UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

December 20, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Preliminary Science and Ethics Review of Protocol for Human Study of Mosquito Repellent Performance

FROM: John M. Carley
Ethics Reviewer

Kevin Sweeney
Science Reviewer

TO: Marion Johnson, Chief
Insecticides Branch, RD

REF: Carroll, S. (2006) Test of Personal Insect Repellents: Efficacy Test Protocol SCI-001, dated November 2, 2006. Unpublished document prepared by Carroll-Loye Biological Research. 78 p.

We have reviewed the referenced protocol for a field test of mosquito repellency from both scientific and ethics perspectives. This review assesses the scientific aspects of the proposed research in terms of the recommendations of the draft EPA Guidelines 810.3700 and of the EPA Human Studies Review Board, and the ethical aspects of the proposed research in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board.

This review is characterized as "preliminary" only because a revised version of the protocol was submitted on December 14, 2006. An updated review will be prepared to reflect the revised protocol submission.

A. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 5. No required elements are missing, but not all were provided in the initial submission, and two documents cited in correspondence between the investigator and the IRB were omitted from the file of correspondence. This deficiency is not considered significant, but it should be corrected.

The following documents were considered in this review:

- Protocol SCI-001 and Informed Consent Form (11/2/06 with IRB approval 11/7/06)
- Email correspondence between Carroll-Loye Biological Research and Independent Investigational Review Board 11/3-11/8/06
- Email from R Roogow of IIRB to John M. Carley of EPA transmitting IIRB minutes and asserting that IIRB procedures and membership were unchanged from previous report (11/15/06)
- Minutes of IIRB consideration of SCI-001 at their meeting of 11/7/06
- Email between Scott P. Carroll of Carroll-Loye Biological Research and John M. Carley of EPA addressing questions raised by EPA and transmitting the site questionnaire and revised protocol
- Site Questionnaire: SCI-001 11/3/06

The following additional documents arrived too late to be considered in this review, but will be addressed in a revised review and in EPA's presentation to the HSRB:

- Revised Protocol SCI-001 v.2 and Informed Consent Form (12/14/2007) [sic]
- Carroll SCI-001 v.2 Support Documents (Labels and MSDSs)

B. Summary Assessment of Ethical Aspects of the Proposed Research

Here is a summary of our observations about the ethical aspects of the proposed protocol. Supporting details are in the attachment.

1. **Societal Value of Proposed Research:** This study will test the field efficacy against mosquitoes of three test formulations and one "comparison article" formulation of the active ingredient DEET. All four materials are registered with EPA. Efficacy testing is required to support proposed label statements for the three test formulations claiming a longer duration of efficacy than has previously been approved. Direct testing of the duration of efficacy is important because consumers, who rely on repellents to avoid insect bites, cannot readily assess the efficacy of a product independent of EPA's approval. The "comparison article" is currently the U.S. DoD standard repellent; comparison of efficacy of the test formulations to the "comparison article" is needed if the sponsors are to market their formulations to DoD. There is potential benefit to society in demonstrating

the long-term effectiveness of DEET repellents that users may prefer to other DEET products because of their cosmetic or other qualities.

2. **Subject Selection:** Subjects are to be recruited from among "communities of friends, neighbors and scientists" near the laboratory, excluding, however, any who are students or employees of the investigators. Explicit factors exclude as subjects children, pregnant or lactating women, those in poor health or physical condition, or those unable to speak and read English. The sample will thus not be fully representative of the population of potential repellent users. There is no indication that any subjects will be from particularly vulnerable populations.

   Two "experienced" subjects will serve as untreated controls to verify ambient biting pressure from mosquitoes in the field. The protocol does not describe how these subjects will be recruited, or how the process of informing them and obtaining their consent to this special role in the research will differ from the process used for the treated subjects. This deficiency must be corrected before the research goes forward.

3. **Risks to Subjects:** Risks of three kinds are identified: risks from exposure to the test materials, risks of exposure to biting arthropods, and risks of exposure to vectors of arthropod-borne disease. Risks from exposure to the test materials themselves are mischaracterized in the Informed Consent Form, which refers to test materials intended for spray application and containing alcohol. This protocol calls for testing only lotions which do not contain alcohol; this passage in the ICF must be replaced by a description of the risks associated with exposure to the test materials. Three of the four formulations tested require the signal word "Warning" because of eye irritation potential.

   All practical steps to minimize subject risks have been taken:

   - Risks from exposure to the test materials are minimized by excluding candidates with known sensitivity to product ingredients, by monitoring the dosimetry phase of the research, and by applying materials in the repellency phase by technicians.

   - Risks from arthropod bites are minimized by excluding candidates with known sensitivity, by training candidates to remove landing mosquitoes before they have time to bite, and by minimizing exposure of skin.

   - Risks of contracting disease are minimized by conducting the research in areas where mosquito-borne viruses have not been detected for at least a month, and by the same steps that minimize mosquito bites.

