5.5

Physiological Effects of Iodinated Water on Thyroid Function

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SUMMARY

Iodine has been used as a potable water treatment and storage bactericidal agent by NASA for over three decades beginning with the Apollo program, and was a critical factor for the achievement of human space flight. Iodine is currently used for Space Shuttle potable water microbial control and is planned for the U.S. component of the International Space Station (ISS). Human consumption of iodinated water is known to transiently affect thyroid-related hormone levels (acute Wolff-Chaikoff effect) and potentially may result in acute and/or chronic thyroid dysfunction in susceptible individuals. NASA's ongoing health surveillance program includes the measurement of thyroid-related hormone levels as part of the medical assessment of thyroid function in all astronauts throughout their careers and natural lives; a summary of these findings and those from an age- and sex-matched peer group is presented. An investigation was undertaken during three ground-based, closed-chamber tests (Phases II, IIa, and III of 30, 60, and 91 days' duration, respectively) to examine thyroid function and hormone levels in chamber subjects who consumed potable water containing iodine. The iodine concentration in the water was within the range planned for use on the ISS. Crewmembers' thyroid function was monitored pre- and postchamber for Phases II and IIa, and pre-, during, and postchamber for Phase III. Although all crewmembers remained free of symptoms and signs of thyroid dysfunction, the data demonstrated that with high levels of iodine intake (4 to 20 mg/day depending on dietary water intake levels), two of the eight crewmembers had notable changes in thyroid-stimulating hormone (TSH) levels, and all crewmembers showed elevations (up to 10-fold in some cases) in urinary iodine levels indicative of the increased iodine intake. Removal of iodine from the drinking water at day 35 in the 91-day chamber test reduced urinary iodine concentrations, but urinary iodine levels remained greater than prechamber values, indicating either possible contamination during urine collection and processing, or persistent iodine exposure of crewmembers from sources other than drinking water.

Urinary iodine levels returned to prechamber baseline levels immediately after crew departure from the chamber. A follow-up study demonstrated that urine collection and processing methods were not the source of the persistent 1.0 to 1.5 mg/day urinary iodine levels. Although no definitive source was identified for these continually elevated urinary iodine levels, there may have been multiple contributing sources. Eventually, TSH levels of all crewmembers returned to prechamber values. As a result of both this study and the recommendations of a NASA-solicited panel of expert thyroidologists, NASA has established an upper limit for daily iodine consumption of 1.0 mg/day from all sources (food and potable water) during space flight. Since iodine still must be used to achieve microbial control, iodine removal technologies have been developed that extract iodine from the spacecraft potable water supply before human use. Independent of this study and NASA's decision to establish a maximum level of daily iodine intake, the U.S. National Academy of Sciences Food and Nutrition Board subsequently established an upper safe limit for iodine intake from all sources at 1.1 mg/day for the general population.

Background

Iodine and Thyroid Function

Iodine, essential for mammalian life, is a component of the two major thyroid hormones, thyroxine (T4) and triiodothyronine (T3), comprising 65 and 59% of their respective weights (7, 10). These hormones regulate many key biochemical processes, especially protein synthesis and enzymatic activity (7). Major target organs are the developing brain, muscle, heart, pituitary, and kidney, but nearly all somatic cells possess nuclear thyroid hormone receptors. Most ingested iodine is reduced in the gut to iodide, which is absorbed almost completely (16). Once in circulation, iodide is removed primarily by the thyroid gland and kidney. The thyroid selectively concentrates iodide with the excess excreted into the urine. Other organs and tissues that can concentrate iodine include the major salivary glands, the mammary glands, the choroid plexus of each brain ventricle, and the gastric mucosa. Thyroid-stimulating hormone (TSH), produced in the anterior lobe of the pituitary gland, regulates the release of thyroid hormones from the thyroid gland into the blood. TSH secretion from the pituitary gland increases when the levels of circulating thyroid hormones decrease. An increased serum TSH level may indicate subclinical (normal serum T3 and T4) or clinical (elevated serum T3 and/or T4) hypothyroidism, while a decreased serum TSH level is usually associated with subclinical or clinical hyperthyroidism. The thyroid responds to the ingestion of elevated quantities of iodine by a transient decrease in thyroid hormone synthesis, termed the acute Wolff-Chaikoff effect (2, 4, 7, 24).

