October 18-19, 2006 EPA Human Studies Review Board Meeting Report Study EMD-003 from Carroll-Loye Biological Research

January 21, 2007

EPA-HSRB-06-04

Subject: October 18-19, 2006 EPA Human Studies Review Board Meeting Report

EMD-003 from Carroll-Loye Biological Research

Charge to the Board

Scientific Considerations

Does the proposed research described in Study EMD-003 from Carroll-Loye Biological Research appear likely to generate scientifically reliable data, useful for assessing the efficacy of a test substance for repelling ticks?

Board Response to the Charge

Protocol EMD-003 from Carroll-Loye Biological Research represents the resubmission of a protocol to evaluate the efficacy of three formulations of IR3535 that was previously reviewed by the HSRB (USEPA, 2006). The revised protocol outlined studies to evaluate the efficacy of IR3535 as a tick repellent in human subjects. The protocol described a laboratory study in which the movement of the Western black-legged tick (*Ixodes pacificus*) up the forearm will be determined. Studies in humans are required to assess the efficacy of such repellents because laboratory animals differ in their attractiveness to the pest, and therefore do not provide an accurate assessment of efficacy in humans.

In its previous review, the HSRB recognized three major limitations to the protocol as initially submitted. These limitations included: (1) the lack of a clear rationale underlying the conduct of the study; (2) the lack of identification and characterization of the formulations to be tested and (3) numerous concerns for the overall scientific design of the study. In the revised protocol, the investigators have carefully, comprehensively and conscientiously addressed the concerns and shortcomings of the original protocol. The work outlined in the revised protocol clearly identifies the purpose and objectives of the study, and justifies that efficacy testing in human subjects is required. Relevant details regarding the formulations (aerosol spray, pump spray and lotion) to be evaluated have been provided. The study size has been increased from 6 to 10 subjects per formulation, and each subject will serve as his own untreated control, thereby enabling a direct comparison between treated and non-treated arms. The investigators have also included information regarding how subjects would be trained to accurately and consistently collect information regarding the number of ticks crossing or repelled from the arm skin. Finally, the investigators have added a dosimetry component

to the protocol that will provide valid information on the applied dose of IR3535 per square centimeter of skin in order to determine individual subject doses of the formulation during the conduct of the repellency portion of the protocol.

IR3535 is commercially available, and there is a large amount of toxicology data available demonstrating that it is a compound of low toxic potential. Therefore, human subjects are unlikely to be at risk of experiencing adverse effects relative to exposure to the proposed formulations. However, reference to the available toxicology data was not included in the protocol. The HSRB recommended that information concerning the no-adverse-effect levels (NOAELs) for toxicity studies should be included in order to assure human safety during the conduct of these studies.

In the revised protocol, the investigators raised the possibility that because the pump and aerosol formulations were identical in composition and differed only in the manner of application, they could be "tested together on alternate limbs of the same subjects" in order to reduce the number of human subjects required for this work. The HSRB recommended that the investigators should not test these formulations together, concluding that they should be tested on separate groups of subjects.

HSRB Consensus and Rationale

The HSRB noted that representatives from Carroll-Loye Biological Research had responded to the numerous concerns raised by the Board in its original review of this protocol. The HSRB concluded that the proposed research as described in Study EMD-003 appears likely to generate scientifically-reliable data that would be useful for assessing the efficacy of a test substance for repelling ticks.

Charge to the Board

Ethical Considerations

Does the proposed research described in Study EMD-003 from Carroll-Loye Biological Research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

Brief Overview of the Study

This protocol was originally reviewed at the June 2006 meeting of the HSRB, at which time the Board concluded that the study failed to meet the requirements established in the Environmental Protection Agency's final human studies rule (40 CFR Part 26). In particular, the study did not comport with the applicable requirements of 40 CFR Part 26, subpart K. The Board also raised questions about: (1) equitable study

subject selection and recruitment; and (2) whether or not the documentation and process of study subject enrollment was sufficient to meet prevailing standards of voluntary informed consent.

A revised, IRB-approved protocol was submitted for review (Carroll 2006a). The research is to be conducted by Carroll-Loye Biological Research, a private laboratory in Davis, California by using healthy volunteers and a controlled environment. The revised research protocol submitted consisted of two interdependent studies: 1) a dosimetry study designed to determine the amount of an insect-repelling compound, known as IR3535, that normal subjects would typically apply when provided with one of three compound formulations (lotion, pump or aerosol); and 2) an efficacy study designed to measure the efficacy of IR3535 as a tick repellent. Dosimetry would 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 IR3535 as a tick repellent would be determined by placing Western black-legged ticks (*Ixodes pacificus)* on IR3535-treated and untreated forearms and measuring the speed and distance that moving insects would penetrate into the treated area.

The dosimetry study, conducted in conjunction with the dosimetry analyses described in protocol EMD-004, would enroll 12 subjects per test formulation, for a total of 36 subjects. The efficacy study will enroll 10 subjects per test formulation, for a total of 30 subjects. Each subject would serve as their own control. Subjects may participate in either or both studies, making the total number of volunteers enrolled no less than 36 but no greater than 66. In addition, three alternate subjects would 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 a potentially stigmatizing condition, as described below.

Critique of Study

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley and Fuentes 2006). With the provision of detailed IRB minutes and the exclusion of children and pregnant women, the proposed research described in Protocol EMD-003 comports with the applicable requirements of 40 CFR Part 26, subparts K and L.

In brief, the risks to study participants are minimal and justified by the likely societal benefits, including data on the efficacy of IR3535 as a tick repellent. As IR3535 is commercially available and has been used as a repellent in Europe for years with no evidence of toxic effects, the subjects enrolled in this study are unlikely to be at increased risk of experiencing adverse side effects upon exposure. 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. Clear stopping rules also have been developed, as have plans for the medical management of any side effects or adverse events. The Board recommended, however, that the nature and likelihood of any side

effects or adverse events be clearly described in the informed consent documents. Carroll-Loye Biological Research also may wish to designate a specific physician to be contacted in the event that any adverse side effects are seen.

At the June 2006 meeting, the Board expressed concern about the potentially coercive nature of study subject recruitment. 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. As the majority of research participants would be recruited from the University's student population, including from Dr. Carroll's own department, the Board previously recommended that the protocol and consent documents be altered to define clearly the mechanisms in place to prevent coercion. The revised protocol included several such mechanisms, including the exclusion of any student or employee of the Study Director, a substantial waiting period between recruitment and study enrollment, and an interview by Dr. Carroll, designed to minimize coercive subject recruitment and enrollment.

In accordance with the newly promulgated provisions in the EPA's final human studies rule (40 CFR §§ 26.1701-1704), children 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. Previously, the Board raised concerns about the potentially stigmatizing nature of a positive test, and recommended that Carroll-Loye develop additional protections to ensure that the results of over-the-counter pregnancy tests would be kept private. The use of so-called "alternate" subjects is one such safeguard; 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.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that the revised protocol, EMD-003, submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.