. 22 HSRB Consensus and Rationale

The Board concurred with the assessment of the Agency that the protocol LNX-001 submitted for review by the Board, if revised as suggested in EPA's review, meets the applicable requirements of 40 CFR 26, subparts K and L. In addition, with the submission of the amended protocol, the Board believed that the protocol meets the applicable requirements of 40 CFR 26, subparts K and L.