UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

June 9, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of Protocol for Human Study of Tick Repellent Performance

FROM: John M. Carley

TO: Clara Fuentes, BPPD

REF: Carroll, S. (2006) Efficacy Test Protocol: Study EMD—003, dated April 13, 2006. Unpublished document prepared by Carroll-Loye Biological Research. 14 p. plus attachments.

I have performed an initial review of the referenced documents. This review assesses the ethical aspects of the proposed research in terms of current ethical standards, applying the "Summary Framework for Ethical Assessment Using Seven Criteria of Emanuel et al." developed by the EPA Science Policy Committee's Human Studies Work Group. The completed "framework" is attached. This framework was derived from the work of Emanuel, et al. (2000), which summarizes seven general principles for ethical treatment of human subjects in scientific research. The Emanuel article was primarily directed at those who consider proposals for new medical research and decide which are worthy of funding or approval. These are analogous to the decisions EPA must make when we review proposals for third-party research involving intentional exposure of human subjects, as provided for in 40 CFR 26.1125.

This is a protocol for a laboratory test of tick repellency. It is described as "functioning with the general permitted Carroll-Loye Protocol C-L-001." Attachments include an associated "Site Questionnaire" provided to the Independent Investigational Review Board, Inc., a five-page "Informed Consent Authorization to Participate as a Research Study Subject", the CDPR "Experimental Subject's Bill of Rights", and the record of approval of the protocol by the IIRB.

A. Summary Assessment of Ethical Aspects of the Proposed Research

Here is a summary of my observations about the proposed protocol under the seven headings used in the Emanuel framework. Supporting details are in the attachment.

1. **Value of the Research to Society**: The stated purpose of the protocol is "to test the repellent characteristics of the test materials. The design measures the barrier efficacy of the test formulation; biting is not assessed nor does it occur. . . . The main endpoint of this study will be the conclusion mosquito and tick repellent efficacy tests conducted in the field of an IR3535-based topical repellent [sic]."

   The purpose is better stated in the Informed Consent material: "to test the repellent characteristics of 3 formulations of the test material compared to an industry standard as a positive control and no treatment as a negative control in a laboratory setting using the western black-legged tick. The information gathered will be used to develop personal repellents for future commercial marketing."

   This is a laboratory test of tick repellency of three unregistered formulations containing the active ingredient IR3535, intended for submission to EPA to support repellent registration. 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. **Scientific Validity of the Research**: I defer to others for a full review of the scientific merits of this protocol. If it were determined not to have scientific validity, it would be unethical to proceed with the research.

3. **Fair Subject Selection**: Methods for recruiting subjects are well described in the cited generic protocol C-L-001. There is no indication that subjects would be subject to any coercion or undue influence, or be recruited or enrolled for reasons inconsistent with the goals of the research. Exclusion factors are employed to ensure exclusion of children and pregnant or lactating women.

4. **Favorable Risk-Benefit Ratio**: Materials have been pre-tested for acute toxicity. Candidates who are phobic about ticks are excluded. Ticks are removed before they have time to bite. Captive-raised ticks are established to be disease-free. There is no discussion of societal benefits or of how these benefits are weighed against risks to subjects. Subjects will be paid $15/hour.

5. **Independent Ethics Review:** The protocol and attachments was unanimously approved by Independent Investigational Review Board, Inc., of Plantation FL on April 18, 2006. IIRB is registered as an IRB with OHRP, and is independent of the investigators.

6. **Informed Consent**: The protocol promises that all subjects will be fully informed and will consent to participate. Procedures described for informing candidates

and seeking their consent are adequate. The informed consent materials provided should be corrected and revised as discussed below before use.

7. **Respect for Potential and Enrolled Subjects**: Subject privacy would not be compromised. Subjects would be free to withdraw at any time, and would be reminded of this from time to time.

B. 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 (considered together with the cited template proposal C-L-001) 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, and because this study would be conducted in California, the provisions of the California Code of Regulations, Title 3, §6710 would apply as well.

Some ethical deficiencies are apparent when this proposal is reviewed against the provisions of these standards:

- In the Informed Consent (IC) materials under "Study Procedures/Study Design" subjects are told they may be randomly assigned to be untreated controls. This is inconsistent with the cited template protocol C-L-001, which states that only the Study Director or experienced management personnel will be used as untreated controls. These conflicting passages should be reconciled. It may be necessary to use different IC documents for treated subjects and untreated controls.

- The procedures to be followed are inadequately described to give potential subjects the information they need to make an informed decision to participate. In the IC under "Procedure" the statement "The ticks are then applied . . . and you will record any crossings or repulsions" should be expanded to explain more clearly all that the subjects will be expected to do—i.e., pick up a tick with an artist's paint brush, place it on their wrist, orient it toward their elbow, monitor its behavior for three minutes, dispose of the tick, record its behavior, and repeat the process every 15 minutes for several hours.

