UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MAY 22, 2007

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of Acrolein Human Study

FROM: John M. Carley
Human Research Ethics Review Officer

TO: Ray Kent, Chief
Reregistration Branch 4, HED

REF: Weber-Tschopp, A.; Fischer, T.; Gierer, R.; and Grandjean, E. (1977) Experimentally Induced Irritating Effects of Acrolein on Man. Unpublished English translation of "Experimentelle Reizwirkungen von Akrolein auf den Menschen". Int. Arch. Occup. Environ. Hlth. 1977 (40): 117-130. MRID 47060601.

This review characterizes the ethical conduct of the research reported in the referenced document in terms of the ethical standards which prevailed when the study was performed. The review applies a variant of the "Summary Framework for Ethical Assessment" developed by the EPA Science Policy Committee's Human Studies Work Group. The completed "framework" is attached.

This study was conducted in Switzerland in the mid-1970s, at the Institute for Hygiene and Occupational Physiology, Swiss Federal Engineering College, Zurich. No standard of ethical conduct is identified in the report. I have assumed the 1975 Declaration of Helsinki 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 attached framework. Supporting details are in the attachment.

1. **Value of Research to Society:** This research was conducted at the Institute for Hygiene and Occupational Physiology, Swiss Federal Engineering College, Zurich, with financial support from the Swiss Association of Cigarette Manufacturers. Its stated purpose was to characterize the relative involvement of acrolein in the effects of the air pollution caused by cigarette smoke; the authors conclude that acrolein is not a significant contributor to the irritancy of cigarette smoke. They further report threshold irritancy effects for pure acrolein at measured concentrations. This latter information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to acrolein when it is used as a pesticide.

2. **Scientific Design:** 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 characterized only as "healthy college students". They may have been students of the investigators, all of whom were associated with the Institute for Hygiene and Occupational Physiology, Swiss Federal Engineering College, Zurich. The number of subjects is reported separately for each of the three sub-studies—the first included 31 men and 22 women; the second included 17 men and 25 women; the third included 21 men and 25 women. The extent to which some may have participated in more than one phase of the research is not reported. The means by which they were recruited are not reported.

4. **Risks and Benefits:** The primary risks to subjects were of eye, nose, and throat irritation from exposure to acrolein—known to be an irritant. These risks are not discussed in the report, nor is their minimization. The research offered no direct benefits to subjects. Societal benefits include an improved understanding of threshold irritation effects of acrolein, confirmation of the US TLV level for 8 h. exposure, and evidence that the associated OSHA limit for peak exposures was set too high. In addition, the authors argue that acrolein does not contribute significantly to the irritancy of sidestream tobacco smoke, which would presumably be a finding beneficial to the sponsoring cigarette manufacturers' association. Insufficient information is provided to assess the relationship between these presumed benefits and the risks to individual subjects in the research.

5. **Independent Ethics Review:** The report is silent with respect to ethics oversight, and does not identify any standard of ethical conduct.

6. **Informed Consent**: The report is silent with respect to informing the participants and obtaining their consent.

7. **Respect for Potential and Enrolled Subjects**: The privacy of subjects was not compromised in the published report. A common subjective response measured was reported as a "wish to leave the room". Although there is no clear evidence of this in the report, it appears from context that subjects who wished to leave the room—i.e., the chamber with acrolein in the atmosphere—were not free to do so until the end of the designed exposure period.

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

The absence of any discussion in the published report of this research of ethical issues or conduct makes it difficult to assess the ethical conduct of the research. Two potential ethical deficiencies are apparent, however, when this report is reviewed against the standards of the Declaration of Helsinki, 1975, which is assumed to have prevailed when the research was conducted in Switzerland in the mid-1970s:

Basic Principle I.5 of the Declaration reads as follows: "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."

Although there is a discussion of relevant prior research, there is no indication in the published report that the risks to the research subjects were carefully assessed in comparison to foreseeable benefits of the research.