   Because of the generally low acute and chronic hazard profile of the materials, the design of the research to minimize exposures, and the training of subjects to

aspirate landing mosquitoes before they have time to probe or bite, the probability of the identified risks is accurately described as “extremely small”.

4. **Benefits:** There are no direct benefits to subjects. If the testing shows long-term efficacy comparable to the comparison article, the direct beneficiary of the research is likely to be the sponsor. Assuming eventual regulatory approval of label claims for longer repellent efficacy for these products, indirect beneficiaries may also include repellent users who prefer these products to other formulations of DEET, or to other less effective repellents.

5. **Risk/Benefit Balance:** No opportunities to further reduce risk to subjects while maintaining the robustness of the scientific design have been overlooked. The residual risk to subjects is very low, and reasonable in light of the potential benefits to repellent users, which are likely to be realized.

6. **Independent Ethics Review:** The Independent Investigational Review Board, Inc. of Plantation FL has reviewed and approved the protocol and informed consent materials. The IIRB is independent of the investigators and sponsors. Documentation of IIRB membership and procedures was not provided, but a statement was made by the IIRB that this information had not changed since it was previously submitted to EPA.

7. **Informed Consent:** The protocol contains a complete and satisfactory description of the process by which potential treated subjects will be recruited and informed, and for seeking their written consent to participate. A copy of the Informed Consent Form showing approval by the IIRB is included in the protocol.

   The Informed Consent material requires revision for use with the untreated control subjects. Either a revised form covering both the untreated and treated subjects, or a separate form for use with the untreated controls, must be provided and approved by the IRB before the research can go forward.

8. **Respect for Subjects**: Methods proposed for managing information about prospective and enrolled subjects will generally protect their privacy from compromise. Greater assurance could be provided, however, if data collection forms referred to subjects only by coded number rather than by name. Subjects will be free to withdraw at any time, and will be reminded of this at several points. Subjects who withdraw will be compensated for time spent up to the point of withdrawal. Medical care for research-related injuries will be provided at no cost to the subjects.

C. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the

pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply. If the test is conducted in California as proposed, the provisions of the California Code of Regulations, Title 3, §6710 would apply as well. A point-by-point evaluation of how the requirements of 40 CFR 26 Subparts K and L and the criteria recommended by the HSRB are addressed is appended as Attachment 1.

These specific deficiencies should be corrected before the research can go forward:

- The protocol does not describe how the "experienced" subjects who will serve as untreated controls will be recruited, or how the process of informing them and obtaining their consent to this special role in the research will differ from the process used for the treated subjects.

- Risks from exposure to the test materials themselves are mischaracterized in the Informed Consent Form, which refers to test materials intended for spray application and containing alcohol. This passage must be replaced by a description of the risks associated with exposure to test materials—all of which are lotions not containing alcohol.

- Either a revised Informed Consent Form covering both the untreated and treated subjects, or a separate form for the untreated controls, must be provided and approved by the IRB.

Once these deficiencies have been corrected, the entire proposal must be re-reviewed and approved by the IRB before research can proceed or subjects can be enrolled.

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

> EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

The protocol requires that subjects be at least 18 years old and exclude female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA to rely on a study executed according to this protocol.

D. Summary Assessment of Scientific Aspects of the Proposed Research

The study will test the field efficacy as mosquito repellents of three test formulations and one comparison product, all containing DEET. All test formulations are current EPA-registered products for which the registrants would like to claim repellency for more than the four hours now approved for their labeling. The main objective of the study is to quantify the lasting

efficacy of the formulations to prevent mosquito landings in the field. A secondary objective of the study is to characterize through dosimetry testing the amount of each formulation typically applied by consumers. A third objective is to compare the efficacy of the three test formulations to the current U.S. military standard DEET lotion repellent, Ultrathon. If comparisons are made between test materials or to Ultrathon, the methods to be used for such comparisons need to be described more fully in the protocol.

Biting pressure will be monitored for one minute every 15 minutes during the test by two untreated subjects, each attended by two technicians. Mosquitoes landing on untreated subjects will be aspirated by the attending technicians to prevent biting and for later identification. Treated subjects are randomly assigned to one of the three test materials or the positive control "comparison product". Treated subjects will work in pairs to facilitate observations, and will expose treated skin for 1 minute at 15 minute intervals until they experience a confirmed landing with intent to bite (LIBe).

1. **Study design:** The protocol has three objectives: to test the long-term repellent efficacy of three registered formulations of DEET, to establish a typical consumer dose for each formulation, and to compare the efficacy of the three test formulations to the DoD standard repellent. The first two objectives can be met by the study as proposed. The protocol does not include a plan for comparison to the DoD standard repellent, or for comparison of results for one test material to those for another; this should be clarified. EPA does not require product-to-product comparison of repellent efficacy, and does not permit statements of comparative efficacy on product labels.

