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John M. Carley
Program Analyst
U.S. Environmental Protection Agency
Office of Pesticide Programs

Re: Summary and rationale for revisions protocol EMD-003 'Test of Personal Insect Repellents' (replacing IIRB-approved version of 18 April 2006)

Dear John,

As you are aware, the version of Protocol EMD-003 that was approved by the IRB on 18 April 2006 has subsequently been reviewed, in its original or draft revised form, by the Office of Pesticide Programs (OPP) of US/EPA, the US/EPA Human Studies Review Board, and the California Department of Pesticide Regulation. While the potentially "final" revised version is still at the IRB, I am sending you this present accounting of the changes we have made in order to facilitate your review process. We anticipate receiving a response from the IRB on Tuesday, September 12th, and we will immediately inform you if they have asked for any additional changes.

The changes we have made are numerous, but all are aimed at either improving the science to better reflect consumer habits, or at improving the clarity and completeness of the information provided to study participants. Importantly, the protocol is now fully independent of the rather generic former protocol C-L-001 that described recruitment and listed safety measures. That information is now directly explained (in new or expanded form) in the present protocol:

§5.1 Objective of research (expanded)
§5.2 Rationale and main endpoint (expanded)
§5.3 Rationale for use of human subjects (new)
§9.1.4 Subject recruitment (new)
§9.1.5 Identification method and records retention (expanded)
§9.1.6 Enrollment of alternate subjects and its relation to individual privacy (new)

§9.5 Stop rule and medical management (new)

The content of those new or expanded sections also includes our responses to direct queries from the HSRB.

The most substantial change to the methods is the addition of a dosage determination phase to precede the repellent efficacy assay. Dosage determination is a behavioral study, and it is described in detail in §10.3. In it, the subjects first familiarize themselves with the operation of the repellent dispensing devices (pump spray, aerosol spray and lotion), and practice using them until they determine their own 'best practice' to give complete and comfortable coverage. Upon achieving that, the amount applied is measured. Frequent and immediate washing of the treated skin is used to minimize the time any repellent remains on the skin during dosimetry.

In discussions with US/EPA, we have arrived at a sample size of 12 subjects for dose measurement, two more than will participate in the efficacy testing of each repellent. The excellent toxicological profile of IR3535 (the active ingredient) suggests that the dosimetry poses little additional risk to the subjects. In addition, those data will be used to insure that subjects receive an appropriate dose during the efficacy testing that follows, improving the scientific merit of that portion of the study. The rationale for the sample sizes is presented in a substantially expanded §9.1.3.

In response to US/EPA staff inquiries about the negative control, the rationale (§6.2.2) and method (§§8.4.1 and 10.3.6) have been augmented, clarified and altered. In addition, in response to the spirit of comments from the HSRB regarding statistical treatments, the positive control (former §6.2) has been eliminated as not justifiable with a sample size of just one subject, and not sufficiently important to merit a larger sample.

In addition, in response to concerns of the HSRB about how adept subjects would be in the handling of arthropods and the tools required to do so, we have designed training sessions to familiarize volunteers with the practices they will use once the repellent efficacy portion of the study commences (§9.6, new, and Informed Consent Form).

We have also addressed HSRB questions about the other ingredients in the test materials in addition to the active ingredients, and in general about the safety

all of the ingredients in the three formulations, in a greatly expanded §6.1.7. Similarly, we now describe practices in process to protect and assess the stability of the Test Materials in the new §6.1.8.

Lastly, the Informed Consent Form is expanded to more clearly explain the purpose of the study, what subjects will experience, and what the risks are. Time commitments are detailed, and compensation, the right to withdraw, restrictions on participation (including pregnancy), and medical coverage are all more thoroughly and clearly explicated.

Thank you for your consideration. Please contact me should you have any questions, and in particular if you would like me to itemize the responses to both you and the HSRB with more direct referencing.

Sincerely,

Scott P. Carroll, Ph.D.
Director and Study Director