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 Tick 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-003: Test of Personal Insect Repellents, dated September 8, 2006. Unpublished document prepared by Carroll-Loye Biological Research. 51 p.

We have reviewed the referenced protocol for a laboratory test of tick 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 elements required by this rule are missing, although the approval of the California Department of Pesticide Regulation, required by California regulations for human pesticide exposure studies

conducted within that state, is not yet available.

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. Handling ticks and observing their movement on the skin
    2. Practicing and performing dosimetry with Pump Spray, Aerosol Spray and Lotion delivery systems
- Minutes of IIRB consideration of EMD-003
- Correspondence between CLBR and IIRB
- IIRB Policy and Procedures (Claimed as CBI)

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 of three new formulations of the active ingredient IR3535 as a repellent for the deer tick—the vector of Lyme disease. Efficacy testing is an EPA requirement for registration of each registered product formulation claiming to repel ticks. Understanding the efficacy of these formulations is important because consumers who rely on repellents to avoid being bitten by ticks cannot readily assess the efficacy of a product independent of EPA's approval.

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 nursing women, those in poor health or physical condition, those unable to speak and write English at a college level, and those in a dependent relationship to the investigator. 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 groups.

3. **Favorable Risk-Benefit Ratio**: Risks are characterized as possible irritation, headache, dizziness or temporary stomach distress from exposure to the test materials themselves, and possible exposure to arthropod-borne disease. Because of the low acute and chronic hazard profile of the materials, the design of the research to minimize exposures, and the use of laboratory-reared disease-free ticks, 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 tick 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 sponsors and investigators.

5. **Informed Consent**: The protocol contains an extensive 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 approved by the IRB is 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. 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

This study is a laboratory bioassay designed for characterizing repellency of new formulations containing IR3535 against nymphs of deer ticks, *Ixodes scapularis*. The hypothesis to be tested is that the test material is effective against the ticks. Efficacy will be measured principally as complete protection time, or CPT, using the First Confirmed Crossing (FCC) approach. The first crossing occurs when a tick walks from its initial position on the first orientation line more than 3 cms. into the treated area toward the elbow within 3 minutes, and is confirmed if it is followed by a second tick doing the same within 30 minutes. Both treated and

untreated arms are marked with 3 orientation lines, arrayed at 3 cms. apart to indicate direction of tick movement. A new tick exposure will occur every 15 minutes.

The typical amount of product applied by consumers will be determined by passive dosimetry. The treatments will consist of treated and untreated controls, using the same subjects. Each treatment will be randomly assigned and replicated 10 times. All ticks are lab reared, pathogen-free, and each tick will be used only once for each trial. All ticks will be tested for active questing behavior on the subjects' untreated arms before testing on the treated arms.

The rationale for the choice of sample size includes ethical as well as economic considerations for minimizing human exposure. Under adequate conditions (ambient, tick activity, and test material known to for exhibiting repellency greater than 0), adding replications beyond the minimum 6, increases precision of the mean estimate only slightly. In this study, the sample size has been increased to 10 to account for variability and improve accuracy. The statistical tests employed for analyses of the data is the mean of the CPT, within 95% confidence intervals, set at a level of significance $P<0.05$.

The negative controls are described as the untreated limb in each treated subject.. They are described as being treated identically as treated subjects except for not having the test material present. The protocol suggests the possibility of testing 2 very similar formulations (Pump and aerosol) simultaneously on the same subjects, pending consultation with US/EPA. That approach is discouraged by Agency guidelines.

E. Compliance with applicable Scientific standards

This protocol adequately addresses the following components, which satisfy applicable scientific standards:

- Hypothesis to be tested, and description of end point.
- Methods for estimating dose of test material,
- Approach for minimization of risk to human subjects
- Characterization of product performance as lasting repellency from time of product application to repellency breakdown, measured by 2 ticks crossing repellent lines within 30 minutes period. That pattern is assessed at a resolution of 15 minutes exposure per tick..

The protocol fully satisfies applicable scientific standards if the Agency's recommendation is followed concerning the experimental design:

- Experimental design for testing the hypothesis: Test materials will be randomly distributed among test subjects as described in tabulated form on page 12 of this protocol. Each subject will be randomly assigned to one treatment, including its own control. Agency's guidelines discourage the simultaneous testing of more than one treatment per subject. Doing so in this study will reduce the sample size for controls, and create an experimental design having unequal number of replications.