TSH levels have circadian phases that change when sleep/wake cycles are disrupted. Allan and Czeisler (1) found TSH levels normally peak in the late evening, fall precipitously at sleep onset, and remain low throughout the morning

and afternoon. For subjects (n = 15) that remained awake on a 40-hour constant routine (missed a single night of sleep), TSH levels remained elevated over a longer period of time extending into the morning hours. They further demonstrated that both the output of the human circadian pacemaker as well as the inhibitory effect of sleep contribute to the regulation of TSH secretion. Furthermore, a lack of corresponding circadian rhythmicity in circulating levels of thyroid hormones (T3, T4) seen under the same experimental conditions indicates that the relatively large peripheral pools of thyroid hormone are not acutely altered by the normal daily rhythmicity in TSH levels.

The U.S. National Academy of Sciences Food and Nutrition Board (9, 10) Recommended Dietary Allowance (estimated average requirement + 2 standard deviations) is 0.150 mg/day for adult men and women, and the Food and Agriculture Organization (25) of the United Nations World Health Organization (WHO) recommendation is 0.130 and 0.110 mg iodine/day for men and women, respectively. Based on the Food and Drug Administration Total Diet Study (10), iodine intake from food in the United States is approximately 0.190 to 0.300 mg/day. Iodine intake from dietary supplements varies but is approximately 0.140 mg/day (9). Urine contains 90% of the excreted iodine with the remainder in stool and sweat, and is a good indicator of recent iodine consumption. From U.S. data (NHANES I and III), urinary iodine ranges in concentration from 0.0110 to 0.0155 mg/dL (10).

Since 1922, iodine has been used as a method of emergency water treatment for U.S. military personnel (8). Subsequent studies in military personnel on the effects of iodinated water intake at various concentrations for periods as short as one week to as long as six months have documented thyroid enlargement and changes in blood levels of thyroid hormones and TSH (6, 13, 15). However, none of these studies documented any acute clinical manifestations with the exception of mild thyromegaly or any long-term sequelae contributable to consumption of iodinated drinking water. In a particularly relevant study (13), seven men and one woman ingested four tablets of tetraglycine hydroperiodate in water per day for 12 weeks (84 days), providing 32 mg total iodine per day to each subject. Serum inorganic iodide rose from a baseline level of 2.7 to approximately 100 μg/dL, while urinary iodide excretion increased 150-fold from a pretreatment mean of 0.276 to 40 mg/day. As expected, mean T4 and T3 levels declined after seven days. The mean T4 level remained below baseline throughout the study but T3 had recovered by the end of the 13-week (91-day) period. Serum TSH and the subject's response to TRH rose significantly after seven days and remained elevated at three months. Thyroid volume determined by ultrasonography increased an average of 37%, but clinical signs of neither hyperthyroidism nor hypothyroidism were observed (15). In another study, prisoners (22) consumed 0.5 to 1.0 mg iodine/L of drinking water with no significant clinical effects. However, 44 (46%) of 96 Peace Corps volunteers, consuming approximately 50 mg iodide/day over a period of up to one year from contamination of water purification units, had enlarged thyroid glands, while 30 of

those had normal thyroid function tests and 33 (34%) of the 96 had thyroid dysfunction (11). In another study (20), no differences were found in T3 and T4 levels with administration of iodine as I^- (iodide) versus I_2 (iodine) in humans. However, elevations were observed in TSH with both forms, which raised concerns about the impact of consumption of iodine in drinking water for spacecraft. There are published reviews of various iodide toxicity population and case studies (2, 19).

