EPA Science Assessment of LeMar et al. (1995)

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Study Information

- Conducted at the Fitzsimmons Army Medical Center
- Study Objective – Determine the effects of subchronic ingestion of iodine purification tablets (tetraglycine hydroperiodide)
- Subjects – 7 Males and 1 Female, age 35-47, healthy, not pregnant, euthyroid, no history of thyroid disease, no chronic medical disorders, no use of medications known to affect thyroid function or previous reactions to iodine

Test Substance

- Tetraglycine hydroperiodide dissolved in water or juice totaling 32,000 µg/day (4 tablets)
- Self administered over the course of the day for 90 days
- Subjects maintained their normal diets.
  - Some diets may be higher in iodine than others but assumed average was 300 µg/day

Study Method

- All subjects had initial evaluations for the study
- On day 0, baseline levels of T_4, T_3, and TSH were measured
- Stimulated TSH was measured after stimulation by TRH after 20 minutes (TSH-20)
- A 24 hour radioactive iodine uptake was recorded after dosing with 1 µCi of ^{131}I, with 10 minute counting times (RAIU)
- Thyroid volume was measured in the recumbent position by ultrasound
- Repeat serum iodine, T_3, T_4, TSH and TSH-20 and urinary iodine measurements were collected on days 7, 28 and 90
- RAIU was re-measured on day 7 and 90
- Thyroid volume was reassessed on day 35 and 90

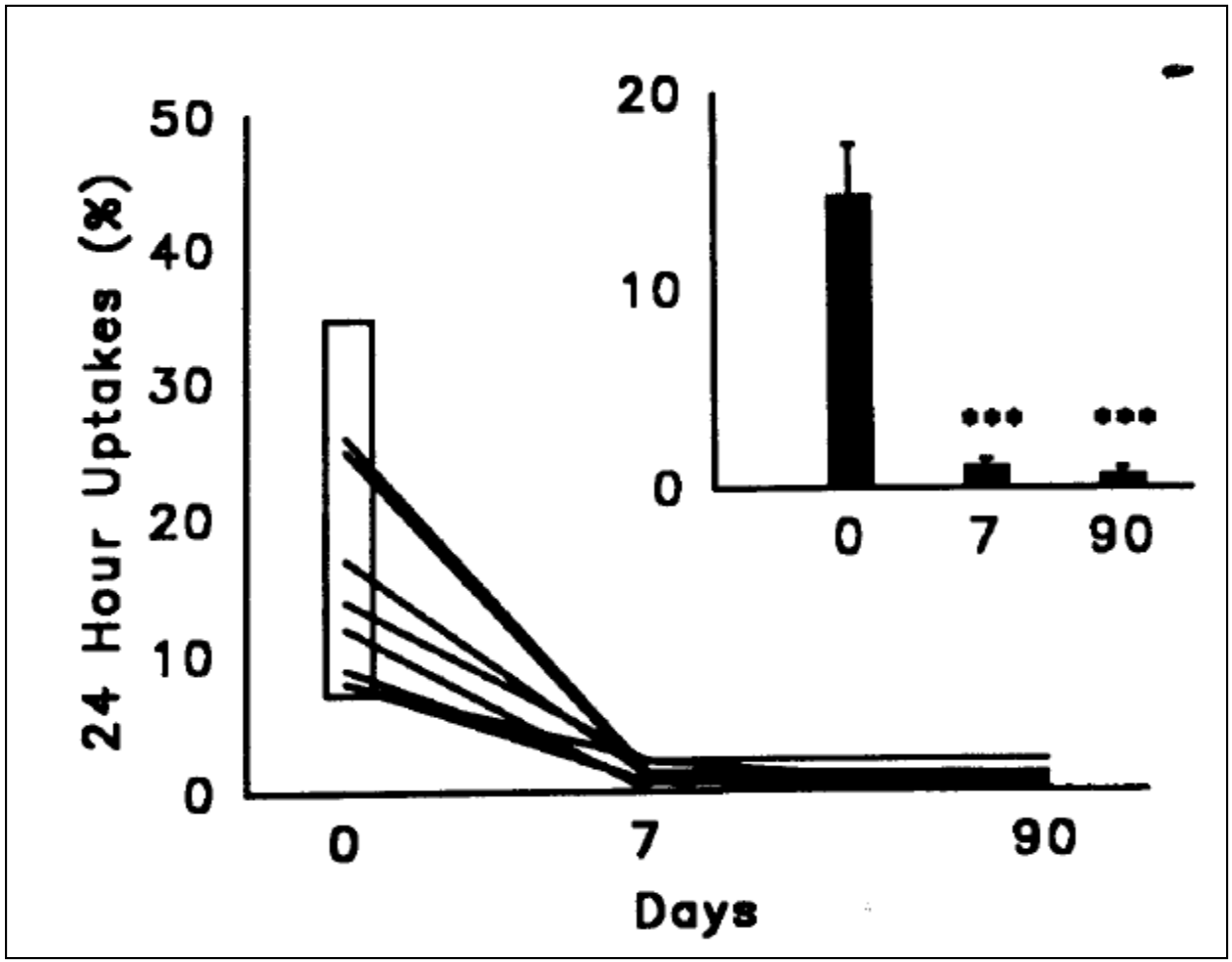
Endpoints

- Serum T_4
- Serum T_3
- TSH
- TSH-20
- RAIU
- Thyroid volume

Results - 1

Figure 1.
Individual 24-hour radioactive iodine uptake before and during treatment.

