



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

OFFICE OF CHEMICAL SAFETY AND  
POLLUTION PREVENTION

May 23, 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:** Paul, T., Meyers, R.J., Witorsch, R.J., Pino, S., Chipkin, S.H., Ingbar, S.H., Braverman, L.E. The Effect of Small Increases in Dietary Iodine on Thyroid Function in Euthyroid Subjects. *Metabolism*, Vol. 37, No. 2 (February) 1988: pp. 121-124. (MRID 48358603)

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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, 9 euthyroid males and 23 euthyroid females self-administered a 0.5 ml solution of sodium iodide every twelve hours for 14 days. The males received 750 µg of iodine twice daily and the females received either 125, 250, or 750 µg of iodine twice daily. The female subjects were between the ages of 23 and 44 and the male subjects were between the ages of 26 and 56. Five additional males served as controls. Urine and serum iodine levels were measured and subjects were studied for changes in weight, symptoms of thyroid dysfunction, and other toxic effects.

The article contains very little information that would be relevant to an ethics review, so EPA contacted Lewis Braverman, M.D., one of the investigators, to ask him questions about the

ethical conduct of the study. Attachments 1 and 2 to this memo (pages 7-8) provide records of two telephone conversations with Dr. Braverman.

## 1. Value of the Research to Society:

The stated objective of this study was to determine whether small increases in iodine intake affect thyroid function. The article states:

“...iodine intake has increased in recent years in the United States. Whether or not such increases in iodine intake may have affected thyroid function in subjects without underlying thyroid disease is unclear. Second, many individuals ingest dietary supplements, such as kelp or multivitamin preparations; these contain more, sometimes much more, than enough iodine to fulfill the minimum daily requirement of approximately 150  $\mu\text{g}$  iodine. When added to the usual dietary sources of iodine, they result in daily intakes well in excess of the norm. Finally, we have recently reported that the ingestion of huge quantities (200 mg/d for 14 days) of the iodine-rich food colorant, 2',4',5',7'-tetraiodofluorescein (erythrosine) resulted in small increases in both basal and TRH-simulated serum TSH concentrations similar to those that follow ingestion of pharmacologic quantities of iodine. This resulted in an increase in daily urinary iodine excretion of approximately 1,200  $\mu\text{g}$ . For these reasons, we evaluated the effects of small increments in iodine intake (1,500  $\mu\text{g}$  daily), thereby determining whether the alterations in TSH secretion induced by erythrosine were due to the dye itself or could have been due to the iodide liberated thereof. Even smaller doses of iodine (500 and 250  $\mu\text{g}$ ) were also given to normal subjects to determine whether these physiologic supplements would affect thyroid function.” (Paul et al., p. 121)

The study was conducted at the University of Massachusetts Medical School in 1985 or sometime prior to 1985 (the results were presented at a meeting in September 1985). The study was funded by grants from the National Institutes of Health (NIH), the Center for Environmental Health and Human Toxicology, and the Joseph and Dorothy Benotti Iodine Research Fund. The results were published in *Metabolism* 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-two subjects – 9 males and 23 females – participated in the study and received iodine doses. They ranged in age from 23 to 56 and were described in the report as volunteers. Before participating in the study, the 32 subjects provided a medical history and underwent a physical examination. All subjects were deemed to be euthyroid, with no evidence of thyroid disease and no detectable quantities of antithyroid antibodies. (Paul et al., p. 121-2)

In addition to the 32 subjects who received iodine doses, five male subjects served as controls and were given placebo doses. The article notes that the five controls were age-matched to the treated subjects, but no further information about them is provided. (Paul et al., p. 122)

- b. Pregnancy and Nursing Status.* Prospective female subjects were tested for pregnancy, and any who tested positive for pregnancy were excluded from the study. (Attachment 1, p. 7). None of the female subjects were nursing. (Attachment 2, p. 8)
- 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 1, p. 7)
- d. Recruitment.* The article is silent about subject recruitment, and Dr. Braverman indicated that he has no recollection about recruitment or subject selection. (Attachment 1, p. 7)

**3. Risks and Benefits:**

- a. Risks.* The article is silent about risks to subjects. Dr. Braverman indicated that it was the investigators' view that the iodine dose levels were comparable to levels of iodine received in the diet, and therefore that no risk minimization measures related to the dosing regimen were necessary. Dr. Braverman stated that subjects were told that ingesting either too much or too little iodine can be harmful. Dr. Braverman indicated that the investigators followed normal medical safety precautions associated with the use of venous catheters. (Attachments 1 and 2, pp. 7-8)
- 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 article does not indicate, and Dr. Braverman does not recall, whether the research underwent independent ethics review. (Attachment 1, p. 7)
- 5. Informed Consent:** Dr. Braverman stated that the subjects provided informed consent before participating in the research, but he said that it is not possible to obtain a copy of the consent form. (Attachment 1, p. 7) Dr. Braverman indicated that the study procedures were explained to the subjects, and they were told of possible effects of ingesting too much or too little iodine. (Attachment 2, p. 8)
- 6. Respect for Subjects.** Subjects were not compensated. (Attachment 1, p. 7) Subjects were free to withdraw at any time from the study. (Attachment 2, p. 8) The subjects' identities were not revealed in the study report.

## **Applicable Standards**

### ***Standards Applicable to the Conduct of the Research***

This research was conducted in the 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.