Attachments:

1. Summary Review of Carroll-Loye Protocol EMD-003 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-003 dated 9/8/06

1. EPA Protocol ID#

(a) Title Test of Personal Insect Repellents EMD-003

(b) Date September 8, 2006

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

(d) Participating Laboratories Carroll-Loye Biological Research, 711 Oak Ave. 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, Plantation FL

2. Societal Value of Proposed Research: This study will test the efficacy of three new formulations of the active ingredients IR3535 as a repellent for the deer tick—the vector of Lyme Disease. Efficacy testing is an EPA requirement for registration of each product formulation claiming to repel ticks. Understanding the efficacy of these formulations is important because consumers who rely on repellents to avoid being bitten by ticks cannot readily assess the efficacy of a product independent of EPA's approval.

(a) What is the stated purpose of the proposed research? "To test the repellent characteristics of the test materials against *Ixodes scapularis* ticks. . . . vector of the Lyme Disease pathogen." *[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 the deer tick—the vector of Lyme Disease. Efficacy testing is an EPA requirement for registration of products claiming to repel ticks. Understanding the efficacy of these formulations is important because consumers, who rely on repellents to avoid being bitten by ticks, cannot readily assess the efficacy of a product independently 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. There are limited data on the efficacy of IR3535 in repelling ticks, and none of the existing tick repellent studies 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." *[p. 4]*

(f) What are the potential societal benefits of the research? "Arthropod-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]*

The data will indicate whether the proposed formulations are effective tick 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 ticks.

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

3. Study Design: This study is a laboratory bioassay designed for characterizing repellency of new formulations containing IR3535 against nymphs of deer ticks, *Ixodes scapularis*. The hypothesis to be tested is that the test material is effective against the ticks. Efficacy will be measured principally as complete protection time, or CPT, using the First Confirmed Crossing (FCC) approach. The typical amount of product applied by consumers will be determined by passive dosimetry. The treatments will consist of treated and untreated controls, using the same subjects. Each treatment will be randomly assigned and replicated 10 times. All ticks are lab reared, pathogen-free, and each tick will be used only once for each trial. All ticks will be previously tested for questing behavior. The rationale for the choice of sample size includes ethical as well as economic considerations for minimizing human exposure. Under adequate experimental conditions (ambient, ticks activity, and test material known for exhibiting repellency greater than 0), adding replications beyond the minimum 6, increases precision of mean estimate only slightly. In this study the sample size has been increased to 10 to account for variability and improve accuracy. . The statistical tests employed for analyzes of the data is the mean of the CPT, within 95% confidence interval, set at a significant level of $P<0.05$. The negative controls are described as the untreated limb in each treated subject**.**

(a) Does the proposed research have a clear scientific objective? Yes. The objective of the research is to measure the length of time that a particular test material repels deer ticks from crawling onto the portion of a subject's skin that has been treated with a specified quantity of the material.

(b) Is there an explicit hypothesis? "The hypothesis that the test materials will significantly reduce the number of ticks Crossing 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 ticks crossing on a subject within a half hour period." *[p. 33]*

(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? The protocol discusses the statistical power of the study on pp. 14-16. "At least ten subjects are required in order to reduce variation around the population means we will describe." *[p. 4]*

(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. In the second, repellent segment of the research investigators will apply test material to one forearm of each subject at a standard concentration. Application will be by pipette, with the applied dose distributed evenly over the forearm by a laboratory technician. Subjects will then place disease-free, laboratory-reared ticks one at a time on their untreated arm to establish active questing behavior by each tick, and then place qualified ticks on the wrist of their treated arm. Behavior of the ticks will be observed and recorded; subjects are taught to remove all ticks before they bite.

(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? "The dosing rate will be the product of the subject's limb surface area multiplied by the grand mean .. . calculated in the dosimetry data analysis for that test material." *[p. 30]* 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? "[E]fficacy will be measured principally as Complete Protection Time. Complete protection time, or CPT, is defined herein as the time between application of Test Material and the First Confirmed Crossing (FCC). The FCC occurs when a questing tick placed adjacent to treated arm skin walks more than 3 cm into the treated area toward the elbow. A crossing will not be designated as an FCC unless it is followed by another crossing within 30 minutes." *[p. 3]* CPT measured in this way will yield a single time value for each subject. 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." *[p. 26]*

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

(j) What is the rationale for the choice of sample size? Protocol *[p. 14-16]* explains the rationale for using 10 subjects per treatment, each serving as its own concurrent negative control.

(k) Are there adequate and appropriate negative and positive controls? "The negative control is untreated for both dosimetry and repellency assays. Each subject simultaneously serves as a treatment and control subject." *[p. 9]* The protocol provides for no positive or vehicle controls. *[p. 10]*

(l) What is the plan for allocating individuals to treatment or control groups? "Subjects will be assigned to the treatment groups on the basis of a randomly assigned subject number." *[p. 12]*

(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 nursing women, those in poor health or physical condition, or those unable to speak and write English at a college level, and those in a dependent relationship to the investigator. 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 groups.

