UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

APR 11, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Initial Ethical Review of Hexavalent Chromium Human Sensitization Study

FROM: John M. Carley

TO: Timothy McMahon, AD
Timothy Leighton, AD

REF: Nethercutt, J., Paustenbach, D., Adams, R, et al.(1994) A study of chromium induced allergic contact dermatitis with 54 volunteers: implications for environmental risk assessment. *Occup. Environ Med* 1994;51:371-380. (MRID 46803602)

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 clinical 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. and Canada in 1992; it cites no standard of ethical conduct. I have assumed that the standards prevailing when the research was conducted were 45 CFR Part 46 (the precursor of the Common Rule) and the Declaration of Helsinki (1989).

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 is a careful and thorough study, designed to provide a solid basis for environmental risk assessments involving Cr(VI). It was designed to address directly many of the questions raised by inconsistencies among earlier studies.

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 selected from patient files by the six participating dermatologists. Study design required subjects who were Cr(VI) sensitive. Inclusion and exclusion criteria seem sound.

4. **Risk-Benefit Ratio**: Risk to subjects was characterized as "allergic dermatitis of type IV, a delayed or cell-mediated reaction . . . similar to a "poison oak" hypersensitive reaction, . . . elicits the standard symptoms of erythema, oedema, and small vesicles. . . . Reactions are most often not life threatening and their effect is generally limited to the skin. " *(p. 371)* The highest dose administered was described as that normally used in dermatologic practice to diagnose Cr(VI) sensitivity; all subsequent testing was at levels from 5x to 244x below this level. There is no explicit discussion of how societal benefits were weighed against risks to individual subjects.

5. **Independent Ethical Review:** The study reports only that "[t]he physicians received approval from their respective human use committees." All five US-based institutions involved in the clinical phase of the work now hold Federal-Wide Assurances from OHRP; their status in 1992 is unknown.

6. **Informed Consent**: The report asserts that written consent was obtained from all subjects, but does not describe what they were told, or by whom, and does not acknowledge the potential role conflict for the doctor/investigators. Since volunteers were recruited from among the past patients of the investigators, the shift in role from personal physician to investigator (and each volunteer's own change from patient to subject) may not have been clear to them. There is also no mention of how additional consent may have been obtained from the thirteen subjects who also took part in the special supplemental studies.

7. **Respect for Potential and Enrolled Subjects**: Subjects' privacy was not compromised. Although their freedom to withdraw was not discussed, eleven potential subjects are reported to have withdrawn "for personal reasons" before any testing began.

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

Some deficiencies are apparent when this study is reviewed against the principles of the Declaration of Helsinki (1989), assumed to have prevailed when the research was conducted:

- General principle #2 of the Declaration reads in part "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor. . . ." No protocol is included in the report; the reviewing ethics committees are inadequately identified, and the scope of their review is undocumented.

- General principle #4 of the Declaration reads "Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject." The study report is silent with respect to the nature and distribution of benefits of the research, and how they were weighed against risks to the subjects.

- General principle #5 of the Declaration reads in part "every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others." If such a careful assessment was conducted it was not reported.

- General principle #9 of the Declaration reads "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 physician should then obtain the subject's freely-given informed consent, preferably in writing." Although the study reports obtaining consent from all subjects, it is silent with respect to informing the subjects.

- General principle #10 of the Declaration reads "when obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship." Subjects were recruited from among the investigators' patients. The role shift from doctor to investigator, and from patient to subject, is not acknowledged. The specific reference to "volunteers" providing "their doctors" with written consent highlights this role ambiguity.

- General principle #12 of the Declaration 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." The study report is silent with respect to ethical considerations involved.

- Principle #6 for "Medical Research Combined with Professional Care" in the Declaration reads "the physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient." The potential diagnostic or therapeutic value for the subjects of this research is not addressed.

