EPA Reviewer: Jonathan Leshin, Ph.D. **Signature:**
RASSB, Antimicrobials Division (7510P) **Date:** 3/12/14
Secondary Review: Michelle Centra, Pharmacologist **Signature:** Michelle Centra
RASSB, Antimicrobials Division (7510P) **Date:** 3/13/14

Template version 02/06

Data Evaluation Record

STUDY TYPE: Subchronic Oral Toxicity – liquid - human; OPPTS 870.3150 [§82-1].

PC CODE: 046905 **DP BARCODE:** 408676
TXR#: 1003331

TEST MATERIAL (PURITY): Iodine

SYNONYMS: None

CITATION: Gardner, D.F., Centor, R.M., Utiger, R.D. (1988) Effects of the low dose oral iodide supplementation on thyroid function in normal men. Medical College of Virginia MRID 47358601: Clinical Endocrinology 28: 283-288

SPONSOR: Department of Medicine, Medical College of Virginia, Richmond, VA 23298

INVESTIGATORS' EXECUTIVE SUMMARY:

In a 14-day oral toxicity study (MRID 47358601), sodium iodide was self administered by patients as a 0.5 ml solution twice daily with doses of either 500, 1500 or 4500 µg/ml with 1mg/ml ascorbic acid. The test group was made up of thirty male volunteers. This dosing was in addition to their normal unadjusted diets. No changes in weight, symptoms of thyroid dysfunction, or other adverse effects were reported.

There were dose related increases in serum total and inorganic iodide concentrations as well as urinary iodide excretion. In the 1500 and 4500 µg/ml dose groups there was a decrease in serum T_4 and free T_4. No change in T_3 charcoal uptake or serum T_3 in any dose group occurred. The 500 µg/ml dose group caused a significant increase in serum TSH response to TRH. The 1500 and 4500 µg/ml dose groups caused a significant increase in both basal and TRH induced TSH concentrations. This indicates that iodide supplementation can have some effects on thyroid hormone secretion.

This study is labeled **qualitative** as it does not provide a lower endpoint than an existing study. It does provide useful information on the effects of nutritional levels of iodine in humans and the results are consistent with existing studies.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Iodine
Description: Sodium iodide dissolved in deionized water
CAS # if TGAI: 74-88-4

2. Vehicle and/or positive control: Deionized water

3. Test animals: Humans
Diet: Typical American
Subject information: 30 normal males, age 22-40, healthy, euthyroid, no history of thyroid disease, use of medications known to affect thyroid function or previous reactions to iodine.

B. STUDY DESIGN AND METHODS:

All subjects had initial evaluations for the study. After an eight hour fast, baseline levels of blood basal serum iodine, T_4, T_3, T_3-charcoal uptake, protein bound iodide (PBI), total iodide and TSH were measured. Stimulated TSH was measured after stimulation by TRH every 15 minutes for an hour. A 24 urine sample was collected to measure baseline urinary iodine. Subjects maintained their normal diets.

Subjects consumed 0.5 ml of dissolved iodine in deionized water twice daily. The subjects were randomly sorted into groups dosed with either 500, 1500 or 4500 µg/ml. On day 15, the initial protocol was repeated.

Results were expressed as mean ± sem, with a level of $p<0.05$ considered statistically significant. Paired Student's t-tests were used to compare within-group changes before and after iodide administration.

II. RESULTS

A. Serum inorganic, protein-bound and urinaryiodides:

Changes in serum and urinary iodide occurred at all three dose levels. The changes were dose dependent. No iodide dose caused a significant change in mean serum protein bound iodine. These changes are outlined in Table 1.

Table 1: Urinary iodide excretion and serum iodide concentrations before and after iodide administration

Iodide dose	Urinary iodide (µg/24 hrs)	Total iodide (µg/dl)	Serum PBI (µg/dl)	Inorganic iodide (µg/dl)
500 µg/day				
Day 1	256 ± 44	6.2 ± 0.3	5.0 ± 0.3	1.2 ± 0.1
Day 15	638 ± 58*	6.7 ± 0.3	4.8 ± 0.2	1.9 ± 0.3*
1500 µg/day				

Day 1	285 ± 49	6.3 ± 0.3	5.0 ± 0.3	1.3 ± 0.2
Day 15	1498 ± 105*	7.7 ± 0.2*	4.7 ± 0.2	3.0 ± 0.2*
4500 µg/day				
Day 1	319 ± 51	6.0 ± 0.3	4.7 ± 0.3	1.3 ± 0.2
Day 15	5035 ± 315*	12.7 ± 1.2*	4.8 ± 0.3	7.9 ± 0.9*

Mean ± SEM.
* p<0.001

B. Serum thyroid hormones:

There were no significant changes in the 500 µg/ml dose group. The 1500 and 4500 µg/ml dose groups resulted in decreases in the mean serum T_4 concentration and free T_4 index. Free T_4 (serum free thyroxine, FTI) was calculated by multiplying serum T_4 concentration by the T_3 charcoal uptake ratio. Serum T_3 concentrations and T_3 charcoal uptake ratio did not change for any dosing group. These results are shown in Table 2.

Table 2: 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				
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				
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				
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

p value, day 15 compared with day 1.
Mean ± SEM.
NS – not significant

C. TSH, stimulated and unstimulated:

There was an increase in basal serum TSH from the 1500 and 4500 µg/ml dose groups, but not the 500 µg/ml group. There was a significant increase in TRH induced TSH in all three dosing groups. Data is shown in Table 3.

Table 3: Effect of iodide on basal and TRH stimulated serum TSH concentration

Iodide dose	TSH (µU/ml) min after TRH					Maximum TSH increment
	0	15	30	45	60	
500 µg/day						
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						
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						
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

p value, day 15 compared with day 1.
Mean ± SEM.
NS = Not significant

III. INVESTIGATORS' DISCUSSION AND CONCLUSIONS:

There were dose related increases in serum total and inorganic iodide concentrations as well as urinary iodide excretion. In the 1500 and 4500 µg/ml dose groups, there was a decrease in serum T_4 and free T_4. No change in T_3 charcoal uptake or serum T_3 in any dose group occurred. The 500 µg/ml dose group caused a significant increase in serum TSH response to TRH. The 1500 and 4500 µg/ml dose groups caused a significant increase in both basal and TRH induced TSH concentrations. This indicates that iodide supplementation can have some effects on thyroid hormone secretion.

This study is labeled **qualitative** as it does not provide a lower endpoint than an existing study. It does provide useful information on the effects of nutritional levels of iodine in humans and the results are consistent with existing studies.