The consequences of iodide supplementation on thyroid function in normal subjects are reported for two studies in Table 5.5-1 (14). TSH concentrations were studied in 30 adult males who received 0.5, 1.5, and 4.5 mg/day as supplemental iodide for two weeks (5). The subject's average prestudy urinary iodine was 0.29 mg/day, and food sources represented approximately 0.3 mg/day. Although still within the normal range, the mean basal serum TSH concentration increased significantly in those receiving the two higher doses of iodine. In a similar study (18), nine men and 23 women received iodine supplementation at 0.25, 0.5, or 1.5 mg/day. Baseline urinary iodine was approximately 0.191 mg/day, and calculated dietary intakes were 0.2 mg/day. Those receiving 1.5 mg/day of iodide showed a significant increase over baseline in their TSH levels, with no effects seen at the two lower doses. In a 28-day study of 225 adult women (treatment plus controls), there were significantly elevated TSH concentrations with iodine intakes of 0.75 mg/day or more (3).

Table 5.5-1 *Effects of low-dose iodide supplementation on thyroid function in normal subjects*[a]

Investigator (ref #)	Iodide (mg/day)	TSH	TSH Response to TRH[b]	T4	Free T4	T3
Paul (15)	0.25	No effect	No effect	No effect	No effect	No effect
Paul (15)	0.5	No effect	No effect	No effect	No effect	No effect
Gardner (5)	0.5	No effect	↑	No effect	No effect	No effect
Paul (15)	1.5	↑	↑	↓	↓	↓
Gardner (5)	1.5	↑	↑	↓	↓	No effect
Gardner (5)	4.5	↑	↑	↓	↓	No effect

[a]Reference 14

[b]Thyroid-releasing hormone

Thyroid dysfunction is more likely to appear with prolonged consumption of pharmacological doses of iodine in susceptible individuals. Generally, most individuals with normal underlying thyroid function remain euthyroid during periods of iodine consumption (2, 3, 19). Individuals who have autoimmune thyroid disease and/or iodine deficiency as well as individuals living in areas of low iodine intake may respond adversely to high iodine intakes. These responses include thyroiditis, goiter, hypothyroidism, and hyperthyroidism. Signs of acute iodine poisoning include burning mouth, throat, and stomach, abdominal pain, fever, nausea, vomiting, and other symptoms (11, 21). Thus, the Food and Nutrition Board (10) reported that adults have no observed adverse effect at levels of 1 to 2 mg/day and a lowest observed adverse effect at a level of 1.7 mg/day for iodine. The Food and Nutrition Board currently recommends an upper limit for total iodine intake from combined food and water sources be less than 1.1 mg/day (10).

History of Iodine in U.S. Space Flight Programs

Iodine has been used for the last 30 years, beginning with the Apollo program, as an effective bactericidal, virucidal, and amebicidal agent for drinking water (20, 23); this includes the potable water system of spacecraft, training galleys, and NASA closed-chamber tests. Microbial quality of potable water first became an issue during the Gemini program because the water consumed by the astronauts had to be stored before the flight and throughout the duration of the flight. This storage would potentially allow proliferation of hazardous microorganisms in the stored water. Of even greater concern was the threat of a microbial hazard from the potential cross-contamination between the potable water supply and the urine disposal system. A variety of chemical disinfectants were used with varying success during the Gemini program. On some missions, a quaternary ammonia compound (Roccal®) that had an undesirable taste was employed while chlorine in the form of hypochlorite, which was effective for only a few days, was used on other missions. There was no capability to add additional chlorine either on the ground during preparation for flight or in flight during missions of up to 14 days, thus limiting the utility of chloride as a disinfectant for space flight.

