UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

May 27, 2014

MEMORANDUM

SUBJECT: Ethics Review of Human Toxicity Study with Iodine

FROM: Kelly Sherman, Human Studies Ethics Review Officer
Office of the Director
Office of Pesticide Programs

TO: Steven Weiss, Chief
Risk Assessment Science Support Branch
Antimicrobials Division
Office of Pesticide Programs

REF: Gardner, D.F., Centor, R.M., Utiger, R.D. Effects of Low Dose Oral Supplementation of Thyroid Function in Normal Men. *Clinical Endocrinology*, Vol. 28 (1988): pp. 283-288. (MRID 47358601)

I have reviewed the referenced human toxicity study with iodine. I conclude that if the study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA relying on this research in actions taken under FIFRA or §408 of FFDCA.

Summary Characteristics of the Research

In this study, 30 euthyroid male subjects between the ages of 22 and 40 years self-administered a 0.5 ml solution of either 500, 1500 or 4500 µg/ml iodine with 1 mg/ml ascorbic acid twice daily for 14 days. Urine and serum iodine levels were measured and subjects were studied for changes in weight, symptoms of thyroid dysfunction, and other toxic effects.

To supplement the information provided in the journal article, EPA contacted D.F. Gardner, one of the principal investigators, to ask him questions about the ethical conduct of the study. The attachment (on page 6 of this review) is a record of that telephone conversation. Subsequent attempts to reach Dr. Gardner to ask follow-up questions were unsuccessful.

1. Value of the Research to Society:

The stated objective of this study was to investigate the effects of low dose iodide supplementation on thyroid function. The article states:

> "Previous studies have demonstrated that short-term oral iodide administration, in doses ranging from 1500 µg to 250 mg/day, has an inhibitory effect on thyroid hormone secretion in normal men. As iodide intake in the USA may be as high as 800 µg/d, we investigated the effects of very low dose iodide supplementation on thyroid function."

The study was conducted at the Clinical Research Center of the Medical College of Virginia in 1987 or sometime prior to 1987 (the submission for publication was received in June 1987). The study was funded in part by General Clinical Research Grants and the A.D. Williams Fund of the Medical College of Virginia. The results were published in *Clinical Endocrinology* in 1988. EPA is proposing to use the study in its risk assessment for iodine as an antimicrobial pesticide.

2. Subject Selection:

a. Demographics. Thirty male subjects aged 22-40 years with normal thyroid function participated in the study and received iodine doses. (Gardner et al., p. 284)

b. Pregnancy and Nursing Status. There were no female subjects in this study.

c. Inclusion/Exclusion Criteria. To participate in the study, subjects had to be healthy, euthyroid, not pregnant, not taking any medications that affect thyroid function, and with no history of thyroid disease. (Attachment)

d. Recruitment. The subjects were medical students or employees of the Medical College of Virginia, or people whose names appeared on a list of possible research subjects maintained by the research center. The students and employees were recruited through flyers posted in the medical school. The other individuals received telephone calls inquiring about their interest in participating in the study.

3. Risks and Benefits:

a. Risks. We have no information about what subjects were told regarding possible risks of participating in this study, and we also do not know what risk mitigation measures were in place.

b. Benefits. There are no benefits to the subjects, and the report is silent on this topic. EPA does not know if the subjects were told whether or not they would benefit from participating in the research.

c. Risk-Benefit Balance. The report is silent regarding the risk-benefit balance. EPA does not know whether the investigators considered the risk-benefit balance, or whether it was described in the consent materials or discussed with the subjects.

4. **Independent Ethics Review**: The study was reviewed and approved by the Virginia Commonwealth University Committee on the Conduct of Human Research. (Gardner et al., p. 284)

5. **Informed Consent**: Dr. Gardner stated that subjects were given an opportunity to read the study protocol and the subjects were asked if they understood the protocol before consent was sought. (Attachment) Each subject provided written informed consent before participating.

6. **Respect for Subjects.** Subjects were compensated approximately $150-200. (Attachment) The subjects' identifies were not revealed in the study report. We do not know whether subjects were free to withdraw during the study.

Applicable Standards

Standards Applicable to the Conduct of the Research

This research was conducted in the mid-1980s, before EPA's Rule for Protection of Human Subjects of Research became effective in 2006. Thus, 40 CFR part 26 did not apply when this research was conducted.

The prevailing ethical standards for medical research conducted in the mid-1980s are articulated in the 1983 Declaration of Helsinki. Key elements are:

1. Research must be scientifically sound and conducted by qualified personnel
2. There must be a clear purpose and protocol, reviewed and approved by an independent ethics committee
3. The interests of science and society should never take precedence over considerations related to the well-being of the subject
4. Participants should give prior, informed, voluntary consent

The Nuremberg Code (1947) and the Belmont Report (1979) are also instructive regarding the prevailing ethical standards. Key principles of the Nuremberg code are: participation must be voluntary, research must avoid unnecessary physical and mental suffering, and benefits must outweigh risks. Key principles from the Belmont Report are: respect for persons, beneficence, and justice.