2. **Statistical design:** The sample size is larger than is required by EPA guidelines—large enough to ensure robust averages across subjects, but small enough to be economical. Two untreated subjects are proposed to establish and confirm ambient biting pressure; no statistical comparisons to the untreated controls are proposed. Another group of subjects will be treated with a "comparison article", in effect a positive control, which is the current U.S. military standard DEET lotion repellent. There is no discussion of how the comparison of the three test formulations to this "comparison article" will be made. Subjects will be assigned to treatment groups randomly and blindly. Repellency will be reported as "Complete Protection Time" for each formulation, calculated as the mean time across all subjects in each group from treatment to the first confirmed landing with intent to bite (LIBe). Time of LIBes will be reported with a precision of 15-minute intervals, with standard deviation and 95% confidence interval.

3. **How and to what will human subjects be exposed?** In the initial dosimetry phase, subjects' lower arms and legs will be exposed for a few minutes to each registered formulation to establish a "typical consumer dose." In the repellency phase the established typical dose, calculated as mass per unit area for each subject, will be applied by a research technician to a lower arm or leg. The repellent will remain in place for up to 14 hours during the field test.

4. **Endpoints and Measures:** In the dosimetry phase the applied dose will be expressed as mass per unit area; a "typical consumer dose" will be calculated as the mean of individual doses for each formulation. In the repellency phase, complete protection time (CPT) will be measured for each formulation as the mean time from initial application of a typical consumer dose to the first confirmed LIBe, and will be presented with standard deviation and 95% confidence interval. Subjects will be trained in the laboratory to recognize a "LIBe", and in the field will work in pairs, checking each other as well as themselves. All reported LIBes will be verified by a research technician.

E. Compliance with applicable Scientific standards

This protocol adequately addresses the following elements according to applicable scientific standards:

- Scientific objectives
- Experimental design for achieving objectives
- Methods for estimating dose of test material
- Quantification of efficacy of the test materials
- Data collection, compilation and summary of test results
- Discussion of the statistical power of the study
- Justification for sample size in dosimetry and repellency phases
- Rationale for use of two untreated negative control subjects to monitor biting pressure.

This protocol does not adequately address methods for comparing efficacy of one test material to another, or of the test materials to the "comparison article."

Attachments:

1. Summary Review of Carroll-Loye Protocol SCI-001 dated 11/2/06
2. §26.1111 Criteria for IRB approval of research
3. §26.1116 General requirements for informed consent
4. §26.1117 Documentation of informed consent
5. §26.1125 Criteria for Completeness of Proposals for Human Research

EPA Protocol Review
SCI-001:12-18-06

Protocol Identification

(a) Title: **Test of Personal Insect Repellents: Efficacy Test Protocol SCI-001**

(b) Date: **2 November 2006**

(c) Principal Investigator: Scott P. Carroll, Ph.D.

(d) Participating Laboratories: Carroll-Loye Biological Research, Davis CA

(e) Sponsor: Scientific Coordination, Inc., Rockville MD

(f) Reviewing IRB: Independent Investigational Review Board, Plantation FL

1. Societal Value of Proposed Research

(a) What is the stated purpose of the proposed research?

"To test the repellent characteristics of the Test Materials against mosquitoes, with efficacy measured as Complete Protection Time, defined as the time between application of the Test Material and the first confirmed "Lite with Intent to Bite." (p. 2)

(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?

This proposed study will test the efficacy of three formulations of the active ingredient DEET as a repellent for mosquitoes. These formulations are already registered by EPA, with permissible label claims of efficacy for 4 hours. They are "intended to improve cosmetic qualities for better user acceptance. Continued consumer concerns about [Deet's] attributes, including poor cosmetic quality, appear to have limited its use even in situations in which its public health value is clear." (p. 3) EPA requires efficacy testing to support label claims for a longer period of protection than has previously been approved. Direct testing of the duration of efficacy of these formulations is important because consumers, who rely on repellents to avoid insect bites, cannot readily assess the efficacy of a product independent of EPA's approval.

(c) How would the study be used by EPA?

To address the requirement to demonstrate product formulation-specific efficacy of mosquito repellents as a condition for their registration and label claims.

(d) Could the research question be answered with existing data? If so, how? If not, why not?

Although Deet products have been in use for many years and the test formulations are already registered, efficacy of these formulations for periods greater than four hours has not previously been established. Since repellent efficacy is known to differ according to formulation, existing data from testing of other formulations cannot establish the duration of efficacy of these formulations.

(e) Could the question be answered without newly exposing human subjects? If so, how? If not, why not?

"Human subjects are . . . the target system for the test materials, and sufficiently reliable models for repellence testing have not been developed. In addition, subjects will self-administer the test articles during dose determination." (p. 3)

2. Study Design

(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?

