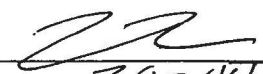



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**Signature:**   
**Date:** 3/13/14  
Template version 02/06

**TXR#:** 1003330

<b>Data Evaluation Record</b>
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**STUDY TYPE:** Subchronic Oral Toxicity (liquid) - human; Non-Guideline Study

**PC CODE:** 046905

**DP BARCODE:** 408676

**TEST MATERIAL (PURITY):** Iodine

**SYNONYMS:** None

**CITATION:** Paul, T., Meyers, B., Witorsch, R.J., et al (1988) The effects of small increases in dietary iodine on thyroid function in euthyroid subjects. University of Massachusetts Medical School MRID 48358603. Metabolism, 37(2) pp 121-124

**SPONSOR:** National Institute of Diabetes and Digestive and Kidney Diseases

**INVESTIGATORS' EXECUTIVE SUMMARY:**

In a 14-day oral toxicity study (MRID 48358603), iodine was self administered by patients as a 0.5 ml solution of sodium iodide every 12 hours. The males in the study received 750 µg twice daily and the women received either 125, 250 or 750 µg twice daily (250, 500 and 1500 µg total). All doses were co-administered with 5 mg of ascorbic acid. The subjects were nine euthyroid men (26-59) and 23 euthyroid women (23-44). Five additional men were age matched controls, receiving no additional iodine. Some women were studied at two dose levels, at least one year apart. This dosing was in addition to their normal unadjusted diets.

No changes in weight, symptoms of thyroid dysfunction, or other adverse effects were reported. Following the administration of 1500 µg, there were small but significant decreases in T<sub>4</sub> and T<sub>3</sub> concentrations and compensatory increases in serum TSH and TSH response to TRH. These changes, while significant, remained within the normal range and are not considered adverse. No effects were seen in the 250 and 500 µg dose groups.

This study is considered quantitative. There is no LOAEL associated with this non-guideline study; the NOAEL is 1500 µg/day.

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: Iodine

Description: NaI

CAS # if TGAI: 74-88-4

2. Vehicle and/or positive control: Deionized water

3. Test animals: Humans

Diet: Typical American

Subject Information: 9 euthyroid men (26-56 yo) and 23 euthyroid women (23-44 yo), no evidence or history of thyroid disease, no antithyroid antibodies detected, not pregnant

### B. STUDY DESIGN AND METHODS:

All subjects had initial evaluations for the study. A 24 hr urine sample was collected for baseline urinary iodine and creatinine excretions. Urinary creatinine was measured to help ensure that a 24 hr urine collection was completed. On day 0, blood was collected for a baseline serum protein bound iodine (PBI) and total iodine (TI), thyroxine ( $T_4$ ), triiodothyronine ( $T_3$ ) and thyrotropin (TSH) as well resin  $T_3$  uptake and free  $T_4$  index ( $FT_4I$ ). Thyrotropin releasing hormone (TRH) was administered via IV and blood was drawn at 15, 30, 45 and 60 minutes for measurement of TRH induced TSH.

All subjects were treated with various doses of iodine in 0.5 ml of deionized water containing 5 mg of ascorbic acid, every 12 hours for 14 days. Men received 750  $\mu$ g and women received either 750, 250, or 125  $\mu$ g twice daily. Some women were studied at two dose levels at least one year apart. A 24 hour urine sample was collected on day 7 and on day 8, prior to morning iodine ingestion, a sample of blood was drawn for analysis. A final 24 hr urine sample was collected on day 14 and the TRH test was repeated on day 15.

Five additional age matched men were studied as above, but not given iodine supplements. No changes in any parameters were seen in these subjects.

## II. RESULTS

### A. Serum inorganic, protein-bound and urinary iodines:

In the subjects receiving the 1500  $\mu$ g daily iodine, there was an increase in mean 24 hr urinary iodine excretion from  $211 \pm 41$   $\mu$ g I/24 hr to  $1360 \pm 74$   $\mu$ g I/24 hr on day seven and  $1308 \pm 58$   $\mu$ g I/24 hr on day 14. This increase in iodine excretion approximated the additional iodine supplementation. Iodine lost through other mechanisms (sweat, feces, salivary gland, choroid plexus and gastric mucosa) could not be evaluated. At this dose level, the increase in iodine uptake induced a small, but significant upward change in serum total iodine, but no change in

protein bound iodine. This indicates there was an increase in the level of serum inorganic iodine levels.

