UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

September 15, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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

FROM: John M. Carley
Ethics Reviewer

Clara Fuentes, Ph.D.
Science Reviewer

TO: Sheryl Reilly, Chief
Biochemical Pesticides Branch, BPPD

REF: Carroll, S. (2006) Efficacy Test Protocol EMD-004: Test of Personal Insect Repellents, dated September 8, 2006. Unpublished document prepared by Carroll-Loye Biological Research. 56 p.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.

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.

The following elements were considered in this review:

- Protocol (9/8/06 with IRB approval 9/12/06)
- Errata 9/14/06
- Training Materials for subjects
    1. Observing mosquito landings and learning mechanical aspiration
    2. Practicing and performing dosimetry with Pump Spray, Aerosol Spray and Lotion delivery systems
- Minutes of IIRB consideration of EMD-004
- Correspondence between CLBR and IIRB
- IIRB Policy and Procedures (Claimed as CBI)
- California DPR Approval Letter

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. **Value of the Research to Society**: This study will test the efficacy in the field of three new formulations of the active ingredient IR3535 as a repellent for mosquitoes. Efficacy testing is an EPA requirement for registration of each product formulation claiming to repel mosquitoes. Understanding the efficacy of these formulations is important because consumers, who rely on repellents to avoid being bitten by insects, cannot readily assess the efficacy of a product independent of EPA's approval. There is potential benefit to society in developing additional safe and effective personal repellents, to protect against both nuisance pests and arthropod vectors of disease.

2. **Fair 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 exclusion factors rule out 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 users of repellents. There is no indication that any subjects will be from particularly vulnerable populations.

3. **Favorable Risk-Benefit Ratio**: Risks are characterized as possible irritation, headache, dizziness or temporary stomach distress from exposure to the test materials themselves, possible exposure to biting arthropods, and possible exposure to vectors of arthropod-borne diseases. Because of the 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 these risks is accurately described as "extremely small". There are no direct benefits to subjects. The low increment of

risk to subjects is reasonable in light of the expected societal benefits if this testing shows the test materials to be effective and, for example, less risky, lower priced, or otherwise more appealing to users than other repellents.

4. **Independent Ethics Review:** The Independent Investigational Review Board, Inc. of Plantation FL reviewed and approved the protocol and informed consent materials. The IIRB is independent of the investigators and sponsors.

5. **Informed Consent**: The protocol contains a complete and satisfactory description of the process by which potential subjects will be recruited and informed, and for seeking their written consent to participate. A copy of the IC material showing approval by the IRB has been incorporated into the protocol.

6. **Respect for Potential and Enrolled Subjects**: Methods proposed for managing information about prospective and enrolled subjects will ensure their privacy is not compromised. Subjects will be free to withdraw at any time, and will be reminded of this at several points. 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, 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.

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 calls for recruiting only subjects who are at least 18 years old and for excluding female subjects if they are pregnant or lactating. Thus if a study were executed according to this protocol, Section 26.1703 would not forbid EPA to rely on it.

D. Summary Assessment of Scientific Aspects of the Proposed Research

The study will test the efficacy of 3 new formulations containing the a.i. IR3535 as

mosquito repellents in the field. These formulations are new products proposed for registration. The main objective of the study is to quantify the lasting efficacy of the formulations to prevent mosquito landings in the field by employing the FCB (first confirmed bite or first confirmed landing with intent to bite) method. Complete protection time (CPT) will be given as an average of time from application of the repellent to FCB, averaged across 10 subjects. The amount of formulation typically applied by consumers will be estimated by passive dosimetry. Biting pressure will be monitored at fixed time intervals (1 minute every 15 minutes) during the test by two untreated subjects, both experienced test assistants. Mosquitoes landing on untreated test assistants will be aspirated for identification. Test subjects will be grouped in pairs to facilitate observations, and will expose small area of their skin to field populations of mosquitoes for 1 minute at 15 minute intervals. There is no need for negative controls to compare treatment means. All treatments are randomly assigned to subjects. Data will be summarized and presented as average CPT with confidence limits set at $P<0.05$, and its associated std. deviations.