"The objective of this study is to test the repellent characteristics of the Test Materials against mosquitoes, with efficacy measured as Complete Protection Time . . . . defined herein as the time between application of Test Material and the First Confirmed 'Lite with Intent to Bite.'" (p. 2)

"Determining dosage is a main objective of this study. Dosage for repellency testing will be the mean of the subject means determined for each product in the dosimetry portion of this study." (p. 6)

"Because the DEET-based products to be tested under this protocol are expected to be superior to Ultrathon . . . , their repellency is most appropriately directly compared to Ultrathon. Indeed, the military is considering new DEET formulations for adoption, but will require efficacy comparisons. . . ." (p. 9)

EPA does not require product-to-product comparison of repellent efficacy, and does not permit statements of comparative efficacy on product labels.

No explicit hypothesis is stated.

(b) Can the study as proposed achieve that objective or test this hypothesis?

The first two objectives cited above can be achieved by the study as proposed. The direct comparison of repellency to Ultrathon is not discussed in the protocol.

2.1 Statistical Design

(a) What is the rationale for the choice of sample size?

See the discussion on pp. 13-15. The sample size reflects a compromise between cost and precision; the sample of ten subjects per treatment group is more than the minimum required by EPA, but promises to provide an acceptably robust measure of average protection time at reasonable cost.

(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

Two untreated control subjects will be used to confirm ambient biting pressure. Six to ten subjects will be treated with Ultrathon, a "comparison article"—in effect, a positive control—for comparison of repellency. (p. 13)

(c) How is the study blinded?

The dosimetry phase is not blinded. In the repellency phase both subjects and investigators are blind to which treatment each receives. (p. 18) The blind can be broken if a subject has an adverse reaction to treatment. (p. 38)

(d) What is the plan for allocating individuals to treatment or control groups?

Assignment to treatment groups (including the positive control group) is random. Untreated controls are not randomly assigned, and must be "experienced" personnel, but by exclusion rule cannot be students or employees of the Study Director. Untreated controls may, however, include Study Director. (p. 5)

(e) Can the data be statistically analyzed?

Yes.

(f) What is the plan for statistical analysis of the data?

Repellency will be reported as "Complete Protection Time" for each formulation, calculated as the mean time across all subjects in each group from treatment to the first confirmed landing with intent to bite (LIBe). Time of LIBes will be reported with a precision of 15-minute intervals, with standard deviation and 95% confidence interval (p. 26). SAS JMP software will be used for statistical analyses (p. 25), but individual tests are not specified.

(g) Are proposed statistical methods appropriate to answer the research question?

The protocol does not discuss statistical analysis of the positive control data, or how comparisons between treatments will be conducted. More detailed specification of planned statistical analyses is needed, especially in these areas.

(h) Does the proposed design have adequate statistical power to definitively answer the research question?

Yes.

2.2 How and to what will human subjects be exposed?

(a) What is the rationale for the choice of test material and formulation?

The test materials are registered formulations for which claims of extended repellent efficacy are proposed. They are the appropriate materials for the test. The comparison article is often used as a positive control material in repellent testing; the implicit rationale for including it in this protocol is to support direct comparison of efficacy with the three test materials.

(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?

A "typical consumer dose" for each formulation will be established in the dosimetry phase as the average quantity of product per unit area of treated skin, for each test formulation and for the comparison article, applied by ten subjects.

(c) What duration of exposure is proposed?

Exposure during the dosimetry phase will be for only a few minutes to each formulation. Exposure during the repellency phase will be for 8-14 hours.

2.3 Endpoints and Measures

(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?

In the dosimetry phase the applied dose will be expressed as mass per unit area. The "typical consumer dose" will be calculated as the mean of individual doses for each formulation. In the repellency phase, "Complete protection time (CPT) is measured as the . . . time from initial application to the first confirmed LIBe. A confirmed LIBe is a LIBe followed by another LIBe within 30 minutes." (p. 26)

(b) What steps are proposed to ensure measurements are accurate and reliable?

- Subjects will be trained to recognize a "LIBe"
- Subjects will work in pairs, checking each other as well as themselves
- LIBes will be verified by a research technician

(c) What QA methods are proposed?

"Protocol Review and Comments must take place before data collection commences. In-Life Inspection must include observing the measurement and recording of key

variables by subjects and researchers. In addition, the final report will be audited for completeness and accuracy. A QAU Statement will address compliance and noncompliance or any omissions in auditing. Findings from the In-Life Inspection and the Final Report, as well as the QAU Statement will be transmitted to both the Study Director and to the Sponsor Monitor." (p. 26)

(d) How will uncertainty be addressed? Will point estimates be accompanied by measures of uncertainty?

"CPT measured in this way will yield a single time value for each subject. Mean CBT will be calculated across all 10 subjects per treatment, and will be presented with standard deviation and 95% confidence interval." (p. 26)

3. Subject Selection

3.1 Representativeness of Sample

(a) What is the population of concern? How was it identified?

The population of ultimate concern consists of people who would purchase and use insect repellents. Little information is available to characterize this population, but it is presumed that users of insect repellents are highly diverse in age, gender, physical size, general health, attractiveness to biting insects, and other characteristics. The population from which subjects are recruited appears to be chosen largely on the basis of convenience, and is not screened for past or likely future use of repellents.

