UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

JUN 11, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Initial Ethics Review of Chloropicrin Human Study

FROM: John M. Carley

TO: Elissa Reaves, Ph.D.

REF: Cain, W. (2004) Human Sensory Irritation Testing for Chloropicrin. Unpublished study prepared by Chemosensory Perception Laboratory, Univ. of California–San Diego under Project No. PIC-1. 378 p. MRID 46443801

Watson, S. (2005) Letter dated April 12, 2005, to Kelly White, EPA, transmitting partial responses to EPA letter of March 3, 2005, seeking additional information about the research reported in MRID 46443801. 278 p. MRID 46566501.

I have performed an initial review of available information concerning the referenced documents. This review characterizes the ethical conduct of the research in terms of current ethical standards, which prevailed 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 2001-2004 at an institution—the University of California-San Diego, which held at the time a Federal-Wide Assurance from HHS/OHRP

promising to comply with the Common Rule in all research with human subjects. I have applied that standard as having 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 explores the lower threshold of human sensitivity to chloropicrin, and the relationship between sensory awareness of chloropicrin and potential effects of exposure to it. This information is of potential value in assessing bystander and worker exposure and risks resulting from agricultural use of chloropicrin as a fumigant. The research was funded by the Chloropicrin Manufacturers Task Force, and has been submitted to EPA and to California Dept of Pesticide Regulation to support regulatory assessments of chloropicrin risk.

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. **Fair Subject Selection**: 127 subjects participated, 25 of them in more than one phase. Subjects were mostly college students, equally divided among men and women age 18-35. Restriction to young adults was because sensory sensitivity declines with age. Well-documented screening factors excluded pregnant females, and were otherwise consistent with the scientific goals of the study. The racial make-up of the subject group closely followed the demographics of the student population at UCSD. There is no indication that any members of particularly susceptible groups were recruited.

4. **Risk-Benefit Ratio**: Risks were characterized as some irritation in the nose, throat, and eyes that could be sharp enough to cause blinking and tearing, but expected to be short lasting. Dose levels were set well below those reported to cause significant adverse effects, and were consistent with standards for occupational exposure set by ACGIH and OSHA. Potential societal benefits were discussed at length in the study report, and characterized very briefly in the IC materials. The report does not address how the expected societal benefits were weighed against risks to subjects.

5. **Independent Ethics Review:** The research was overseen by the UC-SD Human Subjects Committee, an IRB registered with OHRP. Although the report does not mention the Common Rule, it does assert compliance with the requirements of the Human Research Protections Program of the UC-SD. During the period of this research UC-SD held an FWA from OHRP.

6. **Informed Consent**: The consent process was summarized in the report, with a citation to an SOP documenting it in detail. All subjects were asserted to have provided informed consent. The IC materials included in the report met all Common Rule requirements.

7. **Respect for Potential and Enrolled Subjects**: Subject privacy was not compromised. Subjects were free to withdraw at any time without penalty.

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

No noteworthy ethical deficiencies are apparent when this study is reviewed against the standards of the Common Rule, which prevailed when it was conducted in 2001-2004 at the University of California—San Diego, which held at the time a Federal-Wide Assurance from the HHS Office for Human Research Protections.

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.

All subjects were at least 18 years old. Female subjects were tested to ensure they were not pregnant. Section 26.1703 therefore does not prohibit reliance on this study.

From the documentation available, I have identified no noteworthy ethical deficiencies relative to the standards of the Common Rule. Therefore in my judgment there is no clear and convincing evidence that the conduct of this study was fundamentally unethical, or was significantly deficient relative to the ethical standards prevailing at the time it was conducted.

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]

June 11, 2006

Cain, W. (2004) Human Sensory Irritation Testing for Chloropicrin. Unpublished study prepared by Chemosensory Perception Laboratory, Univ. of California–San Diego under Project No. PIC-1. 378 p. MRID 46443801

Watson, S. (2005) Letter dated April 12, 2005, to Kelly White, EPA, transmitting partial responses to EPA letter of March 3, 2005, seeking additional information about the research reported in MRID 46443801. 278 p. MRID 46566501.

1. Value: The study explores the lower threshold of human sensitivity to chloropicrin, and the relationship between sensory awareness of chloropicrin and potential effects of exposure to it. This information is of potential value in assessing bystander exposure and risks resulting from agricultural use of chloropicrin as a fumigant. The research was funded by the Chloropicrin Manufacturers Task Force, and has been submitted to EPA and to California Dept of Pesticide Regulation to support regulatory assessments of chloropicrin risk.

a. What was the stated purpose of the research?
The research was conducted in three phases, each with a different stated purpose:

Phase I: "to establish . . . the sensitivity of olfaction, chemesthesis (i.e., feel or irritation) of the nose, and chemesthesis of the eyes for momentary exposures to chloropicrin directed to the individual sites."

Phase II: "to establish . . . sensitivity for ambient exposures to chloropicrin where all channels for detection are available, and . . . to establish whether sensitivity varies over time with exposures that range up to 30 minutes."

Phase III: "to establish . . . whether mildly irritating ambient exposures to chloropicrin of one hour per day over four days lead to a) evidence of discomfort that lasts materially beyond the periods of exposure and b) evidences of inflammatory changes in the mucosal tissue." (p. 18)

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?
It has not been published. The author states that the study explores the lower threshold of human sensitivity to chloropicrin, and the relationship between sensory awareness of chloropicrin and potential effects of exposure to it. This information is of potential value in assessing bystander exposure and risks resulting from agricultural use of chloropicrin as a fumigant.

e. What government, organization, company and/or institution(s) funded the research?
Chloropicrin Manufacturers Task Force, a data-development consortium of chloropicrin registrant companies.