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

(b) What was the basis for choosing the population of concern? The population of concern consists of people who would purchase and use insect repellents. Little information is available to characterize this population, but it is presumed to be diverse in age, gender, physical size, general health, attractiveness to biting arthropods, and other characteristics. The population from which subjects are recruited appears to be chosen on 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 write English. Exclusion: phobic of ticks, sensitive to any product ingredients, poor physical condition, unwilling 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, inability to deliver test material to own arms, or student or employee of Study Director. *[pp. 13-14]*

(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. 17-18]*

(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. 17]*

5. Risk/Benefit: Risks are characterized as possible irritation, headache, dizziness or temporary stomach distress from exposure to the test materials themselves, and possible exposure to arthropod-borne disease. Because of the low acute and chronic hazard profile of the materials, the design of the research to minimize exposures, and the use of laboratory-reared disease-free ticks, 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 tick repellents.

(a) What are the qualitative risks of the proposed research? "The study-associated risks are of two types: exposure to the test materials themselves, and possible exposure to 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. 49]*

(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. While no bites are expected from this implementation of this protocol, . . . the testing will be conducted with laboratory-reared [ticks] descended from field caught adults. They are reared on quarantined rodents screened to be pathogen-free for all tick-transmitted pathogens and hantavirus using appropriate culture, direct detection (PCR), and immunological screening assays. In summary, the relatively benign quality of the repellents and the technical precautions we employ indicate that the chance that any subject will be at a health or safety risk is extremely small." *[p. 5]*

(c) What steps have been taken to minimize the risks to subjects? "Subjects with known allergic reactions to insect repellents and common cosmetics are excluded from participating." *[p. 5]* "Measures will be implemented to make sure that ticks are removed before they have an opportunity to bury in the skin." *[p. 49]*

(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." *[p. 20]* "Subjects will be trained by technical personnel in handling and observing ticks. . . . This 'hands-on' experience will assist subjects in collecting data accurately and handling ticks safely." *[p. 21]* "Subjects are directed to cease tick exposures when a crossing is followed by another crossing within one-half hour, i.e., in either of the subsequent two exposure periods." *[p. 31]* Medical management is discussed on pp. 20-21; see also 8(c) below.

(e) Is post-exposure monitoring or follow-up 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 (a delayed hypersensitivity reaction) within 48 hours of the conclusion of the test day." *[p. 21]*

(f) What benefits, if any, would accrue to individual subjects? "There are no immediate benefits to you from your participation other than compensation for your participation." *[p. 50]*

(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. 50]*

(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 of Plantation FL has reviewed and approved this revised protocol and informed consent form. The IIRB is independent of the sponsors and investigators.

(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) Are complete records of the IRB review as required by 40 CFR 26.1125 available? Yes
(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. 6]*
7. Informed Consent: The protocol contains an extensive 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 as approved 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 protocol pp. 45-51.
(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. 17]*
(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. 17]*
(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% (English)
(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 §9.1.4 *[pp. 16-18]* and IC document *[pp. 45-51]*.
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. 18]*
(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. 17]*
(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. 49]]*

§26.1111 Criteria for IRB approval of research
Carroll-Loye Protocol EMD-003 dated 9/8/06

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
Carroll-Loye Protocol EMD-003 dated 9/8/06

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 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. 45
(2) A description of any reasonably foreseeable risks or discomforts to the subject	OK	pp. 48-49
(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	OK	p. 50
(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	OK	p. 49
(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	OK	p. 50
(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	Reimbursement p. 50 Treatment p. 49
(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. 50
(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. 50-51
(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. 49
(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	OK	p. 51
(3) Any additional costs to the subject that may result from participation in the research	OK	p. 50
(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. 49
(6) The approximate number of subjects involved in the study	OK	p. 46
(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. 45

§26.1117 Documentation of informed consent
Carroll-Loye Protocol EMD-003 dated 9/8/06

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	IRB-approved consent form pp. 45-51 "I shall receive a copy of the signed Informed Consent Authorization" *[p. 51]*
(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 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-003 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	 Protocol pp. 1-43 Protocol pp. 45-51
		(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	IRB Review of EMD-003
		(3) Records of continuing review activities.	n/a	n/a for protocols
		(4) Copies of all correspondence between the IRB and the investigators.	Y	IRB Correspondence Record
		(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	IRB Review of EMD-003
		(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	Protocol pp. 5, 48-49
		(2) The measures proposed to minimize risks to the human subjects;	Y	Protocol pp. 5, 49
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	Protocol p. 6; weak on distribution of benefits
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Protocol p. 4
		(5) The balance of risks and benefits of the proposed research.	Y	Protocol p. 6
		§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Protocol pp. 45-51
		§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	Protocol p. 16
		§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	Protocol pp. 16-18
		§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	Protocol p. 44