UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

June 9, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of AHETF Protocols for Human Exposure Studies

FROM: John M. Carley

TO: Richard Dumas, SRRD

REF: Johnson, D., (2006) Letter to Richard Dumas transmitting generic protocol and informed consent materials of Agricultural Handlers Exposure Task Force exposure studies. Dated March 2, 2006, with attachments.

Protocol AHE-34 dated 4/7/06: Closed System Mixing and Loading of Liquid Malathion in California

Protocol AHE-36 dated 4/13/06: Airblast Application of Malathion to Grapes in California

Protocol AHE-37 dated 4/7/06: Airblast Application of Diazinon to Grapes in New York

Protocol AHE-38 dated 4/7/06: Closed Cab Airblast Application of Carbaryl to Orchards in Georgia

Protocol AHE-42 dated 3/13/06: Fixed-Wing Aerial Application of Chlorothalonil to Potatoes and Onions in Oregon and Georgia

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 package includes a generic protocol with associated generic informed consent package, as well as five study-specific protocols and supporting documents which closely follow the generic template. Documentation of study-specific proposals includes the application form from the Western Institutional Review Board, and the Western IRB's approval of the protocol.

Because the specific protocols follow the template so closely, this review discusses the template in detail, with supplemental comments concerning a few noteworthy characteristics of the individual studies. All comments on the template protocol and informed consent materials apply equally to all five specific protocols.

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**: Reliable data about the dermal and inhalation exposure of workers who handle agricultural pesticides can improve the quality of EPA risk assessments and support appropriately protective regulation. The studies conducted and planned by the AHETF will significantly improve the completeness and accuracy of the database used by EPA to assess handler exposure in agriculture.

2. **Scientific Validity of the Research**: I defer to others for a full review of the scientific merits of these protocols. If they were determined not to have scientific validity, it would be unethical to proceed with the research.

3. **Fair Subject Selection**: Subjects are professional agricultural workers with specific experience in the tasks to be performed in the research; this is entirely consistent with the scientific goals of the research. Pregnant women and children are excluded. Subjects are recruited through growers or pesticide application services companies, making them potentially vulnerable to coercion or undue influence; the reviewing IRB required as a condition of approval "extra care in the consent process to avoid any coercion or undue influence to participate in the research." It would be appropriate to spell out in the generic protocol and all specific protocols how this extra care will be demonstrated.

4. **Favorable Risk-Benefit Ratio**: By measuring exposures of workers who customarily handle the tested registered pesticides using the methods employed in the research, these studies present a negligible increase in risk to subjects above their own background levels, and may present a lower than background risk from

exposure to pesticides because of the extra layer of underclothing used to estimate dermal exposure. Some increase in risk of heat-induced illness results from wearing the extra layer of underclothing. The discussion of expected benefits of each study and to whom they would accrue is limited, but acceptable. There is no discussion of how the expected benefits to others are weighed against the potential risks to subjects. Subjects are paid $100/day.

5. **Independent Ethics Review:** The specific protocols and attachments have all been approved by the Western Institutional Review Board of Olympia WA. WIRB is registered as an IRB with OHRP, and is independent of the investigators. Approvals noted the potential for coercion or undue influence in recruiting through subjects' employers, and required that "extra care" be taken by the investigators to prevent it.

6. **Informed Consent**: The protocol promises that informed consent of all subjects will be obtained before they participate, but does not describe the circumstances and procedures for informing potential subjects and seeking their consent to participate. An informed consent document is included for each specific protocol, in English only, although in the case of AHE-38 the investigator requested a Spanish translation in his application to the WIRB.

7. **Respect for Potential and Enrolled Subjects**: Subject privacy would not be compromised. Subjects would be free to withdraw without risking their employment. Because of the way they will be recruited, there is a possibility of coercion or undue influence, and extra care is needed to ensure the promised freedom to withdraw is real.

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 if a specific study is 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:

- All protocols should incorporate references to the ethical standards cited above, and should acknowledge the investigators' obligation to report any amendments or deviations from the approved protocol to the cognizant IRB and, if the research is conducted in California, to the California Department of Pesticide Regulation

- The reference in section 5.3 of the protocol to exclusion of subjects with a conflict of interest is unclear, and no mention of conflict of interest is made in the Informed Consent (IC) materials.