Basic Principle I.9 of the Declaration reads as follows: "In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely given informed consent, preferably in writing."

There is no indication in the published report that each potential subject was adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it would entail. There is also no indication that subjects freely gave their consent to participate, nor that they were at liberty to withdraw. This is of particular concern, since one of the subjective measures of irritancy was the subjects' desire to leave the room, which they were apparently not free to do.

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 rule 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, 40 CFR §26.1703 (as amended August 22, 2006) 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), a nursing woman, or a child.

I have applied these two standards in arriving at the conclusions below.

D. Conclusions

There are major gaps in the documentation of the ethical conduct of this study, particularly with respect to methods of recruiting, informing, and seeking consent of subjects, and with respect to subjects' freedom to withdraw from the research. The absence of any mention of independent ethical oversight was common in published research from this period, and was not yet required by the Declaration of Helsinki. But deficient documentation does not itself constitute clear evidence.

Subjects were described as college students, and were likely to have been at least 18 years old. Roughly half the subjects were female, but the report is silent with respect to their reproductive or nursing status. When, as in this case, evidence concerning subject age and reproductive status is both absent and unobtainable, it is EPA's policy that §26.1703 does not prohibit reliance on a study.

In my judgment, there is no clear and convincing evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways, or that the ethical conduct of this study was significantly deficient relative to the standard assumed to have prevailed when it was conducted. Therefore I see no barrier in EPA's regulations to consideration of and reliance on this study, assuming it is deemed to be scientifically valid.

Attachment

Summary Framework for Ethical Assessment

May 22, 2007

Tschopp, A.; Fischer, T.; Gierer, R.; and Grandjean, E. (1977) Experimentally Induced Irritating Effects of Acrolein on Man. Unpublished English translation of "Experimentelle Reizwirkungen von Akrolein auf den Menschen". Int. Arch. Occup. Environ. Hlth. 1977 (40): 117-130. (MRID 47060601)

1. Value of Research to Society:

This research was conducted at the Institute for Hygiene and Occupational Physiology, Swiss Federal Engineering College, Zurich, with financial support from the Swiss Association of Cigarette Manufacturers. Its stated purpose was to characterize the relative involvement of acrolein in the effects of the air pollution caused by cigarette smoke; the authors conclude that acrolein is not a significant contributor to the irritancy of cigarette smoke. They further report threshold irritancy effects for pure acrolein at measured concentrations. This latter information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to acrolein when it is used as a pesticide.

a. What was the stated purpose of the research?
To characterize the relative involvement of acrolein in the effects of the air pollution caused by cigarette smoke in a room.

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 explicit hypothesis is stated. It demonstrates that humans respond to acrolein similarly to previously tested animals.

d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?
Results were published.

e. What government, organization, company and/or institution(s) funded the research?
Financial support for the research was provided by the Swiss Association of Cigarette Manufacturers.

2. Scientific Design:

I defer to others for a full review of the scientific validity and utility 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?
Yes.

b. Was the research designed using accepted principles, methods, and reliable practices?
The design appears to reflect relevant prior research and accepted principles, methods, and practices.

c. In what way were human subjects exposed in this research, and what endpoints were identified or measured?
Subjects were exposed in a 30 m^3 chamber with a controlled atmosphere into which acrolein could be metered. There were three sub-studies, each involving different durations and patterns of exposure. In the first, subjects were exposed over a period of 40 minutes to continuously rising concentrations of acrolein, beginning at 0 and rising every five minutes to a maximum of 0.6 ppm. In the second, subjects were exposed five times for 90 seconds each time to various concentrations of acrolein between 0 and 0.6 ppm, with 8 min. in a well-ventilated room between exposures. In the third, subjects were exposed for 60 min. to a constant acrolein concentration of 0.3 ppm.

Endpoints measured included subjective irritation (i.e., responses to questions concerning perceived air quality and desire to leave the room), eye blink rate, and breathing rate and depth.

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

e. To what purpose is the study used, or proposed for use, in the Agency?
To characterize human threshold irritation responses to acrolein.