(b) From what populations will subjects be recruited?

"Participants are recruited by verbal networking through our academic and personal communities of friends, neighbors and scientists in Davis CA. . . . Initial contact is through word-of-mouth and telephone contact of individuals in our Volunteer Data Base." (p. 15) "[T]he majority of our subjects have worked with us on an occasional basis for a number of years. . . ." (p. 16)

(c) Are expected participants representative of the population of concern? If not, why not?

By excluding children, pregnant or lactating women, non-English speakers, and those in poor physical condition, among others, the exclusion criteria will mean that participants will not be representative of at least some segments of the population of concern.

(d) Can the findings from the proposed study be generalized beyond the study sample?

Yes.

3.2 Equitable Selection of Subjects

(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?

Inclusion: age 18-55, written consent, speak and read English. Exclusion: hypersensitivity to mosquito bites, sensitivity to any product ingredients, poor physical condition, unwillingness to submit to brief query about personal condition, use of insect repellent within one day before study, unwillingness to abstain from alcohol, smoking, and perfumed products, pregnant or lactating, unable to apply test materials, student or employee of Study Director, unaccustomed to outdoor activity. (pp. 12-13)

(b) What, if any, is the relationship between the investigator and the subjects?

Subjects are recruited from the investigator's "academic and personal communities of friends, neighbors and scientists in Davis CA." (p. 15) Students and employees of the investigator are excluded. (p. 13) "Our subjects are mainly University of California—Davis graduate and undergraduate students in life science programs with which the Principal Investigator is associated." (p. 16)

(c) If any potential subjects are from a vulnerable population, what is the justification for including them?

No subjects from a vulnerable population are proposed.

(d) What process is proposed for recruiting and informing potential subjects?

The recruiting/informing process is extensively described in the protocol on pp. 15-17 and in the informed consent documents on pp. 34-43.

(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?

Untreated control subjects are "limited to experienced technical personnel, who are screened with the same exclusion criteria as are other subjects." (p. 15) "Only experienced professionals (the Study Director and/or other qualified researchers) will expose untreated limbs to monitor biting pressure, . . ." (p. 5) "Students in [the PI's] laboratory who depend on him directly for employment or scholastically are not eligible to participate." (p. 16)

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for the subjects?

"For participation in the study, each research study participant will receive a cash payment of $15 per hour. . . . If you are designated as an 'alternate subject', you will be paid for the hours you spent being trained, plus you will receive a payment of $50 dollars to compensate for being inconvenienced by the administration of the study." (p. 41)

(b) Is proposed remuneration so high as to be an undue inducement? No.

(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects? No.

(d) How and when would subjects be paid?

"Payment will be made at the end of each visit or whenever you withdraw from the study." (p. 41)

4. Risks to Subjects

4.1 Risk characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?

"The repellent active ingredient has a low acute and chronic risk profile, . . . The concentrations of the active ingredient in the product being tested are lower than those of many products currently EPA-registered and marketed in the US." (p. 4)

"The ingredients in the proposed insect repellent formulations are mainly on [EPA] lists 4a or 4b [considered relatively safe for all uses] with a few ingredients on list 3 because of ocular irritation potential. EPA normally regulates the presence of materials on list 3 by labeling to avoid contact with eyes and to prohibit application by children. The other ingredients in the test formulations are commonly used in marketed products for application to human skin as components of cosmetic and drug formulations." (p. 7)

"The insect repellent products proposed for testing have all been tested in animals for potential oral and dermal toxicity." (p. 7)

MSDS's and labels are included for the test materials and the positive control, all of which are registered or conditionally registered with EPA. (pp. 44-78)

Insect Guard II:

- Label: “Warning. Causes substantial but temporary eye injury. Do not get in eyes. Due to irritating nature, may be harmful if swallowed. Use of the product may cause skin reactions in rare cases.” (pp. 45-46)
- MSDS: “Eye Hazards: Not a primary eye irritant, but contact with eyes may cause mild, transient irritation. Skin Hazards: None Known. Ingestion Hazards: None Known. Inhalation Hazards: None Known.” “If swallowed, consult a physician immediately.” “Toxicological information: No Data Available.” (pp. 47-49)

Coulston’s Duranon Insect Repellent:

- Label: “Caution. Avoid contact with eyes. Use of this product may cause skin reactions in rare cases. Prolonged or frequent repeated skin contact may cause allergic reaction in some individuals.” (pp. 50-53)
- MSDS: “Immediate concerns: Caution. Avoid contact with eyes. Use of this product may cause skin reactions in rare cases. Prolonged or frequent repeated skin contact may cause allergic reaction in some individuals. Potential Health Effects: EYES: May cause eye injury. SKIN: Avoid contact with eyes and lips. May cause skin reaction in rare cases. INGESTION: Harmful if swallowed. INHALATION: Avoid breathing spray mist or using in an enclosed area. CHRONIC: Not established” (pp. 54-57)