With the recognition of the microbial hazard in the potable water during the Gemini program, the development of the Apollo Command Module and Lunar Module incorporated the requirement to maintain a biocide in the potable water. The Command Module used sodium hypochlorite for microbial control in combination with sodium dihydrogen phosphate for pH control and sodium nitrate for corrosion control. Because of chlorine depletion and the dilution of the stored water with water produced by the fuel cells, nitrate, chlorine, and phosphate had to be added manually by the crew daily. This system provided the required microbial control but was time consuming for the crew and periodically caused adverse chlorine tastes because of spiking of the chlorine level at the time of its addition. In contrast, the Lunar Module water that was stored on board before launch was iodine treated. The configuration of the launch vehicle required that this water be loaded

into the Lunar Module tanks about 30 days before launch. Testing of the system demonstrated that the active reduced form of iodine remained effective throughout the combined water storage period and length of the mission. The successful use of iodine in the Lunar Module of the Apollo program led to its being the agent of choice in the subsequent Skylab program.

The Skylab program, consisting of three serial missions (Skylab 2, 3, and 4) of increasing lengths (28, 56, and 84 days, respectively) over a period of approximately one year, required that all water be stored on board the vehicle before launch. Iodine was selected because of its water system materials compatibility – a flight-compatible (colorimetric starch-iodine reaction) method of monitoring levels to determine when it needed to be replenished – and an in-flight addition method utilizing a $KI:I_2$ stock solution. To better ensure system materials compatibility, the water system was fabricated of stainless steel. Because reduced iodine in time eventually converts to iodide, which is not an effective disinfectant, iodine stock solution was periodically added which resulted in a total iodine content in the potable water of up to 72 mg/L during the longest (84-day) Skylab mission.

The Space Shuttle, like the Apollo Command Module, uses hydrogen and oxygen fuel cells to generate electrical power with continuously produced water as the by-product (23). Prior to the Shuttle program, an iodinated anion-exchange resin system was developed that reliably introduces effective levels of iodine into the fuel cell water as it flows through a packed resin bed into the water storage tanks. Shuttle crewmembers' mean iodine exposure levels have varied from 3.8 to 5.9 mg/L water (Table 5.5-2). This system has proven to be successful as it reliably provided the required level of microbial control during periods between missions and throughout the duration of flight.

Table 5.5-2 *Exposure to iodine during space flight*

Mission	Mean Exposure Time (days)	Mean Iodine Level (mg/L of water)
Skylab 2, 3, 4	57.2	11.2
Shuttle (flights 1-25)[a]	6.4	5.9
Shuttle (flights 26-63)[b]	9.5	3.8

[a]STS-1 to STS-51L

[b]STS-26 to STS-87

The U.S. water recovery system for the ISS is being developed to use iodine for potable water microbial control utilizing an iodinated resin system. The major aspect of the ISS that differs from previous U.S. missions is that for the first time there will be reclamation of water from urine, wash water, and humidity condensate for use as potable water. This will place additional demands on the water disinfection system because of the increased microbial contaminant content of the source waters.

Thyroid Function Among Astronauts as Compared to Controls

As part of the astronaut longitudinal epidemiological research program (Longitudinal Study of Astronaut Health), thyroid function is monitored and compared to age-, sex-, and career-matched controls (14). Since 1994, thyroid peroxidase and thyroglobulin antibody testing has been performed as part of astronaut candidate selection, but such testing has not been done in the comparison population (14). For this longitudinal study, subclinical hypothyroidism is defined as elevated serum TSH values in the presence of normal serum T3 and T4 levels at three or more annual medical physical examinations. As discussed earlier in this chapter, astronauts flown over the history of the U.S. space program have had a variety of exposures to iodine (Table 5.5-2). Calculated iodine water intake was based on an average water intake of 1.9 L/day multiplied by the length of the mission.

There was no documented increased incidence of thyroid disease in the 270 astronauts studied as compared to the peer group (n = 258), and there was also no increased incidence of thyroid dysfunction related to total iodine exposure during space flights (14). While astronauts flying on longer-duration missions, such as Skylab or on multiple Shuttle flights, had increased iodine exposure compared to those who have not flown or who flew only on a single Shuttle flight, there was no association between the incidence of thyroid disease and the number or duration of space fights flown. There was no statistically based evidence that space flight or iodine exposure increased the incidence of subclinical or clinical thyroid disease in U.S. astronauts (14).