- The IC discussion of Risks/Discomforts vaguely states that "Measures will be implemented to make sure that ticks are removed before they have an opportunity to bury in the skin." This should be revised for clarity—perhaps to read "You will be taught how to remove ticks from your arm before they have an opportunity to bury in the skin or bite you. Although it is unlikely, because it takes a tick about 10 minutes to bury before biting, you may be bitten by a tick. The ticks used in this test are captive-bred and free of disease."

- The IC discussion of "Pregnancy Risks" is missing the word "NOT" which should appear in the context ". . . it is important that you do NOT participate in this study if you are, or think you may be pregnant."

- The IC discussion of "Research Related Injuries" is borderline exculpatory, and at the least confusing. The first two sentences are straightforward, promising that the investigators will pay for any treatment required for injury resulting from being in the study. But the third sentence excludes injuries "resulting from normal work activities", which is entirely irrelevant to this research, and the statement that "financial compensation for . . . such things as lost wages, disability, or discomfort due to injury is not available . . ." inappropriately attempts to place responsibility on the subjects for their own safety while they participate in the research. In addition, this passage seems inconsistent with the statement in section 4(H) of the cited template protocol C-L-001 that "there is no plan for compensation for injury due to the low levels of risk involved."

- It is inappropriate to discuss compensation in terms of direct benefits to the subjects, as is done in the IC materials. There are no direct benefits to the subjects from this research. It would, however, be appropriate to discuss here societal benefits of the research, and how they weigh against the risks to the subjects.

- In the IC discussion under the heading of "Confidentiality" the sponsor of the research is erroneously identified as Avon. In the same passage, the California Department of Pesticide Regulation should be added to the list of parties to whom personal information may be disclosed.

- The protocol should be amended to acknowledge the applicability of the standards of ethical conduct cited above, and the obligation to inform both the cognizant IRB and the California Department of Pesticide Regulation of any amendments or deviations from the approved protocol.

C. Standards for Judging Ethical Acceptability

On February 6, 2006, EPA published a final rule, "Protections for Subjects in Human Research," effective on April 7, 2006. Section 26.1703 of the final rule 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) or 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. Conclusion

I have deferred to others for an assessment of the scientific merit of this proposed research; if it is deemed not to be scientifically meritorious, it would be unethical to proceed with it. Also, notwithstanding the unanimous approval of the IRB, I have identified several deficiencies in the informed consent materials relative to the standards of 40 CFR part 26 and FIFRA §12(a)(2)(P). These deficiencies should be corrected before research begins.

Attachment

Cited reference:

Emanuel, E.; Wender, D.; Grady, C. (2000) What Makes Clinical Research Ethical? JAMA 283:2701-2711.

Framework for Ethical Assessment
Using Seven Criteria of Emanuel et al.[1]

June 9, 2006

Carroll, S. (2006) Efficacy Test Protocol: Study EMD—003, dated April 13, 2006. Unpublished document prepared by Carroll-Loye Biological Research. 14 p. plus attachments.

1. Value: The stated purpose of the protocol is "to test the repellent characteristics of the test materials. The design measures the barrier efficacy of the test formulation; biting is not assessed nor does it occur. . . . The main endpoint of this study will be the conclusion mosquito and tick repellent efficacy tests conducted in the field of an IR3535-based topical repellent [sic]."

The purpose is better stated in the Informed Consent material: "to test the repellent characteristics of 3 formulations of the test material compared to an industry standard as a positive control and no treatment as a negative control in a laboratory setting using the western black-legged tick. The information gathered will be used to develop personal repellents for future commercial marketing."

This is a laboratory test of tick repellency of three unregistered formulations containing the active ingredient IR3535, intended for submission to EPA to support repellent registration. 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 research?
"To test the repellent characteristics of the test materials. The design measures the barrier efficacy of the test formulation; biting is not assessed nor does it occur. . . . The main endpoint of this study will be the conclusion mosquito and tick repellent efficacy tests conducted in the field of an IR3535-based topical repellent [sic]" (p. 2) The purpose is better stated in the Informed Consent material: "to test the repellent characteristics of 3 formulations of the test material compared to an industry standard as a positive control and no treatment as a negative control in a laboratory setting using the western black-legged tick. The information gathered will be used to develop personal repellents for future commercial marketing."

b. Does it evaluate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being?
No

c. Does it test a hypothesis that can generate important knowledge about human biological systems?
No

d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?
Society can benefit from development of safe and effective personal repellents. If the tested product is proven effective, it could protect users from tick bites.

e. What government, organization, company and/or institution(s) funded the research?
EMD Chemicals, Inc.

