Completed IR3535 Insect Repellent Efficacy Studies

Studies EMD-003.1 and EMD 003.2

Charge to the Board

Scientific Considerations

Are these studies sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against ticks?

Board Response to the Charge

The active ingredient IR 3535 was tested for its ability to repel ticks on the forearms of volunteers by the protocol presented and modified by Carroll-Loye. The protocol had been modified based on the suggestions and input of EPA and HSRB. The results were reported in EMD-003.1 and EMD-003.2

The active ingredient was formulated into two products, a pump spray and a lotion, but data on the originally proposed aerosol was not provided because of an error in the formulation. The products were produced using Good Manufacturing Practices. All experiments were conducted using Good Laboratory Practices. A passive dosimetry experiment was done, as suggested previously by the HSRB both at its June and October 2006 meeting reviewing this protocol, to determine the amount of product that would be utilized by people using the product as directed. This passive dosimetry experiment was used to determine a grand mean of the 12 individuals tested (3 subsamples each) per product that was then used for all 10 individuals per product participating in the subsequent tick repellency tests for each product. (It should be noted that the dosimetry experiment was in common for both this study and the mosquito repellency study, EMD-004, since the same formulated products were used for both.)

The experiment was a laboratory study and was conducted according to the approved protocol with only very minor deviations, and none of these deviations would have affected the quality of the data or the safety of the subjects. The number of 10 subjects was justified in the text as leading to sufficient statistical power while exposing only a small number of people to the potential risks. Each subject had one limb treated. Each of the subjects served as a negative control in that each tick was tested first on the untreated limb to guarantee that the ticks demonstrated typical questing behavior (all did) prior to being tested on the treated limb. All ticks were laboratory reared with no history of tick-borne pathogens. Each tick was used only once. Repellency was tested during a 3-min interval each 15 minutes, starting 15 minutes after product application, using the criterion of First Confirmed Crossing (FCC) for each individual (replicate) to calculate Complete Protection Time (CPT) for the study. Stopping rules were employed. The study identified a range of 5-12 hr with a mean CPT of 9.1 hr for the lotion and a range of

6.5 to 12 hr with a mean CPT of 12.1 hr for the pump spray. The CPT is probably conservative as a number of the subjects reported no crossings at all, and the experiment was terminated before a FCC.

With respect to the science criteria established earlier by the HSRB for completed studies:

General HSRB Scientific Criteria

- The scientific question was stated (i.e., to test the efficacy of IR3535 in repelling ticks).
- 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 were 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 was determined in controlled experiments.
- The risks are minimal because the formulation products are of very low toxicity and ticks are laboratory-reared with no evidence of pathogens.
- The most likely relevant risk would be irritation from tick bites, but participants were instructed to remove ticks before they were bitten.

Study Design Criteria

- The purpose of the study was clearly defined (i.e., efficacy testing).
- There were specific objectives/hypotheses (i.e., that IR3535 in the proposed formulations is an effective repellent).
- The study as described tested this hypothesis.
- The sample size was 10 individuals per product with each individual serving as his/her own negative control to test for tick questing behavior. A dosimetry experiment prior to the field experiment determined the amount of repellent to be tested.
- There was 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 was justification for the selection of the target population.
- The participants were 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 is considered appropriate and reasonable.

- The inclusion/exclusion criteria were appropriate.
- The sample was not a vulnerable group.

Measurement Criteria

- The measurements were accurate and reliable.
- The measurements were appropriate to the question being asked.
- Quality assurance was addressed; however, some of the quality assurance was not as precise as it should have been.

Statistical Analysis Criteria

- The data can be analyzed to calculate CPT with a range of variability.
- The statistical method will be commented upon in more detail in the Board's response to protocol SCI-001 below. It should be noted that although there are probably better methods than have been traditionally used to calculate the repellent efficacy, new products will likely need to be compared to existing products and it is imperative that potential users of the products be informed accurately of the relative protection among products. Therefore EPA is urged to make certain that any calculations of efficacy be of a nature that allows products to be compared with some common metrics or values. The Agency is also urged to initiate discussion on how a transition to more accurate methods of calculating efficacy can be introduced so that consumers can not only compare relative efficacy of products but also have better information on the degree of protection individual products provide.
- Measures of uncertainty were addressed.

