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 Dermal Study

FROM: John M. Carley

TO: John Liccione, HED

REF: Arnold, J. D. (1977) Carbamate (Carbofuran) Human Dermal Study. Unpublished study prepared by Quincy Research Center. 36 p. (MRID 92827; pp. 106-141 *in* CDL Accession 241303.)

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 late 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**: This research has never been published, suggesting its purpose was not mainly to advance 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 18 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. 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. The critical changes to the protocol to raise the doses in phase 2 were made after ethics approval was obtained, and without consulting the committee.

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 when applied to the skin . . . . 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. Comparable benefit could probably have been achieved through better methods of measuring ChE inhibition, without proceeding to elicitation of frank toxicity requiring administration of an antidote. The decisions to raise dose levels in phase 2 does not show 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 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 (1977) Carbamate (Carbofuran) Human Dermal Study. Unpublished study prepared by Quincy Research Center. 36 p. MRID 92827; pp. 106-141 *in* CDL Accession 241303.

1. Value: This research has never been published, suggesting its purpose was not mainly to advance 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.
a. What was the stated purpose of the research? "To determine the threshold toxicity level in normal male volunteers to single and multiple dermal doses of carbamate (carbofuran) under normal and elevated temperatures and/or humidities." (p. 108) "To find out the maximum safe dosage when applied to the skin for human beings. . . ." (p. 120)
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 "We do not expect you to derive any benefit from taking the test compound; however it 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. 120)
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 item 1(a) above. The scientific objective was to establish a human dermal 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?
Testing took place in three phases. In phase 1, subjects entered the clinic the evening before dosing. After eating a standard breakfast, two subjects at a time entered a controlled environment with high temperature and humidity. They were pre-tested for ChE and neurovegetative signs immediately before administration of the dose, and repeatedly from 15 minutes to 6 h. post-dose. For four hours post-dose subjects alternated 5 minutes on an exercise bicycle with 15 minutes of rest, all the time in the chamber with elevated temperature and humidity. After a first pass with only the vehicle as a control, the initial dose was 0.5 mg/kg; after evaluation of symptoms and data at each dose level, doses escalated by doubling. Escalation was discontinued at 2.0 mg/kg because of frank toxic signs in both subjects.

In phase 2 subjects similarly were dosed after breakfast and then alternated exercise and rest for four hours, but at lower temperature and humidity. In this phase dosing began at 2.0 mg/kg (although the protocol originally specified it should begin at half the LOAEL from phase 1, or 1.0 mg/kg) and doubled each time to 4.0 mg/kg, then to 8.0 mg/kg, and then the planned dose of 16 mg/kg was skipped in favor of 32 mg/kg.

In phase 3 two additional subjects received a dose of 1.0 mg/kg under high temperature and humidity each day for three consecutive days.

Subjects remained in the clinic for 24 hours post-dose. Measures included RBC and plasma ChEI, pulse, blood pressure, pupil size, eye accommodation, Fukuda step test, 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?
To inform the WOE for reassessment of carbofuran

3. Fair Subject Selection: Subjects were 18 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?
Eighteen 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. 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, and was administered intravenously to the two subjects who received the 2 mg/kg dose at high temperature and humidity. A study design with a more robust baseline and better methods for analyzing ChE inhibition could probably have generated similar knowledge without exposing the subjects to doses producing frank toxic signs requiring administration of an antidote. The decision to change the protocol for phase 2 to raise the starting dose level and the subsequent decision to quadruple the NOAEL level of 8 mg/kg did not show a commitment to risk minimization.

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?
Not reported

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. The critical changes to the protocol to raise the doses in phase 2 were made after ethics approval was obtained, and without consulting the committee.

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 pre-dates 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.