In addition, the following deficiencies are apparent when this study is reviewed against the requirements of 45 CFR Part 46:

- Section 46.109(b) reads in part "[a]n IRB shall require that information given to subjects as part of informed consent is in accordance with Sec. 46.116." The study report is silent with respect to the information provided to subjects as part of informed consent.

- Section 46.111 defines criteria for IRB approval of research. There is no documentation of the IRB's determination that all these requirements were satisfied.

- Section 46.116 defines general requirements for informed consent. It is not possible to determine if they were satisfied by this study.

C. Standard for Judging Ethical Acceptability

On February 6, 2006, EPA published a final rule amending 40 CFR Part 26, "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 April 7, 2006, 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.

This research was conducted before the effective date of this rule; thus this criterion is applicable for judging its ethical acceptability.

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.

From the documentation available, I have identified several deficiencies relative to the standards of the 1989 Declaration of Helsinki and the HHS regulations (45 CFR Part 46, subpart A) in effect when this research was conducted. 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 10, 2006

Nethercutt, J., Paustenbach, D., Adams, R, et al.(1994) A study of chromium induced allergic contact dermatitis with 54 volunteers: implications for environmental risk assessment. *Occup. Environ Med* 1994;51:371-380. (MRID 46803602)

1. Value: This is a careful and thorough study, designed to provide a solid basis for environmental risk assessments involving Cr(VI). It was designed to address directly many of the questions raised by inconsistencies among earlier studies.

a. What was the stated purpose of the research?
"To determine the area-based [minimum elicitation threshold] MET (ug Cr/Cm^2 skin) of solubilised Cr(VI) and Cr(III) that will elicit allergic contact dermatitis in chromium-sensitized subjects." *(p. 372)*
A secondary purpose was to replace several old studies with poor methods and inconsistent results with better data, usable for risk assessment.

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?
This study test two "supplemental" hypotheses: (1) that allergen per unit area of skin is a better measure of dose than the concentration of allergen in the patch, and (2) that sub-MET doses over a larger surface area might elicit a response at lower concentrations than the METs identified.

d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?
The results of this research have been published, to the benefit of society.

e. What government, organization, company and/or institution(s) funded the research?
Not reported

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) and 1(c) above.

b. Was the research designed using accepted principles, methods, and reliable practices?
I defer to science reviewers.

c. In what way were human subjects intentionally dosed in this research, and what endpoints were identified or measured?
102 subjects previously diagnosed as Cr(VI)-sensitive were given a "diagnostic dose" of 4.4 ug Cr(VI)/cm^2 skin to confirm sensitivity. 54 subjects with confirmed sensitivity at this dose were then given doses of 0.018 and 0.088 ug/cm^2 (round 2) and, if no response, additional doses of 0.18 and 0.88 ug/cm^2 (round 3). Nine subjects also participated in a test at 0.88 ug/cm^2 comparing concentration of allergen per unit area of skin and concentration of allergen per unit mass of patch as measures of dose, and four subjects who had shown an MET at 0.88 ug/cm^2 were re-tested with five patches at 0.18 ug/cm^2. Endpoint measured was allergic contact dermatitis.

d. Did the research design have sufficient power to definitively test the objective?
An extensive discussion of statistical issues in defining sample size appears on p. 374

e. To what purpose is the study used, or proposed for use, in the Agency?
Risk assessment for pesticide registration of ACC as wood preservative

3. Fair Subject Selection: Subjects were selected from patient files by the six participating dermatologist/investigators. Study design required subjects who were Cr(VI)-sensitive. Inclusion and exclusion criteria seem sound. There is no indication that any subjects came from particularly vulnerable groups, but all were recruited from among the participating dermatologists' patients. No mention is made of the potential for role ambiguity as doctors became investigators and invited their patients to become research subjects.

a. Were the groups and individuals recruited and enrolled determined solely on the basis of the scientific goals of the study?
6000 patient files were screened; 113 potential subjects were found; 11 dropped out for personal reasons. 102 subjects participated in round 1 to confirm Cr(VI) sensitivity; 54 participated in later rounds.

b. Were any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished; or did the burden of participation fall disproportionately on a particular group?
All subjects were over 18. None were pregnant. All but five were employed; those five were described as retired. There is no indication that any subjects came from particularly vulnerable groups, but all were recruited from among the participating dermatologists' patients. No mention is made of the potential for role ambiguity as doctors became investigators and invited their patients to become research subjects.