DermAegis LipoDEET Insect Repellent 302

- Label: “Caution. Avoid contact with eyes. Use of this product may cause skin reactions in rare cases. Prolonged or frequent repeated skin contact may cause allergic reaction in some individuals.” (p. 58, pp. 63-66)
- MSDS: “Immediate concerns: Caution. Avoid contact with eyes. Use of this product may cause skin reactions in rare cases. Prolonged or frequent repeated skin contact may cause allergic reaction in some individuals. Potential Health Effects: EYES: May cause eye injury. SKIN: Avoid contact with eyes and lips. May cause skin reaction in rare cases. INGESTION: Harmful if swallowed. INHALATION: Avoid breathing spray mist or using in an enclosed area. CHRONIC: Not established” (pp. 59-62)

3M Ultrathon Insect Repellent (lotion)

- Label: “Warning. Causes substantial but temporary eye injury. Harmful if swallowed. Do not get in eyes. Use of this product may cause skin reactions in rare cases.” (pp. 74-78)
- MSDS: “Potential Health Effects: Eye Contact: Severe eye irritation: Signs/symptoms may include significant redness, swelling, pain, tearing, cloudy appearance of the cornea, and impaired vision. Skin contact: Prolonged or repeated exposure may cause mild skin irritation: Signs/symptoms may include localized redness, swelling, and itching. Inhalation: No health effects are expected. Ingestion: Ingestion may cause:

Gastrointestinal irritation: Signs/symptoms may include abdominal pain, nausea, diarrhea and vomiting." (pp. 67-73)

(b) What is the nature of the risks to subjects of the proposed research?

"The spray repellents contain alcohol and are flammable." (p. 39) This paragraph in the IC material is irrelevant to the proposed research, since all test formulations are alcohol-free lotions. This must be replaced by an appropriate summary of the risks posed by the repellents themselves.

"In addition, even if you have not had a serious skin reaction to a mosquito bite previously, it is possible that such a reaction could occur if you receive any bites during this study. . . . In addition there is a slight possibility that you will contract a disease carried by mosquitoes if your are bitten, such as West Nile virus or equine encephalitis." (p. 39)

(c) What is the probability of each risk associated with the research? How was this probability estimated?

No numerical probability is estimated. In general, potential subjects are told "you are probably at no more risk than you would experience when engaged in normal outdoor activities in a similar rural area at the same time of year." (p. 39) "Since you will work to quickly remove mosquitoes before they have an opportunity to bite, and few of the mosquitoes present are likely to carry the virus, your chances of getting West Nile fever or another disease from a mosquito bite are probably extremely small." (p. 40)

4.2 Risk minimization

(a) What specific steps are proposed to minimize risks to subjects?

- The risk of a skin reaction to a mosquito bite is reduced by excluding candidate subjects who are aware of having a history of such reaction.
- Candidates with known sensitivity to any product ingredients are excluded.
- Subjects will be trained to quickly remove any mosquitoes that attempt to bite them, before penetration or injection of saliva if possible.
- Mosquitoes used for aspirator training will be lab-reared and disease-free.
- Subjects will be instructed to cover any treated skin immediately if more than one mosquito attempts to bite during any exposure period.
- Subjects will expose small areas of treated skin for only 4 minutes per hour. Other parts of the body will be protected with provided fabric.
- At the end of each one-minute exposure period subjects will move away from the area with mosquito activity. Partners will assist each other to cover the treated area.
- Subjects will be teamed with a partner for joint observation; experienced technical personnel will be present at all times to assist.

- Field tests are conducted in an area where West Nile virus has not been detected by county or state agencies for at least a month.
- Only 2 untreated controls to confirm biting pressure.
- Exposure of untreated controls for no more than 4 min/hour; exposed skin may be covered immediately following the first LIBe.
- Untreated controls will be attended by two assistants with aspirators to remove any mosquitoes that land with intent to bite.
- First Aid materials will be available on-site
- Epi-Pens will be on-site to treat anaphylactic allergic reactions.
- No control with formulation matrix exclusive of active repellent ingredients.
- A physician who has read the protocol and discussed the research with the Study Director will be on call on the day of field testing.

(b) How do proposed dose/exposure levels compare to established NOELs/NOAELs for the test materials?

Actual dose levels will only be established by the results of the first, dosimetry phase of the proposed study. The dosimetry phase is intended to establish a "typical consumer dose", expected to be far below any NOELs/ NOAELs for the test materials, although this relationship is not calculated. Given that animal testing for dermal toxicity is reported to be available for all test materials, the ratio of the dose to the animal NOAEL could be included in the study report, and a stopping rule could be added in case the margin between the "typical dose" and the animal NOAEL is insufficient to justify proceeding.

(c) What stopping rules are proposed in the protocol?

