**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

WASHINGTON, D.C. 20460

*September 27, 2007*

**MEMORANDUM:**

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**SUBJECT:** Ethics Review of Human Clinical Study for Sodium Azide

**FROM:** John M. Carley
Human Research Ethics Review Officer

**TO:** Jack Housenger, Associate Director
Health Effects Division

**REF:** Black, M.; Zweifach, B.; Speer, F. (1954). Comparison of hypotensive action of sodium azide in normotensive and hypertensive patients. Proc Soc Exptl Biol Med 85:11-16. MRID 47221401.

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.

This study was conducted in the U.S. in the early 1950s, over a decade before promulgation of the first generation of the Declaration of Helsinki by the World Medical Association. At the time this research was conducted there were no clear standards of ethical conduct in biomedical research other than the principles asserted in the Nuremberg Code.

## 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 report describes a body of research undertaken to explore further the observation made in previous work with sodium azide as a treatment for cancer that it appeared to lower blood pressure in hypertensive patients. The information reported concerning the effects of sodium azide on blood pressure of both hypertensive and normotensive patients, dosed both

acutely and chronically, is of potential value to EPA in defining a point of departure for assessing risks from exposure to sodium azide 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:** Very little information is reported about the subjects in this research. Acute testing was conducted with at least 35 subjects, including both hypertensive and normotensive subjects. Chronic testing was conducted with at least 30 hypertensive subjects. Subjects included "normal healthy controls (students, laboratory personnel)" and patients "suffering from diverse types of cancer." The means by which subjects were recruited are not reported, nor are their demographic characteristics.

4. **Risks and Benefits:** A general concern for potential risks of sodium azide is evidenced by the authors' reference to the experimental doses being far below the reported lethal range, by their close monitoring of subject responses, and by their discussion of dose reduction for subjects in chronic testing who developed sensitivity to sodium azide while participating in the test. Side experiments comparing different dosing regimens were designed to establish the minimum effective dose. Neither qualitative risks to subjects nor their probability are discussed explicitly in the report. Societal benefits include insight into potentially effective treatments of hypertension, and an improved understanding of thresholds for side effects of sodium azide. In addition, the study reports related research with animals, and demonstrates that humans are more sensitive than animals to the hypotensive effects of sodium azide. With only fragmentary information available it is difficult to conclude whether these benefits were foreseeable at the time the research was conducted or sufficient to justify the unspecified risks to individual subjects.

5. **Independent Ethics Review:** The study is silent with respect to any ethics oversight.

6. **Informed Consent**: In the context of explaining why a placebo effect was unlikely, the authors report that sodium azide "was administered without informing the patient of either the nature of the drug or the change to be expected." There is no other reference to what the subjects may have been told about the research, or to their having participated voluntarily. It is reported, however, that the subjects in the chronic phase of testing self-administered sodium azide three times a day for extended periods; it is difficult to imagine their doing this involuntarily.

7. **Respect for Potential and Enrolled Subjects**: The privacy of subjects was not compromised in the published report.

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

This research was conducted in the early 1950s, by authors affiliated with New York Medical College and New York University, with support from the Leukemia Research Foundation. At that time no generally accepted standards for ethical conduct of biomedical research had been promulgated. The Nuremberg Code was generally considered to apply to war criminals, but not to mainstream research. I have been unable to identify any clear standard prevailing when this research was conducted.

**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**

Very little information is available concerning the ethical conduct of this research. Consistent with prevailing practice at the time, the published report is silent about how subjects were recruited, what they were told, and whether they consented to participate. The report is also silent with respect to the age, sex, and reproductive status of subjects. The use of students and laboratory personnel as control subjects would today be considered a questionable practice because of the potential for undue influence to participate on people in positions subordinate to the investigators, but this was also a common practice when this research was conducted.

With so little information available, and with no clear prevailing standard of ethical conduct, I have relied primarily on the language of 40 CFR §26.1704 prohibiting EPA to rely on research conducted before April 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)."

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. Given the low likelihood that subjects self-dosed three times a day for extended periods involuntarily, I believe it would be erroneous to interpret the reported failure to inform subjects of the "nature of the drug or the change to be expected" as evidence that the subjects were entirely uninformed or did not consent to participate. Certainly if it is so interpreted, the evidence is less than clear and convincing. There is also no evidence that any subjects were pregnant or nursing women, or children. 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.