The normal range of uptake is indicated by the open rectangle. RAIU decreased markedly at 7 days and remained low at 90 days. The mean ± SEM are displayed in inset. ***, P<0.001



Results - 2

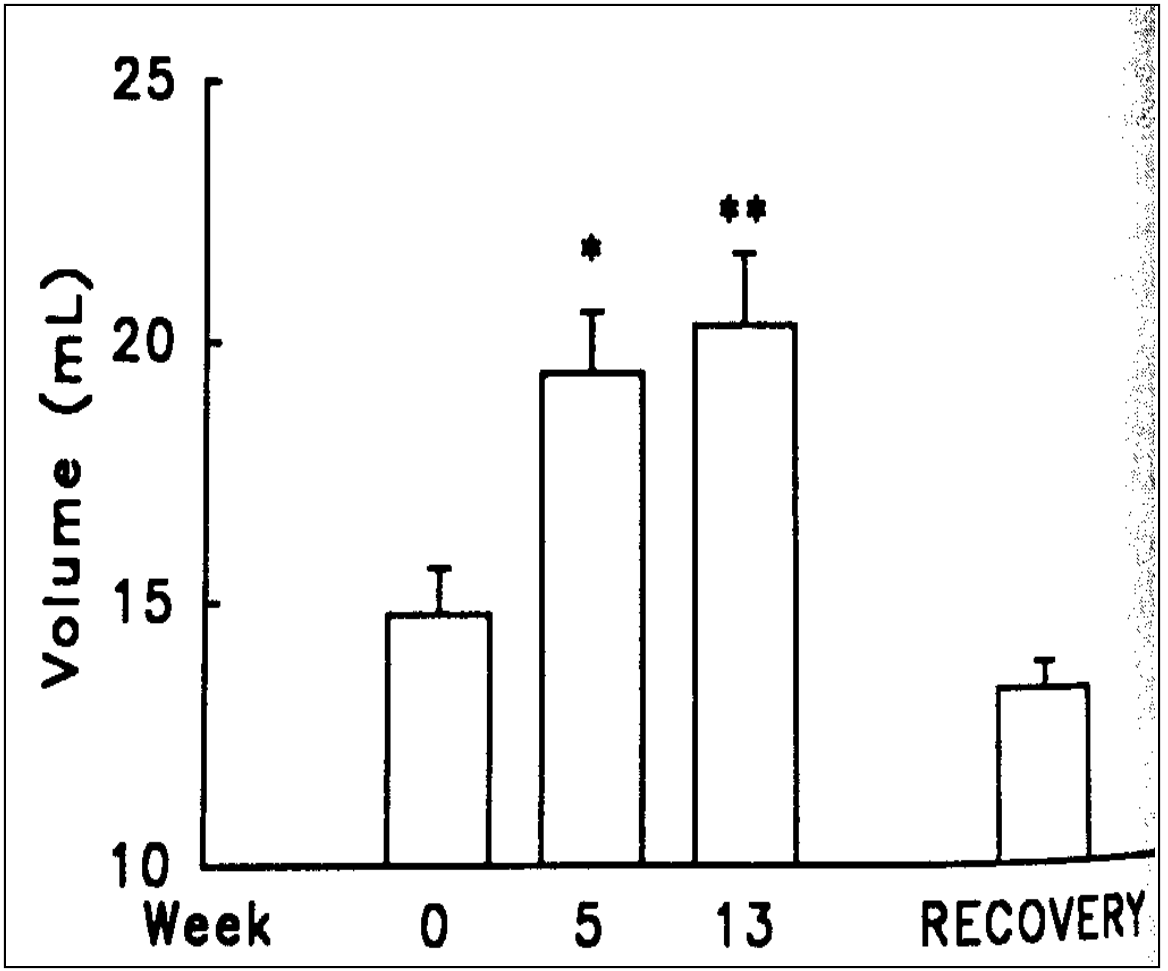
Table 1: Effect of tetraglycine hydroperiodide treatment

ANOVA followed by Student-Newman-Kreuls multiple comparison tests
Mean ± SEM
* $p<0.05$
** $p<0.01$
Tg = Serum thyroglobulin
Dosing – 32,000 µg/day
Comparison Day 0 to Day X

	Before treatment (n = 8)	During Treatment (n = 8)		
		Day 7	Day 28	Day 90
TSH (mU/L)	1.69 ± 0.09	2.80 ± 0.32*	3.30 ± 0.33*	2.98 ± 0.50*
TSH-20	9.90 ± 0.77	14.94 ± 2.41*	18.84 ± 1.72**	16.33 ± 1.69*
T_4 (nmol/L)	83.2 ± 2.9	77.6 ± 4.1	77.6 ± 3.8	78.9 ± 3.3
T_3 (nmol/L)	2.15 ± 0.12	1.97 ± 0.09	2.39 ± 0.15	2.29 ± 0.10
Tg (ng/mL)	13.9 ± 5.6	22.2 ± 9.3	31.4 ± 15.7*	23.3 ± 11.3

