**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

WASHINGTON, D.C. 20460

April 17, 2006

**MEMORANDUM:**

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**SUBJECT:** Initial Ethics Review of a Human Study to Support the Pesticide Handlers Exposure Database

**FROM:** Linda Vlier Moos

**TO:** Jeff Evans, HED

**REF:** Dean, V. (1989) Pryfon 6 Termiticide Applicator Exposure Study. 175p. MRID 41990401

I have performed an initial review of available information concerning the referenced document. This review characterizes the ethical conduct of the research in terms of both current ethical standards and ethical standards prevailing when the study was performed. The review applies 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. 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 very different decisions from those we in EPA must make when we determine whether we can ethically consider already-completed human studies.

The Emanuel article reflects current standards for ethical research prevailing in the U. S. This study was conducted in the U. S. in 1988. EPA published Pesticide Assessment Guidelines: Subdivision U: Applicator Exposure Monitoring in 1987. I have applied relevant provisions of these 1987 exposure guidelines and FIFRA Sec. 12(a)(2)(P) as the standards prevailing when the research was conducted.

## A. Summary Assessment of Ethical Conduct of the Research

Here is a summary of my observations about the study under the seven headings used in the Emanuel framework.

1. **Value of the Research to Society**: Its stated purpose was: "The objective of the study was to determine potential dermal and inhalation exposure to applicators who treat homes with PRYFON 6, and to address the question of long-term cholinesterase depression." (p6) It was funded by Mobay. It was not published, suggesting that its purposes did not include development of generalizeable knowledge. This study was used to support the Pesticide Handlers Exposure Database.

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

3. **Subject Selection**: Subjects were drawn from Pest control operators employed by the Terminix International Company, Overland Park Kansas. They included three adult males. There is no indication that any were from especially vulnerable populations, or that they were selected for reasons unjustified by the design of the research.

4. **Risk-Benefit Ratio**: Risks to subjects were characterized as: "Neither MOBAY nor TERMINIX anticipate I will have exposure to PRYFON of such a level that I will have any physical distress, discomfort, or even awareness of exposure; however, I am aware that PRYFON is a poison classified as an organophosphorous insecticide, and if exposure is high enough it could cause cholinesterase depression. I understand that still further exposure can cause symptoms such as a sense of tightness in the chest, shortness of breath, sweating, contracted pupil, stomach pains, vomiting and diarrhea." (p82). Minimization of subject risks was accomplished by wearing the protective gear provided by Terminix and Mobay, blood cholinesterase monitoring and physical examinations both prior to exposure and post exposure. Blood samples were drawn weekly during the 10-week period, during which time the applicators applied only PRYGON 6. Benefits to subjects were not characterized. The relationship of risks and benefits was not addressed.

5. **Independent Ethical Review**: Independent ethical review was not discussed.

6. **Informed Consent**: Written informed consent was obtained from all subjects. . Information provided to subjects was included. The circumstances in which consent was obtained were: "Prior to commencement of the study, each applicator received an explanation for the purpose of the study and of the procedures that would be followed. Each was asked to read and sign a consent

form (Appendix 3) that stated the above information and summarized the toxicity of isofenphos. Each received a copy of his signed consent form." (p9). The consent forms were clear and easy to understand.

7. **Respect for Potential and Enrolled Subjects**: Identifiable information about individual subjects was included in the report.

## B. Assessment of Compliance with Ethical Standard Prevailing when the Research Was Conducted

Some ethical deficiencies are apparent when this study is reviewed against the 1987 Applicator Exposure Guidelines which are considered, along with FIFRA Sec. 12(a)(2)(P) to have defined the prevailing ethical standard when this research was conducted and with which the report asserts compliance.

To be acceptable under the 1987 guidelines, applicator exposure studies must (1) provide for maximum protection of study subjects' health, (2) provide for fully informed, fully voluntary consent as required by FIFRA 12(a)(2)(P), and (3) incorporate written consent of all subjects. In addition, to be acceptable in some states, exposure studies must meet additional state requirements. Finally, the guidelines state that studies should reflect consideration of the DHHS rules (i.e., 45CFR 46 subpart A—the Common Rule). The 1987 did not specify how compliance with these requirements should be documented, or require submission of that documentation. The only deficiency noted is that the DHHS Common Rule requires that studies involving human subjects receive independent ethical review. There is no documentation regarding independent ethical review in the submission.

## 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 26.1704 of that regulation provides in pertinent part:

> EPA shall not rely on data from any research initiated before [effective date of the final rule] if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

In addition, 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.

I have applied the standards in sections 26.1704 and 26.1703 in arriving at the conclusions below.

## D. Conclusion

Although there are some gaps in the documentation of the ethical conduct of this study, there is no clear evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways. Deficient documentation does not itself constitute evidence that the ethical conduct of this study was deficient relative to standards prevailing when it was conducted.

From the documentation available I have concluded that the research did not involve intentional exposure of any subjects who were pregnant women or children. I have also identified no significant deficiencies relative to the standards of the 1987 Subdivision U Guidelines or of FIFRA Sec. 12(a)(2)(P). Therefore in my judgment there is not "clear and convincing evidence" that the ethical conduct of this study was "fundamentally unethical" or "significantly deficient relative to the ethical standards prevailing at the time the research was conducted."

Cited reference:

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