In the subjects receiving 250 or 500 µg daily iodine, there was an increase in urinary iodine excretion ( $186 \pm 37$  µg daily to  $314 \pm 39$  µg by day 14 for the 250 µg dose,  $177 \pm 21$  µg daily to  $506 \pm 33$  µg daily for the 500 µg dose), but no change in serum iodine, protein bound iodine or inorganic iodine.

### B. Serum thyroid hormones:

The 1500 µg dose caused small but significant decreases in serum  $T_3$ ,  $T_4$  and  $FT_4I$  and a significant increase in TSH concentrations by day 15. The 250 and 500 µg daily doses did not significantly affect the serum levels of these factors. These results are seen in Table 1.

**Table 2: Serum thyroid hormone concentrations before and after iodide administration**

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	$7.3 \pm 0.2$	$6.7 \pm 0.2^{***}$	$7.0 \pm 0.2$	$6.4 \pm 0.2^{***}$	$181 \pm 4$	$173 \pm 4^*$	$1.9 \pm 0.2$	$2.8 \pm 0.4^{**}$
500 µg	9	$7.8 \pm 0.4$	$7.9 \pm 0.6$	$7.1 \pm 0.3$	$7.1 \pm 0.3$	$148 \pm 5$	$144 \pm 4$	$2.1 \pm 0.3$	$2.4 \pm 0.4$
250 µg	9	$7.9 \pm 0.4$	$7.5 \pm 0.3$	$7.6 \pm 0.3$	$6.9 \pm 0.2$	$134 \pm 3$	$135 \pm 4$	$2.3 \pm 0.4$	$2.7 \pm 0.5$

\*,  $p < 0.02$

\*\*,  $p < 0.01$

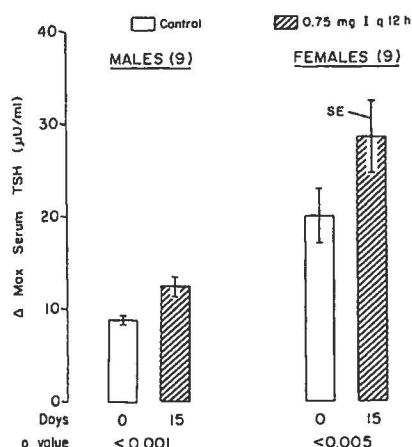
\*\*\*,  $p < 0.001$

NS – not significant

### C. TSH, stimulated and unstimulated:

The maximum increase in TRH stimulated TSH was greater in subjects receiving 1500 µg. This increase in TSH in response to TRH was also significant when integrated TSH response (µU/ml X min) over one hour were calculated. The response was greater in women than in men, both before and after iodine administration. There was no effect from the 500 and 250 µg doses. Data is shown in Figure 1 and Table 2.

**Figure 1: The effect of iodine administration of the maximum increase in serum TSH concentration following the intravenous administration of 500 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.**



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

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

### III. INVESTIGATORS' DISCUSSION AND CONCLUSIONS:

In a 14-day oral toxicity study iodine was self administered by patients as a 0.5 ml solution of sodium iodide every 12 hours. The males in the study received 750 μg twice daily and the women received either 125, 250 or 750 μg twice daily. All doses were co-administered with 5 mg of ascorbic acid. The subjects were nine euthyroid men (26-59) and 23 euthyroid women (23-44). Five additional men were age matched controls, receiving no additional iodine. Some women were studied at two dose levels, at least one year apart. This dosing was in addition to their normal unadjusted diets. No changes in weight, symptoms of thyroid dysfunction, or other adverse effects were reported. Following the administration of 1500 μg, there were small but significant decreases in  $T_4$  and  $T_3$  concentrations and compensatory increases in serum TSH and TSH response to TRH. These changes, while significant, remained within the normal range and are not considered adverse. No effects of any kind were seen in the 250 and 500 μg dose groups.

This study is considered **quantitative**. There is no LOAEL associated with this non-guideline study; the NOAEL is **1500 μg/day**.