E. Compliance with applicable Scientific standards

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

- Hypothesis to be tested,
- Experimental design for testing the hypothesis,
- Methods for estimating dose of test material,
- Approach for minimization of risk to human subjects
- Quantification of lasting 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 of 10 treated subjects
- Rationale for sample size of 2 negative control subjects to monitor biting pressure.
- Justification for sample size of 12 subjects to measure dosimetry.

Attachments:

1. Summary Review of Carroll-Loye Protocol EMD-004 dated 9/8/06
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

Summary Review of Carroll-Loye Protocol EMD-004 dated 9/8/06

1. EPA Protocol ID#

(a) Title: EMD-004 Test of Personal Insect Repellents

(b) Date: 8 September 2006

(c) Principle Investigator and any sub-investigators: Scott P. Carroll, PhD

(d) Participating Laboratories: Carroll-Loye Biological Research, 711 Oak Avenue, Davis CA 95616

(e) Sponsor: EMD Chemicals, Inc., 7 Skyline Drive, Rona-Cosmetic Business Unit, Hawthorne NY 10532

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

2. Societal Value of Proposed Research: This study will test the efficacy of three new formulations of the active ingredient IR3535 as a repellent for mosquitoes. Efficacy testing is an EPA requirement for registration of each product formulation claiming to repel mosquitoes. Understanding the efficacy of these formulations is important because consumers, who rely on repellents to prevent being bitten by insects, cannot readily assess the efficacy of a product independent of EPA's approval. There is potential benefit to society in developing additional safe and effective personal repellents, to protect against both nuisance pests and arthropod vectors of disease.

(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." *[p. 3]*

(b) Does it address an important question? Would it fill an important gap in understanding? Yes. This study will test the efficacy of three new formulations of the active ingredients IR3535 as a repellent for mosquitoes. Efficacy testing is an EPA requirement for registration of products claiming to repel mosquitoes. Understanding the efficacy of these formulations is important because consumers, who rely on repellents to avoid being bitten by insects, cannot readily assess the efficacy of a product independent of EPA's approval.

(c) Have appropriate prerequisite studies been performed? Yes. The toxicity of IR3535 has been evaluated in an appropriate range of animal toxicity studies. In addition, insect repellent efficacy studies of other formulations containing IR3535 have established the ingredient's repellent properties.

(d) Could the question be answered with existing data? No. None of the existing mosquito repellent studies with IR3535 have been performed with the proposed test materials. Since efficacy is known to differ according to formulation of a repellent, EPA requires testing of each product proposed for registration.

(e) Could the question be answered without newly exposing human subjects? "Human subjects are required because they represent 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. There are no accepted methods for modeling the complex relationship between spray delivery systems and target subjects. At least ten subjects are required in order to reduce variation around the population means we will describe." *[p. 4]*

(f) What are the potential societal benefits of the research? "Insect-borne disease is of growing significance in the United States and around the world. . . . Discomfort associated with nuisance biting insects 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 restricted its use below a level ideal for public and personal health issues. . . . This study tests a repellent of well-known high efficacy, consumer safety, and acceptability. . . . [A] test such as this one is the only path toward further product development and greater availability of superior IR3535 products to consumers in the US." *[p. 6-7]*

The data will indicate whether the proposed formulations are effective mosquito repellents. If the products are shown to be effective, the data may support EPA approval of new products. Such products may provide social benefits because, for example, they may be more effective, less risky, lower priced, or otherwise more appealing to users. If the products are ineffective, EPA will not approve their registration.

(g) What is the likelihood those benefits will be realized? The study should provide adequate information to assess the efficacy of the test materials in repelling mosquitoes.

(h) How would the study be used by EPA? To address the requirement for demonstrating product formulation-specific efficacy of mosquito repellents as a condition for their registration.