"Any subject showing adverse skin reactions will immediately stop further participation." (p. 19)

"Subjects are instructed to immediately cover exposed skin with the protective mesh provided if more than one LIBe occurs in a one-minute exposure period. Similarly, if subjects receive a LIBe and recall receiving another in either of the two previous exposure periods, they are to ask their data recording technician to verify the recollection from the data record. If verified, the subject is instructed to immediately cover the limb as above." (p. 24)

"If more than one mosquito attempts to bite you on your treated skin in one of the one-minute periods, or if one mosquito attempts to bite in two of three consecutive exposure periods (that is, 15 or 30 minutes apart), you should cover the skin and not expose it again." (p. 38)

(d) How does the protocol provide for medical management of potential illness or injury to subjects?

"If you are injured as a result of being in this study, a consulting physician who is aware of the study will be contacted immediately by telephone. Medical treatment will be available from a health care facility." (p. 40)

(e) How does the protocol provide for safety monitoring?

"[T]echnical personnal will monitor, and subjects will self-monitor, for allergic and irritant skin reactions, particularly redness, edema, itching or pain, and report any such reactions to the Study Director. Any subject showing adverse skin reactions will immediately stop further participation. The treated skin will be gently washed with clean water and mild soap to remove the test product, and the area will be gently dried with a clean towel. The subject will be removed from further exposure to mosquitoes.

"On the day of testing, a physician who has read the protocol and discussed the research with the Study Director will be on call. In unlikely event of a Type 1 allergic reaction (anaphylaxis), we will contact 9-1-1 by cellular or satellite telephone and cooperate as instructed with emergency personnel. . . .

"[T] Study Director will assess skin condition of affected subjects should any bites inadvertently occur during efficacy testing." (p. 19)

(f) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

"All subjects are asked to contact the Study Director and a physician of their own choice at any time should they develop a rash . . . within 48 hours of the conclusion of the test day." (p. 19) While subjects may indeed be asked to do this, the Informed Consent Document is silent on this point.

"Subjects are instructed to be alert for any flu-like symptoms . . . for up to two weeks after the test." (p. 4)

"If you experience any of the symptoms described above in the month following the field test you should contact a medical practitioner and inform the Principal Investigator." (p. 40)

(g) How and by whom will medical care for research-related injuries to subjects be paid for?

"Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by a third party. If necessary, Carroll-Loye Biological Research will transport you to receive medical attention and pay costs associated with the reasonable and appropriate treatment for any injuries incurred as a result of participation in the study." (p. 40)

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

"There are no immediate benefits to you from your participation." (p. 41)

(b) What benefits to society are anticipated from the information likely to be gained through the research?

"Against the slight risks are balanced substantial and reasonably likely benefits. Insect-borne disease is of growing significance in the United States and around the world where U.S. citizens are active. Discomfort associated with nuisance biting restricts many work and pleasure activities. DEET-based repellents have been the only reliable personal protection for many decades. However, health, comfort and practical concerns about DEET have created a niche for new formulations with better consumer acceptance. Because EPA-registration required efficacy data, a test such as this one is the only path toward further product development and greater availability of superior DEED products to consumers in the United States." (p. 5)

"[B]y serving as a participant you may assist in making new insect repellent products available to consumers." (p. 41)

(c) How would societal benefits be distributed? Who would benefit from the proposed research?

The direct beneficiary of the research is likely to be the sponsor. Assuming eventual regulatory approval of effective new formulations of DEET, indirect beneficiaries would include those repellent users who prefer the new formulations to previously available formulations of DEET, or to other, less effective repellents.

(d) What is the likelihood that each identified societal benefit would be realized?

The testing is likely to demonstrate that the new formulations are effective, and thus the sponsor is likely to realize a direct benefit from the research. Realiza-tion of other societal benefits will depend on consumer acceptance of the new formulations.

6. Risk/Benefit Balance

(a) How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

The protocol systematically reduces risks to subjects without reducing the robustness of the scientific design. No opportunities to further reduce subject risk have been overlooked. Thus the resulting risk to subjects is very low—as low as or lower than the risk to anyone engaged in outdoor activity where mosquitoes are active. The potential

benefits to repellent users of a wider variety of effective alternative formulations of DEET with different cosmetic characteristics are likely to be realized, and make the residual risks to subjects in this proposed research reasonable.

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Independent Investigational Review Board, Plantation FL

(b) Is this IRB independent of the investigators and sponsors of the research? Yes

(c) Is this IRB registered with OHRP? Yes

(d) Is this IRB accredited? If so, by whom? Not reported.

(e) Does this IRB hold a Federal-Wide Assurance from OHRP? No

(d) Are complete records of the IRB review as required by 40 CFR 26.1125 provided?

Correspondence between the IIRB and the investigator was provided only by the Investigator. Documentation of IRB membership and procedures was not provided, although a statement was made by the IIRB that there had been no changes since this information had previously been submitted to EPA.

(e) What standard(s) of ethical conduct would govern the work?

"U.S. EPA Good Laboratory Practice Regulations (40 CFR 160); 40 CFR 26 subparts K and L; FIFRA §12(a)(2)(P); California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710)." (p. 5)

8. Informed Consent

(a) Will informed consent be obtained from each prospective subject? Yes.