Purpose of the Thyroid Function Study

The planned ISS U.S. water system will recycle water from urine and other wastewaters for human consumption and requires long-term storage. Iodine is planned as the disinfectant at 2 to 4 mg/L (I_2) concentration with a total iodine concentration of 3 to 6 mg/L (I_2 and I^-). With the proposed iodine exposure levels and the crewmembers originating from many countries including regions of low iodine intake, additional concerns have been raised regarding the use of iodine in ISS potable water. The purpose of this study was to document the thyroid functional biochemical measurements (n = 12), urine iodine levels (n = 8), and any clinical signs or symptoms of thyroid dysfunction in the 12 crewmembers who participated in the chamber studies.

Methods

Characteristics of Ground-Based Test Subjects and the Chamber Tests

Of the 12 crewmembers, four were female, and all were under 42 years of age. Each selected crewmember was considered healthy. All had normal weight per height, and as part of the selection process each passed a class III Air Force medical examination, had normal thyroid function, and successfully completed an exercise stress test.

The chamber tests, in order of occurrence, were 30 days, Phase II; 60 days, Phase IIa; and 91 days, Phase III. Each chamber test had four crewmembers with one, one, and two women in Phases II, IIa, and III, respectively. In all three chamber tests, after the water recycling process was completed, 3.5 to 5.2 mg iodine/L was added to the water as the disinfectant. In Phase II (30 days) and Phase IIa (60 days), thyroid hormonal status (TSH and thyroid hormone levels) was assessed both in the pre- and postchamber period. In Phase III, the 91-day study, TSH, thyroid hormones, and urinary iodine levels were measured before and several times in chamber (first measurement at the 30-day mark). These were followed up with several more measurements in the postchamber period upon the subjects' exit from the chamber at the completion of the study. Subjects were monitored until all indices of iodine/thyroid status had returned to prechamber levels.

For the Phase III study (91 days), due to changes in TSH levels at the 30-day mark, iodine was removed from the potable water before consumption. This was accomplished by installing an iodine-removal device and a microbial filter (0.2 μm) at the point of use of the water on chamber day 35. This device removed the iodine (I_2 and I^-) from the drinking water but did not affect the iodine levels in the remainder of the water used, i.e., for hygiene activities. Urinary iodine levels (argon plasma mass spectrometer, Mayo Clinic Laboratories, MN) were spot-checked to determine iodine exposure. Anti-thyroidal (anti-thyroglobulin and anti-TPO) antibodies were determined (12) in only the four Phase III test crewmembers.

Methods of Analysis

Table 5.5-3 lists the analyses performed on water, urine, and blood samples. Several methods were used over the course of the chamber studies, reflecting updating of the methodologies. Reference ranges are provided with the results (Tables 5.5-4 through 5.5-6).

Table 5.5-3 *Methods of analysis*

Measurement	Chamber Phase	Method
Urinary iodine	IIa, III	Method described in detail in Appendix Inductively Coupled Plasma Mass Spec (ICP-MS)
T3	II, IIa, III	Microparticle Enzyme Immunoassay (MEIA)
T4	II, IIa, III	Microparticle Enzyme Immunoassay (MEIA)
Free thyroxine index (FTI)	II, IIa, III	Calculated from total T4 and T-uptake
TSH	II, IIa, II	Microparticle Enzyme Immunoassay (MEIA) II and IIa used first-generation test TSH Abbott IMX, Last measure on IIa and all of III used second-generation hTSHII Abbott IMX
Free T4	IIa, III	Radioimmunoassay by direct equilibrium dialysis
Anti-TPO	III	Chemiluminescence
Thyroglobulin AB	III	Chemiluminescence

Classification of Thyroid Dysfunction

Subclinical hypothyroidism is defined as a state of mild thyroid hormone deficiency characterized by elevated TSH levels and normal thyroid hormone levels (21). Subclinical hyperthyroidism is defined as depressed TSH levels and normal thyroid hormone levels. Symptoms and signs monitored were those of thyroid hormone hyperfunction including nervousness, restlessness, tachycardia, tremor, weight loss, and heat intolerance (19). Clinical hypothyroidism is diagnosed in an individual with symptoms of hypothyroidism (muscle cramps, dry skin, cold intolerance, constipation, poor energy, and easy fatigability), elevated TSH, and low thyroid hormone levels (T3 and/or T4).