Laboratory and Field Conditions

- Laboratory experiments were appropriate.
- Field experiments were not conducted.
- The study included a stop rule plan, medical management plan, and a safety monitor.

HSRB Consensus and Rationale

In conclusion, the reported studies on the efficacy of lotion and pump spray formulations of IR3535 (studies EMD-003.1 and EMD-003.2) on repelling ticks are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the two formulations against ticks.

The Board also recognized that recent advances in statistical analyses means that there are probably ways of measuring efficacy of individual products that would be an improvement over traditional techniques. The Board encouraged the Agency to proceed in its efforts to examine how a transition to more accurate methods of calculating efficacy can be introduced so that consumers can not only compare relative efficacy of products

based on traditional methods but also have better information on the degree of protection individual products provide.

The Board commended Dr. Carroll for conducting the preliminary dosimetry phase of the study. Since the Agency noted that this was the first repellency study to have a specific dosimetry phase, the HSRB suggested EPA might wish to provide guidance concerning whether the method employed in this study was the most valid way to determine dose.

Charge to the Board

Ethical Considerations

Does available information support a determination that these studies were conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

Brief Overview of the Study

The protocol for these two studies was initially 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). At that time, the protocol failed to 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, Institutional Review Board (IRB)-approved protocol was submitted and reviewed at the October 2006 meeting of the HSRB, at which the Board concluded that the revised research protocol, as submitted to the EPA, was compliant with the applicable ethical requirements of 40 CFR Part 26, subparts K and L.

Subsequent to the aforementioned October meeting of the HSRB, two dosimetry and efficacy studies for tick repellents containing IR-3535 were conducted from October 23 through November 8, 2006 (Carroll 2006a; Carroll 2006b). The studies were performed in Davis, California by researchers at Carroll-Loye Biological Research. The studies were sponsored by EMD Chemicals, Inc., Gibbstown, New Jersey; EMD Chemicals is the North American subsidiary of Merck KGaA, Darmstadt, Germany. The documents provided by Carroll-Loye specifically state that each study was conducted in compliance with the requirements of the U.S. EPA Good Laboratory Practice Regulations for Pesticide Programs, as promulgated at 40 CFR Part 160 (Carroll 2006a, 3; Carroll 2006b, 3). Each study was also reviewed and approved by a commercial human subjects review committee, Independent Investigational Review Board (IIRB), Inc., Plantation, FL. Documentation provided to the EPA by IIRB indicates that it reviewed these studies

pursuant to the standards of the Common Rule (45 C.F.R. Part 46, Subpart A) and determined them to be in compliance with that Rule.

As submitted to the EPA, each completed study consisted of two interdependent analyses: 1) a dosimetry study designed to determine the amount of an insect-repelling compound, known as IR-3535, that typical users would typically apply when provided with one of two compound formulations (lotion or pump spray); and 2) an efficacy study designed to measure the efficacy of IR-3535 as a tick repellent for each compound formulation. Dosimetry was determined either by passive dosimetry using self-adhesive roll-gauze (pump spray formulation) or by direct measurement of compound application (lotion formulation). The efficacy of IR-3535 as a tick repellent was determined by placing Western black-legged ticks (*Ixodes pacificus)* on IR-3535-treated and untreated forearms and measuring the speed and distance that moving insects would penetrate into the treated area; thus, each subject served as his/her own control. The scientific strengths and weaknesses of each study design were described above.