2. Scientific Validity: I defer to others for a full review of the scientific validity of this protocol. If it were determined not to have scientific validity, it would also not be ethically acceptable.

a. Does the design have a clear scientific objective?
The purpose of the research is stated in overly general terms, with an uninterpretable statement of endpoints.

b. Does the design use accepted principles, methods, and reliable practices?
I defer to others for this judgment

c. In what way will human subjects be exposed in this research, and what endpoints will be measured?
Subject's arms are treated from wrist to elbow with repellent. Once every 15 min. each subject selects an active tick and places it on his/her wrist, and orients it toward the elbow. The subject monitors the tick's behavior for 3 min, removes the tick before it has time to bite, disposes of the tick and records the result for each tick as either "repelled" or "not repelled". This cycle is repeated for several hours until repellency fails.

d. Does the research design have sufficient power to definitively test the objective?
I defer to others for this judgment. The use of 6 subjects per treatment and only one subject per control limits the ability to express results in terms of relative protection.

e. To what purpose is the study used, or proposed for use, in the Agency?
This study is intended for submission to EPA to support registration of personal repellent products.

3. Fair Subject Selection: Methods for recruiting subjects are well described in the cited generic protocol C-L-001. There is no indication that subjects would be subject to any coercion or undue influence, or be recruited or enrolled for reasons inconsistent with the goals of the research. Exclusion factors are employed to ensure exclusion of children and pregnant or lactating women.

a. Are subjects recruited and enrolled solely on the basis of the scientific goals of the study?
Yes

b. Are any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished? Does the burden of participation fall disproportionately on a particular group?
Per the cited generic protocol C-L-001, subjects must be at least 18, in good health and physical condition, and women must not be pregnant or lactating. Recruiting is by word of mouth in an academic setting. Employees or students of the investigators are excluded as subjects. Untreated control subjects are "always Study Directors or experienced management personnel"; it is these who are at greatest risk from tick bites, and their participation may be a requirement of their employment.

c. Will any subjects be under 18? Pregnant? Nursing? Children and pregnant or nursing women are excluded. The Informed Consent package as approved by the IRB, however, erroneously states that it is important that pregnant or nursing women DO participate in the research. (IC p. 3)

4. Favorable Risk-Benefit Ratio: Materials have been pre-tested for acute toxicity. Candidates who are phobic about ticks are excluded. Ticks are removed before they have time to bite. Captive-raised ticks are established to be disease-free. There is no discussion of societal benefits or of how these benefits are weighed against risks to subjects. Subjects will be paid $15/hour.

a. How are the risks to individual subjects minimized?
Materials have been pre-tested for acute toxicity. Candidates who are phobic about ticks are excluded. Ticks are removed before they have time to bite. Captive-raised ticks are established to be disease-free.

b. If the research presents no direct benefits to individual subjects, what are the expected societal benefits from the study, and do they justify the incremental risk to individual subjects?
Society can benefit from additional safe and effective tick repellents. There is no discussion of how these benefits are weighed against risks to subjects.

c. What compensation will be paid to the participants in the study?
This protocol states that subjects will be paid $15/hour.

5. Independent Ethics Review: The protocol and attachments was unanimously approved by Independent Investigational Review Board, Inc., of Plantation FL on April 18, 2006. IIRB is registered as an IRB with OHRP, and is independent of the investigators.

a. Has the research proposal been approved by an ethics review body?
Yes. It was approved by the Independent Investigational Review Board, Inc., of Plantation FL on April 18, 2006.

b. Was the independent ethics review by individuals unaffiliated with the clinical research?
Yes. The IIRB is registered as an IRB with OHRP.

c. Was the research proposal asserted to comply with the Common Rule?
No

d. Does the research institution (or any institution participating in the research) hold a Federal Wide Assurance from DHHS/OHRP?
No

e. Is the research proposal asserted to comply with another standard of ethical conduct?
No. Compliance is asserted with 40 CFR Part 160 (Good Laboratory Practice), and mention is made of "California State EPA study monitoring." (p. 2)

6. Informed Consent: The protocol promises that all subjects will be fully informed and will consent to participate. Procedures described for informing candidates and seeking their consent are adequate. The informed consent materials provided should be corrected and revised before use.

a. Does the research proposal assert that informed consent will be obtained from all participants?
Yes

b. How and under what circumstances will informed consent be obtained?
In a preliminary phone interview the study and test materials are described and subject questions are addressed. Exclusion criteria are exercised at this time. Risks and rewards of participation are described. All interested candidates then participate in a one-hour briefing on risks of participation, test procedures, etc. Copies of the California Experimental Subject's Bill of Rights and of the Informed Consent materials are provided to candidates and read aloud to them. Candidate questions are addressed. Candidates are then asked either to withdraw or to sign the consent form.

7. Respect for Potential and Enrolled Subjects: Subject privacy would not be compromised. Subjects would be free to withdraw at any time, and would be reminded of this from time to time.

a. Is information about individual subjects managed so as to ensure their privacy?
Yes.

b. Are subjects free to withdraw from the research without penalty?
Yes.

[1] Emanuel, E; Wender, D; Grady, C (2000) What Makes Clinical Research Ethical? JAMA 283:2701-2711.