EPA Science Assessment of Gardner et al. (1988)

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Study Information

- Conducted at the Department of Medicine, Medical College, Richmond VA
- Study Objective – Determine a tolerable upper limit for iodine consumption
- Subjects – 30 Males, euthyroid, no history of thyroid disease or use of medications known to affect thyroid function or previous reactions to iodine, age 22-40
- Self control study

Test Substance

- Sodium Iodide dissolved in water (500, 1500 or 4500 µg/ml per day), co-administered with 1 mg/ml of ascorbic acid.
- Administered as two 0.5 ml solutions twice daily
- Study lasted 14 days
- The subjects were randomly sorted into groups dosed with either 500, 1500 or 4500 µg/ml
- 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
- After an eight hour fast, baseline levels of T_4, T_3, T_3-charcoal uptake, and thyroid stimulating hormone (TSH) were measured
- Stimulated TSH was measured after stimulation by thyrotropin releasing hormone (TRH) every 15 minutes for an hour
- On day 15, the protocol was repeated

Endpoints

- Serum T_4
- Serum T_3
- T_3-charcoal uptake
- TSH
- Stimulated TSH

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Table 1: Serum thyroid hormone concentrations before and after iodide administration

Iodide dose	Serum T_4 (µg/dl)	T_3 charcoal uptake ratio	FTI	Serum T_3 (ng/dl)
500 µg/ml (n= 10)				
Day 1	9.2 ± 0.5	1.06 ± 0.04	9.8 ± 0.8	153 ± 8
Day 15	9.2 ± 0.4	1.09 ± 0.04	10.0 ± 0.6	158 ± 7
p-value	NS	NS	NS	NS
1500 µg/ml (n= 10)				
Day 1	8.6 ± 0.4	1.02 ± 0.04	8.7 ± 0.5	162 ± 11
Day 15	7.5 ± 0.9*	1.00 ± 0.05	7.5 ± 0.4*	161 ± 7
p-value	0.005	NS	0.005	NS
4500 µg/ml (n= 10)				
Day 1	8.9 ± 0.6	1.12 ± 0.09	9.9 ± 0.6	151 ± 9
Day 15	8.2 ± 0.7*	1.11 ± 0.04	9.0 ± 0.6*	155 ± 6
p-value	0.02	NS	0.005	NS

Paired Student's t-test p value
Mean ± SEM
NS = Not significant
Day 15 compared with Day 1

Results - 2

Table 2: Effect of iodide on basal and TRH stimulated serum TSH concentration

Paired Student's t-test
p value
Mean ± SEM.
NS = Not significant
Day 15 compared with Day 1.

Iodide dose	TSH (µU/ml) min after TRH					Maximum TSH increment
	0	15	30	45	60	
500 µg/day (n = 10)						
Day 1	3.0 ± 0.3	9.7 ± 1.4	12.0 ± 1.8	11.0 ± 1.7	9.7 ± 1.8	9.0 ± 1.6
Day 15	3.3 ± 0.5	11.1 ± 1.5	15.2 ± 4.8	13.7 ± 2.3	12.8 ± 2.3	12.5 ± 2.2
p-value	NS	0.05	0.02	0.02	0.002	0.03
1500 µg/day (n = 10)						
Day 1	2.5 ± 0.3	9.6 ± 1.5	11.6 ± 1.8	10.7 ± 1.7	8.7 ± 1.5	9.4 ± 1.7
Day 15	3.7 ± 0.5	14.2 ± 2.2	16.3 ± 2.2	14.6 ± 1.9	12.5 ± 1.9	12.8 ± 2.0
p-value	0.04	0.004	0.002	0.01	0.002	0.005
4500 µg/day (n = 10)						
Day 1	2.1 ± 0.4	8.8 ± 1.1	9.5 ± 1.1	8.9 ± 1.0	7.8 ± 0.9	7.5 ± 1.0
Day 15	3.7 ± 0.6	12.7 ± 1.8	15.5 ± 2.0	14.0 ± 1.4	12.0 ± 1.6	12.2 ± 1.6
p-value	0.008	0.003	0.001	0.001	0.001	0.001

Conclusions

- At 1500 and 4500 µg/day there were decreases in serum and free T4
- No change in T3 charcoal uptake or serum T3
- At 500,1500 and 4500 µg/day there were increases in both basal and TRH induced TSH

EPA Ethics Assessment of Gardner et al. (1988)

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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 whether small increases in iodine intake affect thyroid function
- The research was important because at the time of the study, dietary changes were resulting in increased iodine intake
- The data are potentially useful in EPA's human health risk assessments for products containing iodine

Subject Selection

- 30 male subjects, ages 22-40
- The subjects were medical students or employees of the Medical College of Virginia, or people whose names appeared on a list of interested research candidates maintained by the research center
- Inclusion/exclusion criteria:
  - Subjects had to be healthy, euthyroid, not on any medications that affect thyroid function, no history of thyroid disease

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 Virginia Commonwealth University Committee on the Conduct of Human Research

Informed Consent

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

Respect for Subjects

- Dr. Gardner stated that subjects were paid approximately $150-200 to participate
- Subjects' privacy protected
- We do not know whether subjects were free to withdraw during the study

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 1988, 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
- Declaration of Helsinki (1983)
  - Research must be scientifically sound
  - Clear purpose and protocol, reviewed and approved by an independent ethics committee
  - Prior informed consent

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**
  - The subjects were all males above the age of 18
- **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 *Gardner et al. (1988)* study in actions taken under FIFRA or §408 of FFDCA

Charge Questions

1. Is the Gardner et al. (1988) study scientifically sound, providing reliable data?
2. If so, is this study relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine?
3. Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?