3. Study Design: The study will test the efficacy of 3 new formulations containing the a.i. IR3535 as mosquito repellents in the field. These formulations are new products proposed for registration. The main objective of the study is to test the hypothesis that the efficacy of the formulations to prevent mosquito landings lasts at least for 2 hours, minimum PT, by using the FCB method of measuring efficacy. CPT will be given as an average of time from application of the repellent to FCB, averaged across 10 human subjects. The amount of formulation typically applied by consumers will be estimated by passive dosimetry. Biting pressure will be monitored at fixed time intervals during the test by 2 experienced test assistants. Field mosquitoes landing on untreated test assistants will be aspirated for identification. Test subjects will be grouped in pairs to facilitate observations, and will expose small area of their skin to field populations of mosquitoes for 1 minute at 15 minute intervals. There is no need for negative controls to compare treatment means. All treatment are randomly assigned to subjects. Data will be summarized and presented as average CPT with confidence limits set at $P<0.05$, and its associated std. deviations.

(a) Does the proposed research have a clear scientific objective? Yes. The objective of the first dosimetry phase of the research is to establish the typical consumer dose through passive dosimetry. The objective of the repellent phase of the research is to measure the length of time that a particular test material repels mosquitoes from landing with intent to bite on the portion of a subject's skin that has been treated with a specified quantity of the test material.

(b) Is there an explicit hypothesis? Yes, The hypothesis is that each test material will repel native populations of mosquitoes for at least two hours. "The hypothesis that the test materials will significantly reduce the number of mosquitoes LIBing on treated versus untreated skin is not the focus of this study. The focus is to compute, for each test material, a reasonable estimate of mean and standard deviation for the duration between application and sufficient repellency breakdown such that two mosquitoes LIBe on a subject within a half hour period. That pattern is here assessed at a resolution of 15 minutes." *[p.36-7]*

(c) Can the study as proposed achieve those objectives or test these hypotheses? Yes.

(d) Does the study have adequate statistical power to definitively test the objectives/hypotheses? Statistical power is discussed on pp. 15-17

(e) How will human subjects be exposed in the research? In the first, "dosimetry" segment of the research investigators will familiarize the subjects with the application methods for each of three formulations, and then measure the actual dose applied by each subject to achieve "full coverage" of their forearm or lower leg. In the second, main segment of the research investigators will apply test material to one limb of each subject at a standard concentration. Application will be by pipette, with the applied dose distributed evenly over the limb by a laboratory technician. Subjects will be trained to remove mosquitoes landing with the intent to bite before they have time to bite. Ambient mosquito pressure will be established and confirmed by exposure of one untreated control subject limb for 1 minute every 15 minutes during the test period. Efficacy of test materials will be measured by counting landings with intent to bite on treated limbs exposed for 1 min. of each 15 min.

(f) What is the basis for the choice of test material and formulation? The three formulations proposed for testing are the same formulations proposed for registration.

(g) What is the basis for the choice of dose/exposure levels and the staging of dose administration? "Dosage for repellency testing will be the mean of the subject means determined for each product in the dosimetry portion of this study." *[prot. p. 6]* This is consistent with the guideline recommendation to use a "typical consumer-applied dose".

(h) What endpoints will be assessed? Are they appropriate to the question(s) being asked? "The main endpoint of this study will be the conclusion of a mosquito repellent efficacy test conducted in the field . . . , with the data set suitable for submission to US EPA for insect repellent registration purposes." *[p. 4]* "Complete protection time . . . is defined herein as, for each subject, the time between application of Test Material and the First Confirmed 'Lite with Intent to Bite.' A 'Lite with intent to Bite', or 'LIBe', occurs when a mosquito alights on the treated test skin of a subject and extends its proboscis to the skin surface while ceasing locomotion." *[p. 3]* "Mean CPT will be calculated across all 10 subjects per treatment, and will be presented with standard deviation and 95% confidence interval information as well." *[prot. p. 29]*

(i) Will measurements be accurate and reliable? Yes.

