UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

June 5, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of Protocol Template for Human Studies of Arthropod Repellent Performance

FROM: John M. Carley

TO: Clara Fuentes, BPPD

REF: Carroll, S. (2006) Test of Personal Insect Repellents Protocol Number C-L—001, dated March 30, 2006. Unpublished document prepared by Carroll-Loye Biological Research. 14 p.

McSharry, A. (2006) "Approval Template Clinical Research Protocol dated: March 30, 2006. Memo from Independent Investigational Review Board, Inc., of Plantation FL to Scott Carroll reporting approval of protocol CL-001. 1 p.

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 generic protocol. It was developed to submit annually to the California Department of Pesticide Regulation (CDPR) to cover a broad range of both laboratory and field studies of repellent performance against mosquitoes, biting flies, fleas, and ticks. It provides general background information and procedures to be used in research to evaluate the efficacy of

personal repellents performed by Carroll-Loye Biological Research. The investigator has provided additional information in study-specific protocols that are discussed separately.

A. Summary Assessment of Ethical Aspects of the Proposed Research

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

1. **Value of the Research to Society**: 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. Because of the special attraction of biting arthropods to humans and their role in disease transmission, EPA requires testing with human subjects to establish efficacy.

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

3. **Fair Subject Selection**: Methods for recruiting subjects are well described. 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**: The generic protocol evidences concern for risk reduction, but the balancing of risks and benefits can only be done on a study-specific basis.

5. **Independent Ethics Review:** This generic protocol was unanimously approved by Independent Investigational Review Board, Inc., of Plantation FL on April 4, 2006 “as a template for future research.”

6. **Informed Consent**: The generic 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. A promised generic consent form was not attached to the protocol.

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 generic template 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, and for any study conducted in California, the provisions of the California Code of Regulations, Title 3, §6710 apply as well.

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

- Section 4(G)(11) states that subjects "are orally informed of the risks of disease contraction" on several occasions. The risk of contracting disease should also be discussed in writing as part of a complete discussion of risks in the pre-consent information package.

- Section 4(H) states that "there is no plan for compensation for injury due to the low levels of risk involved. . . ." The risk of contracting an arthropod-borne disease through participation in a field test may be low, but it is not zero. Planning for the possibility that subjects may be bitten by a disease-carrying insect is essential both to risk minimization and to fully informing potential subjects.

- The generic protocol should be amended to acknowledge the applicability of the standards of ethical conduct cited above, and the obligation to inform the cognizant IRB and, if a study is conducted in California, 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 identified several deficiencies relative to the standards of 40 CFR part 26 and FIFRA §12(a)(2)(P). These deficiencies should be corrected in future versions of this generic protocol, and before any specific studies are conducted relying on this protocol.

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 5, 2006

Carroll, S. (2006) Test of Personal Insect Repellents Protocol Number C-L—001, dated March 30, 2006. Unpublished document prepared by Carroll-Loye Biological Research. 14 p.

1. Value: 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. Because of the special attraction of biting arthropods to humans and their role in disease transmission, EPA requires testing with human subjects to establish efficacy.
a. What is the stated purpose of the research? "To describe the procedures used to evaluate the efficacy of personal repellents to biting arthropods." (p. 1)
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
e. What government, organization, company and/or institution(s) funded the research? n/a. This is a generic protocol, and requires supplementation before it could be executed or approved.
2. Scientific Validity: I defer to others for a full review of the scientific validity of this generic 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? This generalized template must be supplemented by a more specific study objective and design.
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? This generalized template does not describe how subjects will be exposed. Repellency may be measured and expressed in different ways, depending on the design of the specific test and the target organism.
d. Does the research design have sufficient power to definitively test the objective? I defer to others for this judgment. The use of 6-10 subjects per treatment and 1-2 subjects 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? Studies conforming to this template would be conducted to support registration of personal repellents.

3. Fair Subject Selection: Methods for recruiting subjects are well described. 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?
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 arthropod bites, and their participation may be a requirement of their employment.

4. Favorable Risk-Benefit Ratio: The generic protocol evidences concern for risk reduction, but the balancing of risks and benefits can only be done on a study-specific basis.

a. How are the risks to individual subjects minimized?
The protocol includes a list of 18 risk-reducing steps. These have some merit, but the assessment of risk minimization must be made for each specific protocol. The summary in this protocol is that risks are so low there is no need for a plan for compensation for research-related injury.

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?
Declining use of Deet-based repellents is documented, and alternatives are needed to protect against both nuisance pests and vectors of disease. There is no explicit discussion of how these benefits are weighed against risks to subjects; this balancing must be done for each specific protocol.

c. What compensation will be paid to the participants in the study?
This protocol states that subjects will be paid $14/hour.

5. Independent Ethics Review: This generic protocol was unanimously approved by Independent Investigational Review Board, Inc., of Plantation FL on April 4, 2006 "as a template for future research."

a. Has the research proposal been approved by an ethics review body?
Yes. It was approved "as a template for future research" by the Independent Investigational Review Board, Inc., of Plantation FL on April 4, 2006.

b. Was the independent ethics review by individuals unaffiliated with the clinical research?
Yes

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

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. A promised generic informed consent form was not attached to the protocol.

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 Subjects 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.