Table 5.5-4 *Thyroid and iodine levels for the Phase II crewmembers*

			Prechamber Testing 8 days prechamber	Postchamber Testing		
	Laboratory Measurement	**Reference Range**	**0 days iodinated water**	**2 days postremoval iodinated water**	**19 days postremoval iodinated water**	**42 days postremoval iodinated water**
Subject 1	TSH	0.0-6.0 μIU/mL	1.5	2.0	1.8	nd
	Total T4	4.5-13.0 μg/dl	7.5	7.4	7.6	nd
	Free T4	0.89-1.80 ng/dl	-	-	-	nd
	T3 uptake	0.70-1.07	0.98	1.0	0.90	nd
	FTI	5.00-12.00	7.65	7.40	8.44	nd
	Total T3	57-170 ng/dl	107	90	94	nd
Subject 2	TSH	0.0-6.0 μIU/mL	1.4	2.5	1.6	1.2
	Total T4	4.5-13.0 μg/dl	5.4	5.5	5.6	6.7
	Free T4	0.89-1.80 ng/dl	-	-	-	1.22
	T3 uptake	0.70-1.07	0.77	0.73	0.79	1.22
	FTI	5.00-12.00	7.01	7.53	7.09	8.48
	Total T3	57-170 ng/dl	112	76	90	76
Subject 3	TSH	0.0-6.0 μIU/mL	0.8	1.2	0.6	1.0
	Total T4	4.5-13.0 μg/dl	5.2	6.0	5.8	6.5
	Free T4	0.89-1.80 ng/dl	-	-	-	1.13
	T3 uptake	0.70-1.07	0.73	0.79	0.69	0.75
	FTI	5.00-12.00	7.12	7.59	8.41	8.67
	Total T3	57-170 ng/dl	105	101	74	90
Subject 4	TSH	0.0-6.0 μIU/mL	1.9	2.3	1.6	1.0
	Total T4	4.5-13.0 μg/dl	7.9	7.1	7.3	8.5
	Free T4	0.89-1.80 ng/dl	-	-	-	1.15
	T3 uptake	0.70-1.07	0.86	0.88	0.92	0.92
	FTI	5.00-12.00	9.19	8.07	7.93	9.24
	Total T3	57-170 ng/dl	124	100	108	81

nd = no data collected

Table 5.5-5 *Thyroid and iodine levels for the Phase IIa crewmembers*

			Prechamber Testing 8 days prechamber	Postchamber Testing		
	Laboratory Measurement	Reference Range	0 days iodinated water	2 days postremoval iodinated water	19 days postremoval iodinated water	42 days postremoval iodinated water
Subject 1	TSH	0.0-6.0 μIU/mL	3.1	3.6	1.7	2.9
	Total T4	4.5-13.0 μg/dl	8.2	9.2	10.5	8.9
	Free T4	0.89-1.80 ng/dl	-	nd	-	-
	T3 uptake	0.70-1.07	1.10	1.17	1.24	1.07
	FTI	5.00-12.00	7.45	7.86	8.47	8.32
	Total T3	57-170 ng/dl	126	127	106	123
Subject 2	TSH	0.0-6.0 μIU/mL	2.2	3.1	1.2	1.87
	Total T4	4.5-13.0 μg/dl	5.4	7.4	6.7	6.5
	Free T4	0.89-1.80 ng/dl	-	-	-	1.13
	T3 uptake	0.70-1.07	0.74	0.79	0.71	0.68
	FTI	5.00-12.00	7.30	9.37	9.44	9.56
	Total T3	57-170 ng/dl	93	115	87	86
Subject 3	TSH	0-6.0 μIU/mL	0.6	1.6	0.7	0.87
	Total T4	4.5-13.0 μg/dl	7.9	8.3	7.8	8.0
	Free T4	0.89-1.80 ng/dl	-	-	-	1.03
	T3 uptake	0.70-1.07	0.89	0.89	0.92	8.99
	FTI	5.00-12.00	8.88	9.33	8.48	8.99
	Total T3	57-170 ng/dl	132	143	114	122
Subject 4	TSH	0-6.0 μIU/mL	4.5	1.0	14.9	6.1
	Total T4	4.5-13.0 μg/dl	5.0	6.8	3.4	4.8
	Free T4	0.89-1.80 ng/dl	-	-	-	0.90
	T3 uptake	0.70-1.07	0.62	0.72	0.74	0.66
	FTI	5.00-12.00	8.06	9.44	4.59	7.27
	Total T3	57-170 ng/dl	97	121	81	72