(j) What is the rationale for the choice of sample size? "Dosimetry: 12 subjects per treatment formulation. . . . Repellent efficacy: 10 subjects per treatment formulation and 2 untreated control subjects." *[p. 15]* The rationale for these sample sizes is on pp. 15-17.

(k) Are there adequate and appropriate negative and positive controls? See pp. 10-11. "Two personnel who will monitor ambient biting pressure with untreated limbs are also listed . . . . Negative control subjects are attended by two assistants who use mechanical aspirators to remove all mosquitoes that LIBe before biting commences." *[p. 13-14]* "You will be randomly (by chance) assigned to receive one or two of the three products. . . . Experienced personnel will also be present to record the activity of mosquitoes by exposing their own arms or legs without repellent applied. However, you will not be asked to expose untreated skin and should avoid doing so." *[p. 50]*
The protocol provides for no positive controls.

(l) What is the plan for allocating individuals to treatment or control groups? "Subjects will be assigned to the treatment (but not negative control) groups on the basis of a randomly assigned subject number." *[p. 13]*

(m) Can the data be statistically analyzed? Yes. CPT can be calculated for each individual, and the mean CPT, the standard deviation, and the 95% confidence intervals can be calculated for the subjects receiving each test material. .

(n) Are proposed statistical methods appropriate to answer the question? Yes.

(o) Will point estimates be accompanied by measures of uncertainty? Yes. See 3(h) above.

4. 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 exclusion factors rule out 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 users of repellents. There is no indication that any subjects will be from particularly vulnerable populations.

(a) Can the findings from this proposed study be generalized beyond the study sample? Yes

(b) What was the basis for choosing the target population? The population of concern consists of people who would purchase and use insect repellents. Little information is available to characterize the population of concern, 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 specifically screened for past or future use of repellents.

(c) Are planned 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) Are inclusion/exclusion criteria complete and appropriate? Inclusion: ≥18, 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 3 days 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. *[p. 15]*

(e) How and 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. Follow up contact method: telephone interview, personal interview with the Study Director conducted at the Carroll-Loye Biological Research Offices." *[p. 18]*

(f) Are any potential subjects from vulnerable populations? No. **If so, what is the justification for including them?** n/a

(g) If any subjects are potentially subject to coercion or undue influence, what additional safeguards are proposed to protect their rights and welfare? "Students in [the PI's] laboratory who depend on him directly for employment or scholastically are not eligible to participate." *[p. 18]*

5. Risk/Benefit: Risks are characterized as possible irritation, headache, dizziness or temporary stomach distress from exposure to the test materials themselves, possible exposure to biting arthropods, and possible exposure to vectors of arthropod-borne diseases. Because of the 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 these risks is accurately described as "extremely small". There are no direct benefits to subjects. The low increment of risk to subjects is reasonable in light of the expected societal benefits if this testing shows the test materials to be effective and, for example, less risky, lower priced, or otherwise more appealing to users than other repellents.

(a) What are the qualitative risks of the proposed research? "The study-associated risks are of three types: exposure to the test materials themselves, exposure to biting arthropods, and possible exposure to vectors of arthropod-borne diseases." *[p. 5]* "The spray repellents contain alcohol and are flammable. The repellents may cause skin, lung, and eye irritation. Excessive inhalation can cause lung irritation, headache and dizziness. Swallowing the products may cause temporary stomach distress." *[p. 53]*

(b) What is the probability of each risk associated with the research? "The repellent active ingredient has a low acute and chronic risk profile, established both through experimentation and through long-term consumer use. . . . 'Repeat' exposures during dosimetry are all of very brief [duration] before the repellent is washed off, and total a much briefer duration of exposure than a typical single consumer application likely would. Risks associated with inhalation and ingestion would require gross intentional mishandling by subjects, a factor that the study methods do not promote." *[p. 5]* . "In summary, the combination of technical precautions and natural factors means that the chances that any subject will contract West Nile fever or another disease from a mosquito bite are probably extremely small." *[p. 6]* "In addition, there is a slight possibility that you will contract a disease carried by mosquitoes if you are bitten, such as West Nile virus or equine encephalitis. This test is being conducted in an area in which such viruses have not been detected by state health or mosquito control agencies for at least a month, so the risk is probably low that any individual mosquito that might bite you carries a disease. In addition, since you are wearing repellent and other protective measures, and are carefully watching for mosquitoes that land and try to bite, 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. 53]*