- Section 5.3 of the protocol promises a description of the "worker selection process" for IRB review. It does not appear to be present.

- The IC materials should include a statement about the pesticide use pattern involved in the study, as is provided in section 5.6.b of the protocol.

- The MSDS and label should be made available to the subjects as well as to the investigators, as promised in section 5.6.c of the protocol.

- The provision in section 5.9 of the protocol for altering dilution or application rates to extend the time of exposure may make the exposure scenario atypical or inconsistent with the label, and undermine the justification for the research. Investigators should ensure that plots selected for treatment in the research are large enough to meet the design requirement for at least 4 hours exposure.

- Section 8.1 of the protocol should address the requirement to fully document the ethical conduct of the research consistent with the reporting requirement of 40 CFR 26.1303. This includes documentation of the processes of recruiting (including the "extra care" required by the IRB to minimize the risk of coercion or undue influence), informing potential subjects, obtaining consent, reporting deviations or amendments, and any adverse events. These requirements should also be addressed in section 12 of the protocol

- The generic statement of purpose is inadequately informative for the IC materials. It should specify the formulation and the active ingredient(s) of the pesticide, the site to which it will be applied, and the equipment that will be used. Subjects should be told they are being asked to participate because they are experienced at performing those activities as part of their job.

- A bullet for state government agencies should be added under the heading of "Confidentiality" to the list of organizations which may see personal information, particularly when research is conducted in California.

- The discussion of "Payment for Participation" in the IC material is not linked to the discussion of "Voluntary Participation/Withdrawal." Would a subject who decided to withdraw early in the research be entitled to full payment? This should be clarified.

- The discussion of "Compensation for Injury" in the IC material promises to pay for treatment of injuries resulting from being in the study, but excludes injuries "resulting from your normal activities." This is confusing, since the studies are designed to

measure exposure of workers while they perform their normal activities. This makes the exclusion unacceptable exculpatory language.

- It would be appropriate to translate the generic IC material into Spanish, and perhaps as well into other languages.

C. Study-Specific Comments

AHE-34: Closed System Mixing and Loading of Liquid Malathion in California

- The "Investigator's Confirmation of Board Requirements" form provided by the WIRB is not signed

AHE-36: Airblast Application of Malathion to Grapes in California

- On p. 7 the protocol says there will be 13 "replicates"; on page 14 the protocol says there will be 9 "workers (or replicates). This needs to be reconciled.

AHE-37: Airblast Application of Diazinon to Grapes in New York

- On p. 7 the protocol says there will be 13 "replicates"; on page 14 the protocol says there will be 9 "workers (or replicates). This needs to be reconciled.

AHE-38: Closed Cab Airblast Application of Carbaryl to Orchards in Georgia

- Item 36 in the application to the WIRB requests a Spanish translation of the IC materials. No translation was included in the submitted package.

- The "Investigator's Confirmation of Board Requirements" form provided by the WIRB is not signed

AHE-42: Fixed-Wing Aerial Application of Chlorothalonil to Potatoes and Onions in Oregon and Georgia

- No study-specific comments

D. 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 protocols calls for recruiting only subjects who are at least 18 years old, and for excluding female subjects if they are pregnant. Thus if studies were executed according to these protocols, Section 26.1703 would not forbid EPA to rely on it.

E. 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 approval of the IRB, 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 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]

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1. Value: Reliable data about the dermal and inhalation exposure of workers who handle agricultural pesticides can improve the quality of EPA risk assessments and support appropriately protective regulation. The studies conducted and planned by the AHETF will significantly improve the completeness and accuracy of the database used by EPA to assess handler exposure in agriculture.
a. What is the stated purpose of the research? Each protocol is "an integral part of a multi-phase, multi-year series of field studies, which will form a generic database designed to provide estimates of exposure for workers who handle and apply pesticides." A representative statement of specific study purpose (from AHE-42) is "to determine the potential exposure for workers who make aerial applications of spray mixtures using closed-cockpit fixed-wing aircraft. The secondary objective is to determine the potential exposure to workers who mix and load a liquid pesticide product using either open-pouring or closed system transfer techniques." (p. 4)
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 better assessments of exposure of agricultural pesticide handlers
e. What government, organization, company and/or institution(s) funded the research? Agricultural Handlers Exposure Task Force, LLC, a data-development consortium of 18 agricultural chemical companies
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? Yes. Each study measures dermal and inhalation exposure of workers who mix/load or apply representative agricultural pesticides in typical use scenarios.
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?
In general, subjects wear full-body underwear under their usual work clothing and any PPE required by the pesticide label, and breathing zone air monitors connected to belt-mounted pumps. After a representative work shift handling or applying registered pesticides according to the subjects' usual practices, the underwear and face- and neck-wipes are analyzed to estimate dermal exposure, and the filter on the belt pump is analyzed to estimate inhalation exposure.

d. Does the research design have sufficient power to definitively test the objective?
I defer to others for this judgment. Neither the generic nor the specific protocols explain how sample size was determined.