4. Favorable Risk-Benefit Ratio: Risk to subjects was characterized as "allergic dermatitis of type IV, a delayed or cell-mediated reaction . . . similar to a "poison oak" hypersensitive reaction, . . . elicits the standard symptoms of erythema, oedema, and small vesicles. ...Reactions are most often not life threatening and their effect is generally limited to the skin. " *(p. 371)* The highest dose administered was described as that normally used in dermatologic practice to diagnose Cr(VI) sensitivity; all subsequent testing was at levels from 5x to 244x below this level. There is no explicit discussion of how societal benefits were weighed against risks to individual subjects.

a. How were the risks to individual subjects minimized? Risk to subjects was characterized as "allergic dermatitis of type IV, a delayed or cell-mediated reaction . . . similar to a "poison oak" hypersensitive reaction, . . . elicits the standard symptoms of erythema, oedema, and small vesicles. ...Reactions are most often not life threatening and their effect is generally limited to the skin. " *(p. 371)* The highest dose administered was described as that normally used in dermatologic practice to diagnose Cr(VI) sensitivity; all subsequent testing was at levels from 5x to 244x below this level.

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?
Nearly half the subjects in round 1 (48/102) benefited directly by learning that they were not, after all, sensitive to Cr(VI). In addition, the study provides a basis for rigorous risk assessment of Cr(VI) in the environment. There is no explicit discussion of how societal benefits were weighed against risks to individual subjects.

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

5. Independent Review: The study reports only that "[t]he physicians received approval from their respective human use committees as appropriate." All five US-based institutions involved in the clinical phase of the work (Johns Hopkins Univ., Stanford Univ., Univ of Louisville, Pennsylvania State Univ., and Cleveland Clinic Foundation) now hold FWAs from OHRP; their status in 1992 is unknown.

a. Was the research asserted to have been overseen by an ethics review body?
Yes.

b. Was the research subject to independent review by individuals unaffiliated with the clinical research?
The report says only that "[t]he physicians received approval from their respective human use committees as appropriate." (p. 374)

c. Was the research conducted in compliance with the Common Rule?
The research was conducted very soon after promulgation of the Common Rule, but as practicing dermatologists the investigators were likely familiar with the earlier DHEW rules at 45 CFR Part 46.

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?
All five US-based institutions involved in the clinical phase of the work (Johns Hopkins Univ., Stanford Univ., Univ of Louisville, Pennsylvania State Univ., and Cleveland Clinic Foundation) now hold FWAs from OHRP; their status in 1992 is unknown.

e. Was the research conducted in compliance with another standard? What standard?
n/a

6. Informed Consent: The report asserts that written consent was obtained from all subjects, but does not describe what they were told, or by whom, and does not acknowledge the potential role conflict for the doctor/investigators. Since volunteers were recruited from among the past patients of the investigators, the shift in role from personal physician to investigator (and each volunteer's own change from patient to subject) may not have been clear to them. The report is silent about whether or how separate consent may have been obtained from the thirteen subjects who participated in follow-up testing.

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

b. How and under what circumstances was informed consent obtained?
"All volunteers provided their doctors with written consent to participate in the study". *(p. 374)* What potential subjects were told, and by whom, is not reported.

7. Respect for Potential and Enrolled Subjects: Subjects' privacy was not compromised. Although their freedom to withdraw was not discussed, eleven potential subjects are reported to have withdrawn "for personal reasons" before any testing began.

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?
Not reported. Eleven potential subjects were reported to have withdrawn "for personal reasons" from the original group of 113 former patients screened for Cr(VI) sensitivity.

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