(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR 26.1117? Yes.

(c) Do the informed consent materials meet the requirements of 40 CFR 26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research? Yes.

(d) What is the literacy rate in English or other languages among the intended research subjects?

100%. English literacy is a requirement for participation.

(e) What measures are proposed to overcome language differences, if any, between investigators and subjects? n/a

(f) What measures are proposed to ensure subject comprehension of risks and discomforts?

Frequent opportunities to ask questions.

(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

See pages 16-18 and ICF pp. 34-43

(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

Candidates are offered repeated opportunities to decide not to participate; participants are offered repeated opportunities to withdraw. Exclusion factors rule out participation by employees or students of the Study Director. Recruitment of alternate subjects ensures that subjects will not be reluctant to withdraw lest the validity of the investigation be compromised.

9. Respect for Subjects

(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?

Subjects are identified by name and by number. Only the number is used on data collection forms for repellency phase, but both name and number are appear on the sample form for the dosimetry phase (p. 31.) It would be better to use only the subject number on all but one master directory that linked names to numbers. Recruitment of alternate subjects provides an opportunity for discrete withdrawal without explanation. Subjects are told they have access to their own records, and that they will not be identified in any published reports of the study. (p. 41)

(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

Subjects are so informed in the recruitment process (pp. 16-17) and in the Informed Consent Form (pp. 40-41).

(c) How will subjects who decline to participate or who withdraw from the research be dealt with?

Subjects who decide not to participate will simply go their way. Subjects who withdraw from the research will be paid for their time (p. 41). How soon after they withdraw they will be able to leave the field study site will depend on how they got to the field study site; this is not explained.

§ 26.1111 Criteria for IRB approval of research
Protocol SCI-001

Criterion	Y/N	Comment/Page Reference
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	N/A	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	N	Informed Consent Form provided is not appropriate for untreated control subjects
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	N/A	

§26.1116 General requirements for informed consent
Protocol SCI-001

Criterion		Y/N	Comment/Page Reference
No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative		OK	All subjects will provide legally effective informed consent.
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		OK	The procedure described in §9.1.4.2 provides sufficient opportunity to consider. . . and minimizes the possibility of coercion or undue influence.
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		OK	Information is clearly presented in plain English
No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence		OK	The IC contains no exculpatory language
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	OK	p. 34
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	N	pp. 39-40. Second para p. 39 not applicable; must be replaced. Else OK
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	OK	p. 41
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	OK	p. 40
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	OK	p. 41
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	OK	Compensation p. 41 Treatment p. 40
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	OK	p. 41
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	OK	p. 41-42
(b) When appropriate, one or more of the following elements of information shall also be	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	OK	p. 40
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	OK	p. 42
	(3) Any additional costs to the subject that may result from participation in the research	OK	p. 41
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	N/A	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	OK	p. 40
	(6) The approximate number of subjects involved in the study	OK	p. 35
(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		OK	p. 34

§26.1117 Documentation of informed consent
Protocol SCI-001

Criterion	Y/N	Comment/Page Reference
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.	OK	Form pp. 34-43 Procedures pp. 16-18
(b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or	OK	Proposed IC form meets requirements of §26.1116; procedure described in protocol §9.1.4.2 provides adequate opportunity to read it before it is signed.
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	N/A	

40 CFR 26.1125 Submission of proposed human research for EPA review
Carroll-Loye SCI-001 (Version of 11/2/2006)

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

	Requirement		Y/N	Comments/Page Refs
The following Information, to the Extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 4-5, 39-40
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 4, 5, 8, 12, 19, 22-24
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	pp. 5, 41
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	p. 3
		(5) The balance of risks and benefits of the proposed research.	Y	pp. 4-5
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	pp. 33-43. 11/7Revised ICF approved by IRB. 11/3 ICF not provided; explained by PI in email 11/17
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 15-16. No advertisements used
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	pp. 16-17
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Part	See separate file of email 11/3-11/8. Cited fax and set-up form not included. Cited site questionnaire submitted by Email 11/17.
	§1125(f): Official notification to the sponsor or investigator. . . that research involving human subjects has been reviewed and approved by an IRB.		Y	p. 33
all information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	pp. 1-32, 34-78 None accompanied the proposal p. 34-42 Initial review of new proposal
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y Y Y n/a n/a	IRB minutes in separate document submitted by R Roogow via Email 11/15/06 No changes required by IRB No controverted issues
	(3) Records of continuing review activities.		n/a	n/a for protocols
	(4) Copies of all correspondence between the IRB and the investigators.		N	Not provided by IIRB; see note above re §1125(e)
	(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y Y	Reported in R Roogow Email of 11/15 to be unchanged from prior submission associated with protocols EMD-003 and EMD-004 and on file with EPA
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		Y	On file with EPA (Claimed CBI)
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	n/a for protocols