nd = no data collected

Table 5.5-6 *Thyroid and iodine levels for the Phase III crewmembers*

			Prechamber Testing	In-Chamber Testing						Postchamber Testing	
			8 days prechamber	31 days chamber	33 days chamber	41 days chamber	60 days chamber	91 days chamber		2 days postchamber	
	Laboratory Measurement	Reference Range	0 days iodinated water	31 days iodinated water	33 days iodinated water	7 days postremoval iodinated water	28 days postremoval iodinated water	59 days postremoval iodinated water	61 days postremoval iodinated water		
Subject 1	TSH	0.047-5.01 µIU/L	1.00	4.06	nd	2.69	2.70	1.85	nd		
	Total T4	4.5-13.0 µg/dl	8.5	7.1	nd	7.7	7.8	7.6	nd		
	Free T4	0.89-1.80 ng/dl	1.15	1.02	nd	1.12	1.11	1.32	nd		
	T3 uptake	0.70-1.07	0.92	0.82	nd	0.72	0.85	0.78	nd		
	FTI	5.00-12.00	9.24	8.66	nd	10.69	9.18	9.74	nd		
	Total T3	57-170 ng/dl	81	86	nd	82	108	106	nd		
	Anti-TPO AB	0.0-2.0 IU/ml	nd	< 2.0	nd	nd	nd	nd	nd		
	Anti-thyroglobulin AB	0.0-2.0 IU/ml	nd	< 2.0	nd	nd	nd	nd	nd		
	Urine volume	760-2500 ml	nd	1905	nd	1635	1900	750*	1363		
	Urine iodine	100-460 µg/24hr	nd	9458	nd	2367	975	698*	269		
	Cum. iodine intake	in mg	0	388	413	429	431	432	432		
Subject 2	TSH	0.047-5.01 µIU/L	1.90	3.34	4.06	3.27	2.70	2.89	nd		
	Total T4	4.5-13.0 µg/dl	8.5	6.5	7.2	7.1	7.5	7.6	nd		
	Free T4	0.89-1.80 ng/dl	1.09	0.83	1.03	0.93	0.99	1.14	nd		
	T3 uptake	0.70-1.07	0.93	0.9	0.88	0.79	0.86	0.82	nd		
	FTI	5.00-12.00	9.14	7.22	8.18	8.99	8.72	9.27	nd		
	Total T3	57-170 ng/dl	85	73	79	74	93	102	nd		
	Anti-TPO AB	0.0-2.0 IU/ml	nd	< 2.0	nd	nd	nd	nd	nd		
	Anti-thyroglobulin AB	0.0-2.0 IU/ml	nd	< 2.0	nd	nd	nd	nd	nd		
	Urine volume	760-2500 ml	nd	4105	nd	2475	3790	3381	3357		
	Urine iodine	100-460 µg/24hr	nd	16857	nd	733	1020	1467	1249		
	Cum. iodine intake	in mg	0	446	467	481	484	485	485		

