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. (1987) Pryfon 6 Termiticide Applicator Exposure Study. 173p. MRID 41990402

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. 1987. FIFRA Sec. 12(a)(2)(P) therefore defined the prevailing standard at the time this study 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 purposes were: "Although PRYFON 6 is fully approved by the EPA (EPA Reg. No. 3125-339) and is approved for use in most states, this study was designed and conducted to determine the potential exposure to PCOs during their treatment of homes with PRYFON 6 and to evaluate the safety and potential health risk of this product." (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. (Note, one of the volunteers was named "Kim" and in this study the gender was not identified. In a subsequent study by Mobay/Terminex, "Kim" also participated, however in this study "Kim' was identified as a male.) 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." (p20). Minimization of subject risks was accomplished by wearing the protective gear required by Terminix, blood cholinesterase monitoring and brief physical examinations both prior to exposure and post exposure. 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 starting the application, each PCO volunteer was given an explanation for the purpose of the study and how it was to be conducted. Each was informed of the toxic nature of PRYGON 6 and give the broadest range of symptoms which could result from excessive exposure. The PCOs were told that their portion of the study would last approximately three weeks, and would include having four pre-application blood samples taken, making three termiticide treatments each, and having one post-application blood

sample taken. They were informed that an additional blood sample would be taken if the y showed a cholinesterase depression after the treatments. In addition they would each receive a brief physical examination, including a medical history before the three treatments, and another brief physical subsequent to the treatments. They were instructed not to use anticholinesterase compounds in any of their normal work activities prior to or during their participation in the study. All of the workers were encouraged to question Mobay personnel at any time during the study and were advised to promptly report any symptoms or heath concerns….Each participant was asked to sign a consent form …that restated the above information and confirmed his willingness to participate in the study." (p6). 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

No ethical deficiencies are apparent when this study is reviewed against FIFRA Sec. 12(a)(2)(P). FIFRA Sec. 12(a)(2)(P) states:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

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

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 noteworthy deficiencies relative to 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.