Results - 3

Figure 2:
Thyroid volumes before, during and after treatment. Thyroid volume increased significantly after day 35 and enlarged slightly more after day 90. Thyroid volumes had returned to pretreatment values when re-measured at variable time intervals in seven subjects (mean 7.1 months; range 0.5 – 16.1 months. Shown are the mean ± SEM, *, $p<0.05$, ** $p<0.01$



Conclusions

- Mean serum T_4 and T_3 decreased, with T_4 remaining below baseline throughout study and T_3 recovering
- RAIU decreased during the study
- Serum TSH and TSH-20 increased by day 7 and remained elevated
- The average thyroid volume increase was 37%
- No hypo or hyperthyroidism was found in any subject
- For the seven subjects with repeat volume determinations on average after 7.1 months, thyroid level returned to baseline
  - This indicates a reversible, TSH dependent thyroid enlargement occurred in response to increased iodine load from daily use of water purification tablets

EPA Ethics Assessment of LeMar et al. (1995)

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Introduction

- Research was conducted in the 1980s, before promulgation of the 2006 Human Studies Rule
- Considered an intentional exposure human toxicity study because it evaluated potential the toxic effects of iodine intake on thyroid function
- 40 CFR §26.1602 requires HSRB review for pre-rule intentional exposure toxicity studies upon which EPA intended to rely
- Study was located by EPA, not submitted to the Agency, so 40 CFR §26.1303 does not apply

Value to Society

- Provides data about the effects of 12 weeks of daily ingestion of iodine in tetraglycine hydroperiodide tablets for water purification
- The research was important because of the use of tetraglycine tablets to purify drinking water
- The data are potentially useful in EPA's human health risk assessments for products containing iodine

Subject Selection

- 7 male subjects, 1 female subject; ages 35-47
- The female subject was not pregnant or nursing; pregnancy testing performed
- The subjects were employees of the hospital
- Inclusion/exclusion criteria:
  - Subjects had to be healthy, euthyroid, not on any medications that affect thyroid function, no history of thyroid disease
  - Not pregnant

Risks, Risk Minimization, Benefits & Risk:Benefit Balance

- Article is silent
- Benefits
  - No benefits to subjects; Societal benefit from knowledge about iodine intake
- Risk:Benefit Balance
  - Not discussed in article
  - Risks were minimal, so the potential benefits to society outweigh the risks

Ethics Oversight

- Research was reviewed and approved by the institutional review board for the Fitzsimmons Army Medical Center

Informed Consent

- Article states that each subject provided written informed consent
- Dr. McDermott stated:
  - Subjects were given the opportunity to read the protocol
  - Investigators confirmed subject's understanding
  - Each subject signed the consent form
- Copy of the form is not available

Respect for Subjects

- Subjects were not compensated
- Subjects were told that they could withdraw from the study at any time
- Subjects' privacy protected

Standards for Documentation

- The requirement at 40 CFR §26.1303 to document the ethical conduct of research submitted to EPA does not apply:
  - Study was obtained from the public literature, not submitted to EPA
  - EPA located the study at its own initiative

Standards of Conduct

- Conducted prior to 1995, before EPA's Rule at 40 CFR part 26 took effect
- FIFRA §12(a)(2)(P) does not apply
  - Did not involve use of a pesticide
- Common Rule
  - IRB oversight and prior approval
  - Fully voluntary, fully informed consent
  - Favorable risk:benefit balance
  - Equitable subject selection

Standards for EPA Reliance

- **40 CFR §26.1703**
  - Prohibits EPA reliance on data involving intentional exposure of pregnant or nursing women or of children
- **40 CFR §26.1704**
  - Prohibits EPA reliance on data if there is clear and convincing evidence that:

    (1) Conduct of the research was fundamentally unethical; or

    (2) Conduct of 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 or impaired their informed consent.

Compliance with Standards for EPA Reliance

- **40 CFR §26.1703**
  - All subjects were above the age of 18
  - The female subject was not pregnant or nursing
- **40 CFR §26.1704**
  - No clear and convincing evidence that the conduct of the research was fundamentally unethical
  - No clear and convincing evidence that the conduct of the research was deficient relative to prevailing ethical standards

Conclusion

If it is deemed scientifically valid and relevant, there are no barriers in FIFRA or in 40 CFR §26.1703 or §26.1704 to EPA's reliance on the *LeMar et al. (1995)* study in actions taken under FIFRA or §408 of FFDCA

Charge Questions

1. Is the LeMar et al. (1995) study scientifically sound, providing reliable data?
2. If so, is this study relevant to establish the reversibility of high dose iodine exposure?
3. Also, is this study sufficient to establish that there are no sustained adverse effects from high dose iodine exposure?
4. Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?