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 1(a) above.

b. Was the research designed using accepted principles, methods, and reliable practices?
I defer to others for this assessment.

c. In what way were human subjects exposed in this research, and what endpoints were identified or measured?
In Phase I 64 subjects received brief exposures up to 25 sec. each to airborne concentrations of chloropicrin ranging from 335 to 1200 ppb. In Phase II 60 subjects received 20-30 minute exposures to airborne concentrations ranging from 50 to 150 ppb. In Phase III 32 subjects were exposed for one hour a day for four days to 100 or 150 ppb airborne chloropicrin. Endpoints were detection in Phase I nasal exposures, and chemesthesis (feel) and irritation in other exposures.

d. Did the research design have sufficient power to definitively test the objective?
I defer to others for this assessment.

e. To what purpose is the study used, or proposed for use, in the Agency?
To inform the risk assessment of chloropicrin

3. Fair Subject Selection: 127 subjects participated, 25 of them in more than one phase. Subjects were mostly college students, equally divided among men and women age 18-35. Restriction to young adults was because sensory sensitivity declines with age. Well-documented screening factors excluded pregnant females, and were otherwise consistent with the scientific goals of the study. The racial make-up of the subject group closely followed the demographics of the student population at UCSD. There is no indication that any members of particularly susceptible groups were recruited.

a. Were subjects recruited and enrolled solely on the basis of the scientific goals of the study?
"A total of 127 individual subjects participated, the overwhelming majority of them college students. . . . 25 subjects participated in more than one phase. (p. 38) Subjects were equally divided among men and women age 18-35. Restriction to young adults was because sensory sensitivity declines with age. (p. 38) "An SOP for phone interviewing and eligibility screening was followed to ensure that subjects were healthy, nonsmokers free from exposure to chloropicrin, mood-altering drugs, medications that could interfere with the conduct of the study, and not pregnant." (p. 40)

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?
"Recruitment of subjects occurred via distribution of flyers at college campuses and via contact with subjects already in the pool of the Chemosensory Perception Laboratory." (p. 39) The racial make-up of the subject group closely followed the demographics of the student population at UCSD.

4. Favorable Risk-Benefit Ratio: Risks were characterized as some irritation in the nose, throat, and eyes that could be sharp enough to cause blinking and tearing, but expected to be short lasting. Dose levels were set well below those reported to cause significant adverse effects, and were consistent with standards for occupational exposure set by ACGIH and OSHA. Potential societal benefits were discussed at length in the study report, and characterized very briefly in the IC materials. The report does not address how the expected societal benefits were weighed against risks to subjects.

a. How were the risks to individual subjects minimized?
Dose levels were set well below those reported to cause significant adverse effects, and were consistent with standards for occupational exposure set by ACGIH and OSHA. Investigators were alert for signs of allergic response, and medical assistance was available if needed. Risks to subjects were characterized as "some irritation in the nose, throat, and eyes that could be sharp enough to cause blinking and tearing. . . . We expect the discomfort to be short lasting. You will be free to discontinue exposure at any instant. If you [are] in the middle of an exposure and wish to stop, a staff member will guide you out of it." (p. 215)

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?
Subjects were told the investigators "may learn more about how to set standards for public health regarding exposure to chloropicrin."

c. What compensation was paid to the participants in the study?
Subjects were paid $15/hour.

5. Independent Ethics Review: The research was overseen by the UC-SD Human Subjects Committee, an IRB registered with OHRP. Although the report does not mention the Common Rule, it does assert compliance with the requirements of the Human Research Protections Program of the UC-SD. During the period of this research UC-SD held an FWA from OHRP.

a. Was the research asserted to have been overseen by an ethics review body?
The research was overseen by the UC-SD Human Subjects Committee, an IRB registered with OHRP.

b. Was the independent ethics review by individuals unaffiliated with the clinical research?
Yes.

c. Was the research asserted to comply with the Common Rule?
The report does not mention 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?
UC-SD held an FWA from the HHS/OHRP during the period of the study.

e. Was the research asserted to comply with another standard? What standard?
The research was asserted to comply with the requirements of the Human Research Protections Program of the UC-SD

6. Informed Consent: The consent process was summarized in the report, with a citation to an SOP documenting it in detail. All subjects were asserted to have provided informed consent. The IC materials included in the report met all Common Rule requirements.

a. Does the research assert that informed consent was obtained from all participants?
Yes.

b. How and under what circumstances was informed consent obtained?
"The process of informed consent apprises potential subjects of the nature of and rationale for the study, as well as the risks and procedures to manage any adverse effects. It also explains potential benefits to the subjects (if any) and to society, payment for participation, voluntary participation/withdrawal, terms of additional medical care and whom to contact with specific questions or unexpected symptoms. The process for obtaining Informed Consent is documented in SOP CPL-OP-022, Revision 0." (p. 39) IC forms used in this study were included, and met all Common Rule requirements.

7. Respect for Potential and Enrolled Subjects: Subject privacy was not compromised. Subjects were free to withdraw at any time without penalty.

a. Was information about individual subjects managed so as to ensure their privacy?
Yes

b. Were 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.