FIFRA §12(a)(2)(P) was in effect at the time of this study. The provision reads:

> 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.

Since this study was medical research related to iodine dietary intake, not research designed to study the toxicity of iodine as an antimicrobial pesticide, EPA does not consider FIFRA

§12(a)(2)(P) to be applicable. But even if we consider FIFRA §12(a)(2)(P) to apply, the outcome of this review is unchanged because the ethical principles of fully informed, fully voluntary consent articulated in §12(a)(2)(P) are contained in the Declaration of Helsinki, which EPA believes provide the prevailing ethical standard for this study.

Standards Applicable to the Documentation of the Research

EPA identified this study through a review of the public literature. No person has independently submitted the published article or any results of this research to EPA. Consequently, the requirements for the submission of information concerning the ethical conduct of completed human research contained in EPA regulations at 40 CFR part 26, subpart M do not apply.

Standards Applicable to EPA's Reliance on the Research

The Agency's rule (40 CFR part 26 subpart Q) defines standards for EPA to apply in deciding whether to rely on research—like this study—involving intentional exposure of human subjects. The applicable acceptance standards from 40 CFR part 26 subpart Q are these:

> **§26.1703.** Except as provided in **§**26.1706, EPA must not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> **§26.1704** EPA must not rely on data from any research subject to this section if there is clear and convincing evidence that: (1) 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 (2) The conduct of the research was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.

EPA has submitted this study for review by the Human Studies Review Board (HSRB) because 40 CFR §26.1602 requires HSRB review for pre-2006 studies intended for EPA reliance that were conducted for the purpose of identifying or measuring a toxic effect. This study meets those criteria.

Compliance with Applicable Standards

All of the subjects in this study were adult males, and thus this research did not involve intentional exposure of any pregnant or nursing female subjects or any children. Based on this information, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

The subjects provided written informed consent and the protocol underwent independent ethics review and approval. Based on these facts, and the absence of any information suggesting that the research was fundamentally unethical or intended to harm participants, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(1).

With regard to the study's compliance with prevailing ethical standards, I considered all available information in the article and obtained from the telephone conversation with Dr. Gardner. Subjects were given the opportunity to read the protocol and researchers confirmed the subjects' understanding of the protocol before seeking their consent. All of the subjects provided written informed consent. Some of the subjects were employees or students at the medical school, so it is possible that some of the subjects may have had a subordinate relationship with one or more of the researchers. However, recruiting among employees and students was common practice at the time of this study, and there is no clear and convincing evidence to suggest undue influence or lack of fully informed, fully voluntary consent. The article indicates that the research was reviewed and approved by the Virginia Commonwealth University Committee on the Conduct of Human Research. Given that there is no clear and convincing evidence that this study was deficient with regard to the prevailing ethical standards, I conclude that reliance on this study is not prohibited by 40 CFR §26.1704(2).

Conclusion

I find no barrier in law or regulation to reliance on MRID 47358601in EPA actions taken under FIFRA or §408 of FFDCA. 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.

Attachment

Record:	Phone conversation between Jonathan Leshin (EPA) and D.F. Gardner, M.D.
Date/Time:	February 14, 2014; 9:00 am
Subject:	Questions regarding ethical conduct of *Gardner* et al. (1988)
Publication:	Gardner, D.F., Centor, R.M., Utiger, R.D. Effects of Low Dose Oral Supplementation of Thyroid Function in Normal Men. *Clinical Endocrinology*, Vol. 28 (1988): pp. 283-288. (MRID 47358601)

Leshin:	From what population were subjects recruited / selected?
Gardner:	Students of the Medical College of Virginia and employees of the hospital were recruited. Also, subjects were obtained from a list of study volunteers maintained by research center.
Leshin:	What was the recruitment process?
Gardner:	Students and employees were recruited via flyers in the medical school. Individuals on the list of volunteers were called and asked if they wanted to participate.
Leshin:	Were subjects compensated?
Gardner:	Yes, ~$150-200 dollars over course of study.
Leshin:	Did the subjects provide informed consent? Did they sign an informed consent form? Is it possible to get a copy of the informed consent form?
Gardner:	Yes, subjects provided informed consent and signed forms. However, it is unlikely copies of the forms still exist as this study was conducted in the 1980s.
Leshin:	What were the circumstances and methods by which informed consent was obtained from the subjects?
Gardner:	Subjects read the study protocol and were asked if they understood.
Leshin:	Were there exclusion/inclusion criteria for subject selection?
Gardner:	Subjects had to be healthy, euthyroid, not on any medications that affect thyroid function and with no history of thyroid disease.
Leshin:	Were there stopping rules for the study?
Gardner:	We had no specific rules for stopping the study.
Leshin:	Did the protocol undergo independent ethics evaluation before the study was initiated (review by an institutional review board or equivalent)?
Gardner:	Yes, the Virginia Commonwealth University Board on the Conduct of Human Research reviewed this study.