The dosimetry study enrolled a total of 12 individuals, seven women and five men, each of whom tested both the lotion and pump spray formulations. The efficacy study for each formulation enrolled 10 subjects: seven women and three men tested the lotion formulation, and four women and six men tested the pump spray formulation. Two subjects enrolled in the dosimetry study participated in both the lotion and pump spray efficacy studies. All remaining subjects participated in only one of the three analytic phases of EMD-003.1 and EMD-003.2, giving a total of 28 subjects enrolled. In addition, three alternate subjects were enrolled to: 1) replace any subject who withdrew; 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. Study documents, however, also include limb measurement information for an additional nine subjects who were not enrolled in either the dosimetry or the efficacy studies. These subjects appear to be enrolled in two additional studies also submitted to the EPA by Carroll-Loye Biological Research, EMD-004.1 (Completed Efficacy Studies for Mosquito Repellents Containing IR-3535 – Lotion) and EMD-004.2 (Completed Efficacy Studies for Mosquito Repellents Containing IR-3535 – Pump Spray) (Carroll 2006c; Carroll 2006d).

Critique of Study

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley 2006a). In general, the research described in EMD-003.1 and EMD-003.2 comports with the applicable requirements of 40 CFR Part 26, subparts K and L. The risks to study participants were minimal and were justified by the likely societal benefits, including data on the efficacy of IR-3535 as a tick repellent. As IR-3535 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 were unlikely to be at increased risk of experiencing

adverse side effects upon exposure. The ticks used for the study were reared in a laboratory environment and are considered to be pathogen-free, minimizing the risk of vector-borne disease. Clear stopping rules also were developed, as were plans for the medical management of any side effects or adverse events; no side effects or adverse events were reported. The study protocol also included several mechanisms designed to minimize coercive subject recruitment and enrollment, compensation was not considered to be so high as to unduly influence participation, and minors and pregnant or lactating women were explicitly excluded from volunteering (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study). The potential stigmatization resulting from study exclusion was minimized by the use of so-called "alternate" subjects, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

The revised protocol and informed consent documents were reviewed and approved by IIRB, Inc., on November 1, 2006, nine days after study subject enrollment began. In email correspondence between Dr. Scott Carroll of Carroll-Loye Biological Research and Mr. John Carley of the EPA's Office of Pesticide Protections, dated December 18-19, 2006, Dr. Carroll reported that subjects were enrolled using a previously approved protocol and consent form, dated September 12, 2006; these were modified to reflect protocol and consent form changes under review but not yet approved by the IIRB. For example, Dr. Carroll reported that, "to each of the 12 September consent forms used for subject enrollment … corrections were made by hand, and acknowledged by initialing by the subject and Study Director (Carley and Carroll 2006).

Although it is unlikely that these changes knowingly and/or seriously impaired the informed consent process, enrollment of subjects using unapproved protocols and consent forms represents a significant and serious departure from accepted review and approval practices. EPA regulations regarding review and approval of human subjects research, for example, prohibit investigators from implementing any protocol changes without prior IRB approval unless such changes are necessary to prevent immediate, serious harm to study participants. The regulations also require investigators to only obtain consent using IRB-approved forms. Furthermore, it is the policy of the IIRB, available online at http://iirb.com, that all "significant protocol deviations [be] reported to the Independent Investigational Review Board, Inc. in a timely manner." Protocol violations or deviations occur when there is a variance in a research study between what is described in the protocol approved by the IRB and the actual activities performed by the research team. The failure of Carroll-Loye Biological Research to 1) obtain IRB approval of the revised protocol and consent forms prior to enrollment of study subjects, and 2) report these deviations to the Independent Investigational Review Board, are serious regulatory breaches. The Board thus recommended that Carroll-Loye Biological Research report these deviations to the IIRB as soon as possible and work with that organization to develop and implement a corrective course of action.

HSRB Consensus and Rationale

The Board concurs with the initial assessment of the Agency that the studies EMD–003.1 and EMD-003.2 submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

The Board also noted that there were a series of deviations from Subpart K that while not adversely affecting the right and welfare of human subjects of the study, reflected a lack of familiarity with IRB procedures and protocol requirements described in Subpart K. The HSRB advised the Agency that it recommend investigators perform human research protection training and include completion of such training as part of their submission of protocols or completed studies to the Agency. Examples of such training could include the on-line training program offering by NIH/NCI or development of such a program by the Agency.