Guidelines from the Department of Health, Education and Welfare (1971), codified as regulations in 1974 at 45 CFR part 46, were in effect when this study was conducted. The 1974 DHEW regulations applied to all research with human subjects conducted or supported by the DHEW (now the Department of Health and Human Services) or any of its component agencies, including NIH. Given that this study was partially funded by NIH, the DHEW regulations applied to this study and provide the prevailing ethical standard. The key principles of the 1974 DHEW guidelines were:

- Prior Institutional Review Board (IRB) review and approval of research
- IRB oversight of ongoing research
- Written, fully informed, voluntary consent of subjects

Also instructive about the prevailing ethical standards when this study was conducted are the Declaration of Helsinki (1975 or 1983), The Nuremberg Code (1947), and the Belmont Report (1979). Key principles from the Declaration of Helsinki are:

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

Key principles of the Nuremberg code are: participation must be voluntary, research must avoid unnecessary physical and mental suffering, and benefits must outweigh risks. Three key principles from the Belmont Report are: respect for persons, beneficence, and justice.

FIFRA §12(a)(2)(P) was also 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 DHEW regulations, which EPA believes did apply to 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. Braverman stated that female subjects were tested for pregnancy, pregnant women were excluded from the study, and none of the female subjects were nursing. (Attachments 1 and 2, pp. 7-8) Based on this information, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

There is no clear and convincing evidence that the research was fundamentally unethical. The subjects were volunteers, they provided informed consent, and the researchers attempted to protect the subjects' welfare by testing the females for pregnancy and following normal medical protections associated with intravenous catheter use. Based on this information, 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).

Likewise, there is no clear and convincing evidence that the conduct of the study was deficient with regard to the ethical standards prevailing of the time of this research. There is essentially no information in the article about the ethics of this study, but EPA was able to speak with Dr. Lewis Braverman, one of the investigators. Dr. Braverman stated that the subjects provided informed consent, they were informed about the study procedures and risks, they were permitted to withdraw during the study, and they were advised to seek medical attention if they became ill during the study; the researchers excluded pregnant women and individuals with thyroid disease from participating in the study, and used normal medical precautions. These facts suggest that the conduct of the study was consistent with the prevailing ethical standards at that time.

Independent ethics review is a key principle of the prevailing ethical standards at the time this study was conducted. The published article about this study is silent – and Dr. Braverman does not recall – whether the study underwent independent ethics review. Thus we do not have affirmative evidence that there was independent ethics oversight, nor do we have clear and convincing evidence of the absence of independent ethics oversight. Thus, I conclude that there is no clear and convincing evidence that this study was deficient with regard to the prevailing ethical standards. Reliance on this study is therefore not prohibited by 40 CFR §26.1704(2).

## **Conclusion**

I find no barrier in law or regulation to reliance on MRID 48358603 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 1

Publication: Paul, T., Meyers, R.J., Witorsch, R.J., Pino, S., Chipkin, S.H., Ingbar, S.H., Braverman, L.E. The Effect of Small Increases in Dietary Iodine on Thyroid Function in Euthyroid Subjects. *Metabolism*, Vol. 37, No. 2 (February) 1988: pp. 121-124. (MRID 48358603)

Subject: Record of telephone conversation between Jonathan Leshin (EPA) and Lewis Braverman

Date/Time: February 12, 2014; 11:30 am

Subject: Questions regarding ethical conduct of *Paul et al.* (1988)

Leshin: Were the female subjects tested for pregnancy before participation?

Braverman: Yes. If a subject tested positive for pregnancy, she was excluded from study. None of the subjects in the study were pregnant.

Leshin: From what population were subjects recruited or selected?

Braverman: I can't remember and I don't believe any documentation exists at this point.

Leshin: Were subjects compensated?

Braverman: 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?

Braverman: Yes, the subjects provided informed consent and signed forms before participating. However, it is not possible to locate a copy of the form as too much time has passed.

Leshin: Were there exclusion/inclusion criteria for subject selection?

Braverman: Subjects had to be healthy, euthyroid, not pregnant and not on any medications that affect thyroid function and with no history of thyroid disease.

Leshin: What measures were taken to minimize risks to subjects?

Braverman: The subjects had to be euthyroid, without a history of thyroid disease. The doses used in the study were comparable to the levels of iodine normally available via the diet, so no measures were taken to minimize risks other than those associated with normal i.v. use.

Leshin: Were there stopping rules for the study?

Braverman: The doses used in the study were considered comparable to the levels of iodine normally available via the diet, so no special rules were in place 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)?

Braverman: I don't remember.

## Attachment 2

Publication: Paul, T., Meyers, R.J., Witorsch, R.J., Pino, S., Chipkin, S.H., Ingbar, S.H., Braverman, L.E. The Effect of Small Increases in Dietary Iodine on Thyroid Function in Euthyroid Subjects. *Metabolism*, Vol. 37, No. 2 (February) 1988: pp. 121-124. (MRID 48358603)

Subject: Record of telephone conversation between Kelly Sherman (EPA) and Lewis Braverman

Date/Time: May 23, 2014; 9:20 am

Subject: Questions regarding ethical conduct of *Paul et al.* (1988)

Sherman: Were any of the female subjects nursing/breastfeeding a baby during the study?  
Braverman: No.

Sherman: Were the subjects allowed to drop out in the middle of the study if they no longer wished to participate?  
Braverman: Yes. But no one dropped out during this study.

Sherman: Do you recall what were subjects told during the consent process?  
Braverman: We walked them through the study procedures and explained to them what they were agreeing to do. Whatever was normal at the time, I am sure that's what we did. I can't remember all of the details.

Sherman: Did you tell subjects about potential risks?  
Braverman: The dose levels in this study were low. I am sure we explained to subjects that iodine affects thyroid function, and that either too little or too much iodine can be harmful.

Sherman: Were subjects told that if they felt ill during the study, they should contact one of the investigators or a doctor?  
Braverman: Yes, of course. But nothing happened. This was a very benign study.