UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

APR 14, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Initial Ethical Review of Carbofuran Human Oral Study

FROM: John M. Carley

TO: John Liccione, HED

REF: Arnold, J. D. (1976) Evaluation of the Safe Exposure Levels to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers. Unpublished study prepared by Quincy Research Center. 82 p. MRID 92826.

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. 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 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 1976, but cites no standard of ethical research conduct. I have applied FIFRA §12(a)(2)(P), and assumed the Declaration of Helsinki (1975) to have prevailed 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. Supporting details are in the attachment.

1. **Value of the Research to Society**: The study has never been published, suggesting that its purpose was not mainly to obtain generalizable knowledge. Its purpose is characterized differently for different audiences. It is clear from the protocol that the scientific purpose was to define a LOAEL; it was described to volunteers in terms of a "safe dosage", perhaps to make them more likely to consent to participate. The study may provide some information on the toxicity of carbofuran to humans that could help to inform EPA's assessment of human health risks.

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 nine healthy adult men. Restriction to men was consistent with the stated intent to explore occupational exposure patterns. Based on documentation in MRID 92829, the pool from which subjects were drawn consisted mainly of unemployed semi-skilled workers.

4. **Risk-Benefit Ratio**: Potential symptoms were accurately listed in the information for volunteers, but risks were not minimized by the study design, which committed to dose escalation until toxic signs were observed, followed by further dosing of additional subjects at the LOAEL. Volunteers were also told plainly that they would not benefit from participating. How the potential societal benefit of improved safety for production workers was weighed against the risks to subjects—either by the investigator or by the review committee—was not reported.

5. **Independent Ethical Review:** The protocol and related materials, including both the procedures and the information associated with informed consent, were reported to have been approved by the Community Review Committee, Inc., of Kansas City, MO.

6. **Informed Consent**: Both the information for subjects and the consent form itself were remarkably clear and complete for research conducted in this period. Subjects were given no indication, however, that the design of the research required dose escalation until frank toxic signs were elicited.

7. **Respect for Potential and Enrolled Subjects**: Subjects' privacy was not compromised. They were free to withdraw at any time.

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

No standard of ethical research conduct is cited, either by the reviewing ethics committee or by the authors. The research was conducted in the U.S. after 1972, so FIFRA §12(a)(2)(P) applies. In addition, as clinical research this falls within the scope of the Declaration of Helsinki. I have applied both standards in assessing the conduct of this study.

- 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.

  Although the information provided to subjects was extraordinarily complete for research from this period, subjects were not told that the design of the study required dose escalation until frank toxic effects were elicited. Instead they were told that "The purpose of the testing . . . is to find out the maximum safe dosage for human beings exposed to the test compound . . . . The nature of the test compound . . . is such that we do not expect serious complications from its use." This falls short of the requirement that they be "fully informed of . . . any physical . . . consequences which are reasonably foreseeable."

- Basic Principle #5 of the Declaration of Helsinki (1975) reads "Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison to foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society."

  Societal benefits are not explicitly weighed against the risks to subjects. The same benefit could probably have been achieved through better methods of measuring ChE inhibition, without proceeding to elicitation of frank toxicity. Exposure of additional subjects to a dose which had already been shown to cause illness—notwithstanding that this was planned for in the protocol—does not indicate that the interests of the subjects prevailed over other interests.

- Basic Principle #12 of the Declaration of Helsinki (1975) reads "The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with."

  No discussion of substantive ethical considerations appears in the 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 26.1704 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

All subjects were healthy adult males. Section 26.1703 therefore does not prohibit reliance on this study.

Although there are some gaps in the documentation of the ethical conduct of this study, it is extraordinarily well documented for research from this period. 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 identified some deficiencies relative to the standards of FIFRA §12(a)(2)(P) and the 1975 Declaration of Helsinki. These deficiencies do not, in my judgment, amount to "clear and convincing evidence" that this study was "fundamentally unethical." This review, however, does not take a position on either the persuasiveness of the evidence or the overall significance of the identified deficiencies relative to the prevailing ethical standards. This decision is deferred pending review of the research by the Human Studies Review Board as required by EPA regulation before EPA takes an action relying on this study.

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]

April 14, 2006

Arnold, JD (1976) Evaluation of the Safe Exposure Levels to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers. Unpublished study prepared by Quincy Research Center. 82 p. (MRID 92826)

1. Value: The study has never been published, suggesting that its purpose was not mainly to obtain generalizable knowledge. Its purpose is characterized differently in different places and for different audiences. It is clear from the protocol that the scientific purpose was to define a LOAEL; it may have been described to volunteers in terms of a "safe dosage" to make them more likely to consent to participate.
a. What was the stated purpose of the research? "To determine the threshold toxicity level in normal male volunteers to single oral doses of carbamate" (protocol, p. 3) "To find out the maximum safe dosage for human beings exposed to the test compound" (information for volunteers, p. 10) "To evaluate the toxic effect and cholinesterase inhibitive qualities of carbamate in man. [T]o determine which of six oral doses . . . is the minimum dose necessary to induce toxic effects . . . in normal male volunteers, and to establish the cholinesterase blood levels at which symptoms occur." (final report, p. 15)
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 structure or function of human biological systems? No
d. Will society benefit from the knowledge gained from this research? Will its results be disseminated? It has never been published. Subjects were told "[Your taking the test compound] is essential to determine the levels of this test compound that are safe for the people making it as well as the people exposed to it during its use." (p. 10)
e. What government, organization, company and/or institution(s) funded the research? FMC
2. Scientific Validity: 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.
a. Did the research have a clear scientific objective? See responses to 1(a) above. The scientific objective was to demonstrate a LOAEL.
b. Was the research designed using accepted principles, methods, and reliable practices? I defer to the science reviewer