3. Subject Selection:

Subjects were characterized only as "healthy college students". They may have been students of the investigators, all of whom were associated with the Institute for Hygiene and Occupational Physiology, Swiss Federal Engineering College, Zurich. The number of subjects is reported separately for each of the three sub-studies—the first included 31 men and 22 women; the second included 17 men and 25 women; the third included 21 men and 25 women. The extent to which some may have participated in more than one phase of the research is not reported. The means by which they were recruited are not reported.

a. Were subjects recruited and enrolled solely on the basis of the scientific goals of the study?
There is no indication that subjects were recruited on any basis other than the scientific goals of the study.

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?
Subjects are characterized only as "healthy college students". They may have been students of the investigators, all of whom were associated with the Institute for Hygiene and Occupational Physiology, Swiss Federal Engineering College, Zurich.

4. Risk-Benefit Ratio:

The primary risks to subjects were of eye, nose, and throat irritation from exposure to acrolein—known to be an irritant. These risks are not discussed in the report, nor is their minimization. The research offered no direct benefits to subjects. Societal benefits include an improved understanding of threshold irritation effects of acrolein, confirmation of the US TLV level for 8 h. exposure, and evidence that the associated OSHA limit for peak exposures was set too high. In addition, the authors argue that acrolein does not contribute significantly to the irritancy of sidestream tobacco smoke, which would presumably be a finding beneficial to the sponsoring cigarette manufacturers' association. Insufficient information is provided to assess the relationship between these presumed benefits and the risks to individual subjects in the research.

a. What were the risks to individual subjects? How were they minimized?
The primary risks to subjects were of eye, nose, and throat irritation from exposure to acrolein—known to be an irritant. These risks are not discussed in the report, nor is their minimization, beyond mention that subjects in the second phase of the research were permitted 8 min. in a well-ventilated room between acrolein exposures in the chamber. The maximum exposure levels in this research were at 0.6 ppm acrolein, known to the authors to be twice the transient peak level permitted by the US OSHA TLV.

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?
The research offered no direct benefits to subjects. Societal benefits include an improved understanding of threshold irritation effects of acrolein, confirmation of the US TLV level for 8 h. exposure, and evidence that the associated OSHA limit for peak exposures was set too high. In addition, the authors argue that acrolein does not contribute significantly to the irritancy of sidestream tobacco smoke, which would presumably be a finding beneficial to the sponsoring cigarette manufacturers' association.

Insufficient information is provided to assess the relationship between these presumed benefits and the risks to individual subjects in the research.

c. What compensation was paid to the participants in the study?
Not reported.

5. Independent Ethics Review:

The report is silent with respect to ethics oversight, and does not identify any standard of ethical conduct.

a. Was the research asserted to have been overseen by an ethics review body unaffiliated with the research?
No mention is made of any ethics oversight.

b. Was the research asserted to comply with a standard of ethical conduct? What standard?
No standard of ethical conduct is identified.

6. Informed Consent:

The report is silent with respect to informing the participants and obtaining their consent.

a. Does the research assert that informed consent was obtained from all participants?
The report is silent with respect to informed consent of the participants.

b. How and under what circumstances was informed consent obtained?
Not reported.

7. Respect for Potential and Enrolled Subjects:

The privacy of subjects was not compromised in the published report. A common subjective response measured was reported as a "wish to leave the room". Although there is no clear evidence of this in the report, it appears from context that subjects who wished to leave the room—i.e., the chamber with acrolein in the atmosphere—were not free to do so until the end of the designed exposure period.

a. Was information about individual subjects managed so as to ensure their privacy?
No information about individual subjects was reported.

b. Were subjects free to withdraw from the research without penalty?
Not reported. A common subjective response measured was reported as a "wish to leave the room". Although there is no clear evidence of this in the report, it appears from context that subjects who wished to leave the room—i.e., the chamber with acrolein in the atmosphere—were not free to do so until the end of the designated exposure period.