



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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

May 28, 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: LeMar, H.J, Georgitis, W.J. and McDermott, M.T. Thyroid Adaptation to Chronic Tetraglycine Hydroperiodide Water Purification Tablet Use. *Journal of Clinical Endocrinology and Metabolism*, Vol. 80 (1995): pp. 220-223. (MRID 49318802)

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, eight euthyroid subjects (seven males and one female) ranging in age from 35 to 47 years consumed the iodine released by four water purification tablets dissolved in water or juice every day for 90 days. Urine and serum iodine levels were measured and subjects were studied for symptoms of thyroid dysfunction and other toxic effects.

To supplement the information provided in the journal article, EPA contacted Michael McDermott, 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. McDermott 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 ingesting tetraglycine hydroperiodide tablets used to purify water. The article states:

“Tetraglycine hydroperiodide (TGH) tablets containing 20 mg of the germicidal ingredient globaline, are marketed for the purpose of purifying water. Globaline, $C_{16}H_{42}I_7N_8O_{16}$, is an iodine-rich compound with a solubility in water of approximately 380 g/L. Each tablet effectively disinfects 1 quart clear water or 0.5 quart tainted water by releasing approximately 8 mg free iodine consumption of water purified by this method delivers a daily iodine intake in amounts known to alter thyroid function in man...The present investigation studied the effects of consuming the free iodine generated from dissolved TGH water purification tablets on thyroid size, thyroid radioiodine uptake, serum thyroid hormone levels, and basal and TRH-stimulated TSH levels over 12 weeks.”

The study was conducted in the early 1990s and was funded in part by the U.S. Army Medical Research and Development Command. The results were published in the *Journal of Clinical Endocrinology and Metabolism* in 1995. EPA is proposing to use the study in its risk assessment for iodine as an antimicrobial pesticide.

2. Subject Selection:

- a. **Demographics.** Eight subjects (7 males and 1 female) aged 35-47 years with normal thyroid function participated in the study. (LeMar et al., p. 220)
- b. **Pregnancy and Nursing Status.** Prospective female subjects were tested for pregnancy, and any who tested positive were excluded from the study. (Attachment) We have no information to suggest that the one female subject in this study was nursing.
- 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, with no kidney or liver disease, and no history of thyroid disease. (Attachment)
- d. **Recruitment.** The subjects were recruited from the employees of the hospital (residents, fellows, and faculty); some were civilian and some were military personnel. Dr. McDermott indicated that the researchers asked individuals if they were interested in participating. (Attachment) We do not have any additional information about the recruitment process.

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 institutional review board for the Fitzsimmons Army Medical Center. (LeMar et al., p. 220; Attachment)
- 5. Informed Consent:** Dr. McDermott stated that subjects read the study protocol and were asked if they understood it. Each subject provided written informed consent before participating. Dr. McDermott stated that it would likely not be possible to obtain a copy of the form because the military base closed in 1999. (Attachment)
- 6. Respect for Subjects.** Subjects were not compensated. Subjects were free to withdraw from the study at any time. (Attachment) The subjects' identifies were not revealed in the study report.

Applicable Standards

Standards Applicable to the Conduct of the Research

This research was conducted in the early 1990s, 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.

This study was funded by the U.S. Army and conducted at the Fitzsimmons Army Medical Center. The U.S. Department of Defense adopted the Common Rule in January 1991, and thus the Common Rule provides the ethical standards for this research. The article states that "[t]he protocol adhered to the policies for protection of human subjects, as prescribed in 40 CFR 46¹ in accordance with AR [Army Regulation] 40-38." Key elements of the Common Rule and AR 40-38 are IRB oversight and prior approval, an acceptable informed consent process and consent form, risk minimization, a favorable risk:benefit balance, equitable subject selection, and fully informed, fully voluntary participation by subjects.

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.

¹ *LeMar et al.* cites to 40 CFR 46, although it seems that the intended citation was 45 CFR 46, which is HHS' codification of the Common Rule. 40 CFR 46 is unrelated - it sets forth requirements for EPA fellowship awards.

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 Common Rule, which EPA believes provides the prevailing ethical standards 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

This research did not involve intentional exposure of any pregnant or nursing female subjects or any children. The article indicates that all subjects were over the age of 18, and Dr. McDermott stated that prospective female subjects were tested for pregnancy and that pregnant women were excluded from the study. We have no evidence to suggest that the one female subject in this study was nursing. Based on this information, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

The subjects provided written informed consent, the protocol underwent independent ethics review and approval, and subjects were allowed to drop out of the study at any time. 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. McDermott. 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. The subjects were employees of the hospital, 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 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 protocol was reviewed and approved by an IRB and that it complied with the policies for protection of human subjects as prescribed in the Common Rule and Army Regulation 40-38. 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 49318802 in 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 Michael McDermott
Date/Time: February 11, 2014; 4:13 pm
Subject: Questions regarding ethical conduct of *LeMar* et al. (1995)

Publication: LeMar., H.J, Georgitis, W.J. and McDermott, M.T. Thyroid Adaptation to Chronic Tetraglycine Hydroperiodide Water Purification Tablet Use. *Journal of Clinical Endocrinology and Metabolism*, Vol. 80 (1995): pp. 220-223. (MRID 49318802)

Leshin: Were female subjects tested for pregnancy before participation?
McDermott: Yes and if a subject was pregnant, she was excluded from the study.

Leshin: From what population were subjects recruited /selected?
McDermott: The subjects were employees of the hospital (residents, fellows, faculty); a mix of civilian and military personnel.

Leshin: What was the recruitment process?
McDermott: We asked if anyone wanted to volunteer to take part in a study about iodine water purification tablets.

Leshin: Were subjects compensated?
McDermott: No.

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?
McDermott: Yes, subjects were provided informed consent forms and they all signed the form before participating. It is unlikely copies of the form still exist as this base was shut down in the late 1990s.

Leshin: What were the circumstances and methods by which informed consent was obtained from the subjects?
McDermott: Subjects read the study protocol and were asked if they understood it.

Leshin: Were there exclusion/inclusion criteria for subject selection?
McDermott: Subjects had to be healthy, euthyroid, not on any medications that affect thyroid function, no history of kidney or liver disease, and with no history of thyroid disease.

Leshin: Were there stopping rules for the study?
McDermott: Subjects could drop out at any time but otherwise there were no special stopping rules.

Leshin: Did the protocol undergo independent ethics evaluation before the study was initiated (review by an institutional review board or equivalent)?
McDermott: Yes, it was reviewed and approved by the IRB for the Fitzsimmons Army Medical Center.