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 assessment of worker exposure in representative agricultural pesticide use scenarios.

3. Fair Subject Selection: Subjects are professional agricultural workers with specific experience in the tasks to be performed in the research; this is entirely consistent with the scientific goals of the research. Pregnant women and children are excluded. Subjects are recruited through growers or pesticide application services companies, making them potentially vulnerable to coercion or undue influence; the reviewing IRB required as a condition of approval that "extra care" be taken to ensure that participation is truly voluntary.

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 generic protocol, subjects must be at least 18, in good health and physical condition, and women must not be pregnant. Subjects are recruited through growers or pesticide application services companies, making them potentially vulnerable to coercion or undue influence; the reviewing IRB required as a condition of approval that "extra care" be taken to ensure that participation is truly voluntary.

c. Will any subjects be under 18? Pregnant? Nursing?

Children and pregnant women are excluded. The protocol is silent with respect to nursing.

4. Favorable Risk-Benefit Ratio: By measuring exposures of workers who customarily handle the tested registered pesticides using the methods employed in the research, these studies present a negligible increase in risk to subjects above their own background levels, and may present a lower than background risk from exposure to pesticides because of the extra layer of underclothing used to estimate dermal exposure. Some increase in risk of heat-induced illness results from wearing the extra layer of underclothing. The discussion of expected benefits of each study and to whom they would accrue is limited, but acceptable. There is no discussion of how the expected benefits to others are weighed against the potential risks to subjects. Subjects are paid $100/day.

a. How are the risks to individual subjects minimized?
Research involves handling or application of registered pesticide products by experienced workers, in compliance with label requirements, including any for personal protective equipment (PPE). Subjects are told in the IC material that they face no increment of risk from the pesticides, but some increment of risk of heat-induced illness from wearing the extra layer of underclothing. The extra layer of clothing, in fact, lowers the risk of dermal exposure to the pesticide used.

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—and agricultural pesticide handlers in particular—can benefit from improved assessments of worker exposure in representative agricultural use scenarios. The protocols do not directly address how these expected benefits are weighed against the risks to individual subjects.

c. What compensation will be paid to the participants in the study?
This protocol states that subjects will be paid $100/day for participating, and may be "re-used," but will normally participate for only one day.

5. Independent Ethics Review: The specific protocols and attachments have all been approved by the Western Institutional Review Board of Olympia WA. WIRB is registered as an IRB with OHRP, and is independent of the investigators. Approvals noted the potential for coercion or undue influence in recruiting through subjects' employers, and required that "extra care" be taken by the investigators to prevent it.

a. Has the research proposal been approved by an ethics review body?
Yes. It was approved by the Western Institutional Review Board of Olympia WA.

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

c. Is 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?
Compliance is asserted with 40 CFR Part 160 (Good Laboratory Practice), and EPA Guidelines for Applicator/Mixer/Loader Exposure studies.

6. Informed Consent: The protocol promises that informed consent of all subjects will be obtained before they participate, but does not describe the circumstances and procedures for informing potential subjects and seeking their consent to participate. An informed consent document is included for each specific protocol, in English only, although in the case of AHE-38 the investigator requested a Spanish translation in his application to the WIRB.

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?
The generic protocol and all specific protocols state in section 5.3: "[a] signed informed consent form will be obtained from each worker prior to their participation in the study. This protocol, as well as the informed consent form and worker selection process, will be reviewed and approved by an Institutional Review Board (IRB) prior to worker exposure monitoring." No more detailed description of the "worker selection process" or the circumstances and procedures for informing candidates and seeking their consent is provided.

7. Respect for Potential and Enrolled Subjects: Subject privacy would not be compromised. Subjects would be free to withdraw without risking their employment.

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.