EPA Science Assessment of Paul et al. (1988)

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Introduction

- The Agency is conducting a quantitative assessment of the risks of iodine exposure via the oral route
- These assessments require the determination of a toxic effects and point of departure (POD) of iodine exposure.
- There are a number of studies conducted on the safety of iodine exposure via the oral route in humans, due to its ubiquitous nature and medical relevance

Introduction - 2

- The Agency is proposing the use of the following studies in a weight of evidence manner to quantitatively determine the toxicity and NOAEL for iodine exposure
  - Paul et al, 1988
  - Gardner et al, 1988
  - LeMar et al, 1995
- As these are open literature studies, there is no raw data available for analysis
- These studies represent a subset of the studies used by the NAS in assessing iodine for nutritional purposes

NAS Report (2000)

Examined ~100 papers in a report on nutritional dietary reference intakes

Table : Existing Iodine Background Exposure Levels	
Exposure Scenario	**Exposure Level**
RDA set by the NAS for adult men and women.	150 µg/day or 0.0021 mg/kg/day
Tolerable Upper Intake Level set by the NAS for adult men and women	1100 µg/day or 0.016 mg/kg/day.
U.S. Estimated dietary adult intake established by the U.S. Department of Agriculture Continuing Survey of Food Intakes by Individuals (1994-1996)	190 to 210 µg/day for women 240 to 300 µg/day for men

NAS Report (2000)

- The National Academy of Sciences report cited *Paul* et al (1988) and *Gardner* et al (1988) as the standard for establishing a tolerable upper limit
- *LeMar* et al (1995) chosen to show range of safety after high dose exposure
- Are these studies scientifically valid and ethically acceptable for use in risk assessment for systemic iodine toxicity?

Study Information

- Conducted at the University of Massachusetts Medical School
- Study Objective – Determine a tolerable upper limit for iodine consumption
- Subjects – 9 Males and 23 Females, euthyroid, no history of thyroid disease or use of medications known to affect thyroid function or previous reactions to iodine, age 23-56, not pregnant (if Female), no antithyroid antibodies detected
- An additional 5 age-matched males were studied but not given iodine supplements as controls

Test Substance

- Sodium Iodide dissolved in water (250, 500 or 1500 µg/ml per day), co-administered with 5 mg/ml of ascorbic acid.
- This was administered as two 0.5 ml solutions for 14 days.
- Men received 1500 µg per day and women received either 250, 500 or 1500 µg per day (total)
- Some women were studied at two dose levels (14 day dosing schedule) at least one year apart.
- 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 thyroxine (T_4), triiodothyronine (T_3) and thyroid stimulating hormone (TSH) as well resin T_3 uptake and free T_4 index (FT_4I) were measured.
- Stimulated TSH was measured after stimulation by thyrotropin releasing hormone (TRH) every 15 minutes for an hour.
- On day 15, the initial protocol was repeated.

Endpoints

- Serum T_4
- Serum T_3
- Resin T_3 uptake
- Free T_4 index
- TSH
- Stimulated TSH

Results - 1

Table 1 Serum thyroid hormone concentrations before and after iodide administration

Student's paired t-test

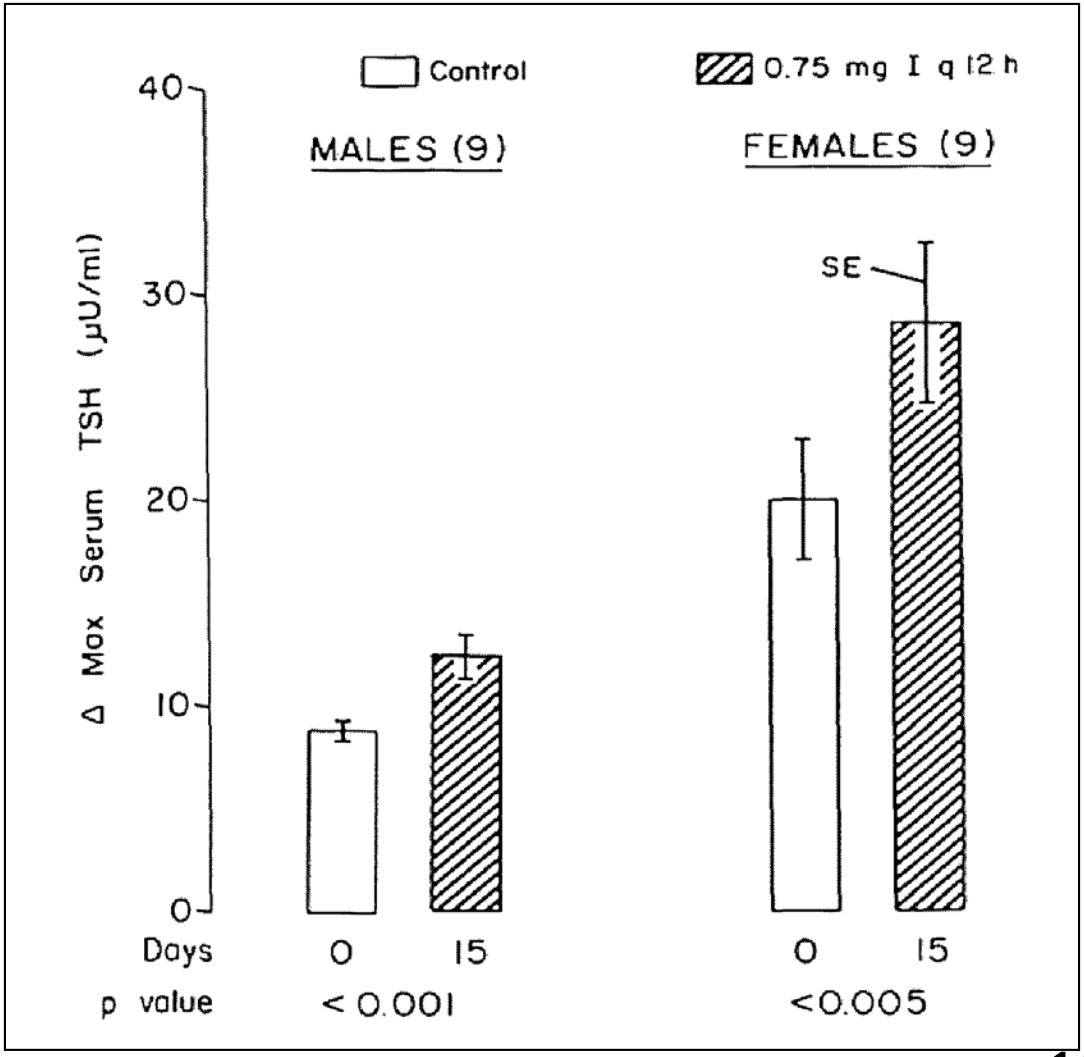
Mean ± SEM
*, p<0.02
**, p<0.01
***, p<0.001
NS – not significant