(c) What steps have been taken to minimize the 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. In addition, subjects will be trained to quickly remove any mosquitoes that attempt to bite them, before penetration or injection of saliva if possible. Moreover, a stopping rule instructs subjects to cover any treated skin immediately if more than one mosquito attempts to bite during any exposure period. Subjects will be exposing small areas of treated skin for only 4 minutes per hour. Other parts of the body will be protected with provided netting." *[p. 5]*
[Untreated] control subjects will be chosen only from among individuals that are experienced in field biology or entomology. *[p. 12]* "Negative control subjects are attended by two assistants who use mechanical aspirators to remove all mosquitoes that LIBe before biting commences." *[p. 14]*

"Preparatory training of the subjects to recognize and remove mosquitoes that lite with intent to bite contributes to subject safety. Subject safety is also enhanced by brief periods of exposure at intervals, as well as careful dosing and application." *[p. 31]*
"You will also be given protective material to prevent bites on other parts of your arms and legs, plus a head net." *[p. 51]*
"If any mosquitoes land and attempt to bite the skin with repellent, you will remove them immediately with the mosquito catcher. If at any time you have difficulties using the mosquito catcher you should push the mosquito from your skin with the plastic nozzle of the catcher. You may also use your finger to brush any mosquito aside." *[p. 52]*

(d) Does the protocol include a stopping rule? A medical management plan? Safety monitoring?
"Any subject showing adverse skin reactions will immediately stop further participation. . . . On the day of testing, we will alert the nearest hospital of the scope of our activities in advance of commencing treatment and data collection. 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. . . . In addition, we will personally transport affected persons to the nearest hospital if so advised by emergency personnel. There is sufficient redundancy in personnel that in such a case subjects remaining at the study site will still receive appropriate technical, scientific and safety guidance. All subjects are asked to contact the Study Director and a physician of their own choice at any time should they develop a rash (a delayed hypersensitivity reaction) within 48 hours of the conclusion of the test day. . . . As part of Medical Management, the Study Director will record all benign and adverse health observations." *[p. 22]*
"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 subject 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 that recollection . . . . If verified, the subject is instructed to immediately cover the limb." *[p.34]* "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 . . , you should cover that skin and not expose it again." *[p. 52]*

(e) Is post-exposure monitoring or follow-up of long enough duration to discover adverse events which might occur? "For up to two weeks after the test, be alert for any flu-like symptoms (unusual tiredness or unusually severe headaches, body aches, fever, or a rash on the trunk of the body). About 1-in-150 infected people will develop more serious symptoms including neck stiffness, stupor, disorientation and possibly coma and paralysis. . . . 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." *[pp. 53-4]*

(f) What benefits, if any, would accrue to individual subjects? "There are no immediate benefits to you from your participation." *[p. 54]*

(g) 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. Payment will be made at the end of each visit or whenever you withdraw from the study." *[p. 55]*

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

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

(j) How do anticipated societal benefits of the research weigh against the risks to individual subjects? The protocol *[p. 6]* characterizes risks as "slight" and societal benefits as "substantial and reasonably likely."

(k) Are the risks to subjects reasonable in light of the anticipated societal benefits of the research? Yes

6. Independent Ethics Review: The Independent Investigational Review Board, Inc. of Plantation FL reviewed and approved the protocol and informed consent materials. The IIRB is independent of the investigators and sponsors.

(a) What IRB reviewed the proposed research? Independent Investigational Review Board, Inc., 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) Are complete records of the IRB review as required by 40 CFR 26.1125 available? No

(e) Does the protocol identify the standard(s) of ethical conduct which will 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. 7]*

7. Informed Consent: The protocol contains a complete and satisfactory description of the process by which potential subjects will be recruited and informed, and for seeking their written consent to participate. A copy of the IC material showing approval by the IRB is incorporated into the protocol.