c. In what way were human subjects intentionally dosed in this research, and what endpoints were identified or measured?
Two subjects each received oral doses of 0.05 mg/kg, 0.1 mg/kg, or 0.25 mg/kg (the LOAEL), without controls. Planned dose levels of 0.5, 1.0, and 2.0 mg/kg were not administered after toxic signs were elicited at 0.25 mg/kg. Although the protocol called for repeating the LOAEL dose in six additional subjects with two controls, in fact only two additional subjects and one placebo control were used. Subjects remained in the clinic for 24 hours post-dose. Measures included RBC and plasma ChEI, pulse, blood pressure, pupil size, eye accommodation, and ECG.

d. Did the research design have sufficient power to definitively test the objective?
I defer to the science reviewer

e. To what purpose is the study used, or proposed for use, in the Agency?
Informing the WOE review of carbofuran

3. Fair Subject Selection: Subjects were nine healthy adult men. Restriction to men was consistent with the stated intent to explore occupational exposure patterns. Based on documentation in MRID 92829, the pool from which subjects were drawn consisted mainly of unemployed semi-skilled workers.

a. Were the groups and individuals recruited and enrolled determined solely on the basis of the scientific goals of the study?
Nine healthy adult men participated in the research. Limitation to adult men was consistent with the stated intent to explore occupational exposure patterns. Exclusion factors included organic disease, use of medications before or during the study, or use of alcohol during the study. The protocol states "special attention will be paid to the use of tobacco", but does not indicate that it was controlled.

b. Were any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group?
The pool from which volunteers were drawn was described in these terms: "[V]olunteers were 19 to 58 year old men with 60% between 20 and 40 and a median age of 34. Seventeen percent were black, 80% were white, and 3% were from other ethnic groups. Fifty-two percent had completed the twelfth grade, and 16 percent had attended college. Sixty percent were semi-skilled workers and 8% were steadily employed." [MRID 92829, p. 85]

4. Favorable Risk-Benefit Ratio: Potential symptoms were accurately listed in the information for volunteers, but risks were not minimized by the study design, which committed to dose escalation until toxic signs were observed, followed by further dosing of additional subjects at the LOAEL. Volunteers were also told plainly that they would not benefit from participating. How the potential societal benefit of improved safety for production workers was weighed against the risks to subjects—either by the investigator or by the review committee—was not reported.

a. How were the risks to individual subjects minimized?
Research was conducted in a clinic under medical supervision. Subjects were told what kinds of symptoms they might experience, and encouraged to report any complaints. Atropine was available in the clinic.

b. If the research presents no health-related benefits to individual subjects, what are the societal benefits in terms of knowledge from the study, and do these justify the excess risk to individual subjects?
The results of this research may have been used to improve safety of Furadan production workers.

c. What compensation was paid to the participants in the study?
The volunteer information form indicates that participants were compensated. It does not say how much they received.

5. Independent Review: The protocol and related materials, including both the procedures and the information associated with informed consent, were reported to have been approved by the Community Review Committee, Inc., of Kansas City, MO.
a. Was the research asserted to have been overseen by an ethics review body? Yes, the protocol and informed consent materials were reportedly reviewed and approved by the Community Review Committee, Inc., of Kansas City, MO.
b. Was the research subject to independent review by individuals unaffiliated with the clinical research? Yes
c. Was the research conducted in compliance with the Common Rule? It predates the Common Rule.
d. Does/did the research institution (or any institution participating in the research) hold a Federal Wide Assurance or Multi-Project Assurance during the period of the study? n/a
e. Was the research conducted in compliance with another standard? What standard? No ethical standard was cited. FIFRA §12(a)(2)(P) applies, as does the Declaration of Helsinki (1975).
6. Informed Consent: Both the information for subjects and the consent form itself were remarkably clear and complete for research conducted in this period. Subjects were given no indication, however, that the design of the research required dose escalation until frank toxic signs were elicited.
a. Does the research assert that informed consent was obtained from participants? Yes
b. How and under what circumstances was informed consent obtained? The "Volunteer agreement and informed consent" was read aloud, verbatim, and then the subjects were asked to sign the consent form.
7. Respect for Potential and Enrolled Subjects: Subjects' privacy was not compromised. They were free to withdraw at any time.
a. Was information about individual subjects managed so as to ensure their privacy? "The collection and submission of the medical information from this study will be accomplished with strict adherence to professional standards of confidentiality."
b. Were subjects free to withdraw from the research without penalty? "As a volunteer, I understand that I am free to withdraw and discontinue my participation at any time upon my request. Both participation in the study as well as possible withdrawal are at my own free will without coercion, duress, or intimidation of any sort."

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