Comparison is day 0 to day 15

Iodide dose	n	Serum T_4 (µg/dl)		Serum FT_4I		Serum T_3 (ng/dl)		Serum TSH (µU/ml)	
		Day 0	Day 15	Day 0	Day 15	Day 0	Day 15	Day 0	Day 15
1500 µg	18	7.3 ± 0.2	6.7 ± 0.2***	7.0 ± 0.2	6.4 ± 0.2***	181 ± 4	173 ± 4*	1.9 ± 0.2	2.8 ± 0.4**
500 µg	9	7.8 ± 0.4	7.9 ± 0.6	7.1 ± 0.3	7.1 ± 0.3	148 ± 5	144 ± 4	2.1 ± 0.3	2.4 ± 0.4
250 µg	9	7.9 ± 04	7.5 ± 0.3	7.6 ± 0.3	6.9 ± 0.2	134 ± 3	135 ± 4	2.3 ± 0.4	2.7 ± 0.5

Results - 2

Figure 1: The effect of iodine administration of the maximum increase in serum TSH concentration following the intravenous administration of 1500 µg TRH. The numbers in parenthesis represent the number of subjects in each group. Statistical significance was determined using a Student's paired t-test



Results - 3

Table 2: Effect of 500 or 250 µg iodine administered daily to euthyroid women on the TSH response to TRH

Student's paired t-test
Mean ± SEM
Comparison is
day 0
to day 15

Iodide dose	n	Delta Max Serum TSH (µU/ml)		Integrated Serum TSH response (µU/ml x min)	
		Day 0	Day 15	Day 0	Day 15
500 µg	9	18.4 ± 2.8	20.7 ± 2.8	975 ± 151	1088 ± 159
250 µg	9	19.1 ± 3.9	21.6 ± 5.8	1008 ± 196	1170 ± 298

Conclusions

- No change in weight, symptoms of thyroid dysfunction or other adverse affects reported
- At 1500 µg/day there were small but statistically significant decreases in T4 and T3
- At 1500 µg/day there were compensatory and statistically significant increases in serum TSH and TRH induced TSH
- These biological changes, while statistically significant, remained within the normal range and were not considered adverse
- No effects were seen at 250 or 500 µg/day

EPA Ethics Assessment of Paul 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

- 32 subjects (9 males, 23 females); ages 23-56
- None of the female subjects were pregnant or nursing; pregnancy testing performed
- No information about the population from which subjects were recruited
- 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 and Risk Minimization

- Article is silent about risks and risk minimization
- Dr. Braverman stated:
  - Subjects were told about possible risks associated with ingesting too much or too little iodine
  - Investigators believed that risk minimization measures related to iodine doses were not necessary because doses were low
  - Investigators followed normal medical safety precautions for blood draws and i.v.'s

Benefits & Risk:Benefit Balance

- 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

- Article is silent
- Dr. Braverman did not recall if the research underwent independent ethics oversight

Informed Consent

- Subjects are referred to as volunteers in article
- Dr. Braverman stated:
  - Subjects provided written informed consent
  - Study procedures were explained to the subjects, and they were told of possible effects of iodine ingestion
- Copy of the consent form not available

Respect for Subjects

- Subjects were offered freedom to withdraw at any time
- Subjects were not paid for participation
- 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 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
- 1974 DHEW Regulations
  - IRB review and approval
  - Written, fully informed, voluntary consent
- Declaration of Helsinki (1983)

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 subjects were 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 *Paul et al. (1988)* study in actions taken under FIFRA or §408 of FFDCA

Charge Questions

1. Is the Paul 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?