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

(b) Will informed consent be appropriately documented? Yes. See IC document pp. 48-56

(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, if any, is the relationship between the investigator and the subjects? "Our subjects are mainly University of California—Davis graduate and undergraduate students in life science programs with which the Principal Investigator is associated." *[p. 18]*

(e) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence? "Students in [the PI's] laboratory who depend on him directly for employment or scholastically are not eligible to participate." *[p. 18]*
(f) What measures are proposed to ensure subject comprehension of risks and discomforts? Repeated opportunities to ask questions.
(g) What is the literacy rate in English or other languages among the intended research subjects? 100%
(h) What measures are proposed to overcome language differences between investigators and subjects? n/a
(i) What procedure will be followed to inform prospective subjects and to seek and obtain their consent? See protocol pp. 18-20 and IC document pp. 48-56.
8. Respect for Subjects: Methods proposed for managing information about prospective and enrolled subjects will ensure their privacy is not compromised. Subjects will be free to withdraw at any time, and will be reminded of this at several points. Medical care for research-related injuries will be provided at no cost to the subjects.
(a) Will information about prospective and enrolled subjects be managed so as to ensure their privacy? "Subjects will initially be identified by first and last name, and assigned a unique number for purposes of this study. Individual data will be entered into the computer for retention and analysis with reference to individual number, not name. Records relating individual names to individual numbers will be retained separately." *[p. 19]*
(b) Will subjects be free to withdraw from the research at any time without penalty? "To candidates that pass screening the PI describes the test purpose in plain language (in English), and the procedures and comportment to be followed are described in detail. Candidates are then asked if they would like to retire from consideration at that point. If they wish to remain in consideration, it is explained and emphasized that they may withdraw from the test at any time during the test without penalty to their compensation." *[p. 19]*
(c) Will subjects receive needed medical care for research-related injuries at no cost? "If you are injured as a result of being in this study, medical treatment will be available from a health care facility that is aware of the study. 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. 54]*

§ 26.1111 Criteria for IRB approval of research

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.	Y	
(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

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 the protocol §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. 48
(2) A description of any reasonably foreseeable risks or discomforts to the subject	OK	pp. 52-54
(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	OK	p. 54
(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	OK	p. 54
(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	OK	p. 55
(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. 55 Treatment p. 54
(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. 55
(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. 55
(b) When appropriate, one or more of the following elements of information shall also be provided: (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. 54
(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	OK	p. 55-56
(3) Any additional costs to the subject that may result from participation in the research	OK	p. 55
(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. 54
(6) The approximate number of subjects involved in the study	OK	p. 49
(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. 49

§26.1117 Documentation of informed consent

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	pp. 48-56
(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	

§26.1125 Criteria for Completeness of Proposals for Human Research
Carroll-Loye Protocol EMD-004 dated 9/8/06

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
all information relevant to the proposed research specified by § 26.1115(a)		(1) Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.	 Y n/a Y n/a	 pp. 1-46 pp. 48-56
		(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	See IRB Review of EMD-004
		(3) Records of continuing review activities.	n/a	n/a for protocols
		(4) Copies of all correspondence between the IRB and the investigators.	Y	See IIRB—Carroll-Loye Correspondence
		(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	See IRB Review of EMD-004 See IRB Review of EMD-004
		(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).	Y	IRB procedures submitted under claim of confidentiality
		(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).	n/a	n/a for protocols
and the following additional information, to the extent not already included	§1125(a) A discussion of:	(1) The potential risks to human subjects	Y	pp. 5-6; pp. 52-54
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 5, 12, 14, 31, 51, 52
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 6-7; weak on distribution of benefits
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	p. 4
		(5) The balance of risks and benefits of the proposed research.	Y	p. 6-7
		§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	p. 48-56
		§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	p. 18-20
		§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	p. 18-19
		§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	Overlaps §1115(a)(4) above
		§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.	Y	p. 47