*Data may not represent complete 24-hour collection
nd = no data collected

Table 5.5-6 continued *Thyroid and iodine levels for the Phase III crewmembers*

			Prechamber Testing	In-ChamberTesting					Postchamber Testing	
			8 days prechamber	31 days chamber	33 days chamber	41 days chamber	60 days chamber	91 days chamber	2 days postchamber	
	Laboratory Measurement	Reference Range	0 days iodinated water	31 days iodinated water	33 days iodinated water	7 days postremoval iodinated water	28 days postremoval iodinated water	59 days postremoval iodinated water	61 days postremoval iodinated water	
Subject 3	TSH	0.047-5.01 µIU/L	0.80	3.07	nd	2.00	1.41	0.75	nd	
	Total T4	4.5-13.0 µg/dl	6.9	6.8	nd	7.6	6.6	7.6	nd	
	Free T4	0.89-1.80 ng/dl	1.30	1.1	nd	1.33	1.16	1.55	nd	
	T3 uptake	0.70-1.07	0.71	0.76	nd	0.74	0.75	0.71	nd	
	FTI	5.00-12.00	9.72	8.95	nd	10.27	8.80	10.70	nd	
	Total T3	57-170 ng/dl	94	97	nd	108	89	111	nd	
	Anti-TPO AB	0.0-2.0 IU/ml	nd	< 2.0	nd	nd	nd	nd	nd	
	Anti-thyroglobulin AB	0.0-2.0 IU/mnd	nd	< 2.0	nd	nd	nd	nd	nd	
	Urine volume	760-2500 ml	nd	830	nd	725	1625	269*	1579	
	Urine iodine	100-460 µg/24hr	nd	7192	nd	755	986	287*	276	
	Cum. iodine intake	in mg	0	259	280	295	297	298	298	
Subject 4	TSH	0.047-5.01 µIU/L	1.40	2.28	2.31	2.03	2.50	2.30	nd	
	Total T4	4.5-13.0 µg/dl	7.0	6.8	7.1	7.2	7.4	7.3	nd	
	Free T4	0.89-1.80 ng/dl	0.96	0.78	0.96	1.02	0.89	1.13	nd	
	T3 uptake	0.70-1.07	0.93	0.98	0.99	0.89	0.97	0.83	nd	
	FTI	5.00-12.00	7.53	6.94	7.17	8.09	7.63	8.80	nd	
	Total T3	57-170 ng/dl	97	104	88	93	113	114	nd	
	Anti-TPO AB	0.0-2.0 IU/ml	nd	< 2.0	nd	nd	nd	nd	nd	
	Anti-thyroglobulin AB	0.0-2.0 IU/ml	nd	< 2.0	nd	nd	nd	nd	nd	
	Urine volume	760-2500 ml	nd	3130	nd	3555	3010	3761	1944	
	Urine iodine	100-460 µg/24hr	nd	16764	nd	1113	1261	1892	303	
	Cum. iodine intake	in mg	0	587	621	641	644	646	646	

*Data may not represent complete 24-hour collection
nd = no data collected

Results

Water, Urinary, and Dietary Iodine Levels

While individual water consumption was not determined for Phases II and IIa crewmembers, analysis of diet records and the systematic evaluation of water usage indicates the crewmembers consumed from 4 to 10 mg total iodine/day. For Phase IIa (60 days), drinking water contained approximately 2 to 4 mg I/L (Figure 5.5-1) and subjects excreted approximately 4.5 to 14 mg/day (Figure 5.5-2). Intake measurements were only completed twice during the study (Figure 5.5-2).

The actual individual water iodine intakes and urinary losses were quantified for the Phase III, 91-day test (Figures 5.5-3, 5.5-4). Figure 5.5-3 shows that the total iodine in the water varied from approximately 3 to 8 mg/L with an average level for the first 35 days around 5 mg total iodine/L. Urinary iodine levels reflect recent iodine consumption (Figure 5.5-4). In all subjects, urinary iodine levels increased about 10-fold during the first 30 days of the Phase III chamber study, with iodine consumption levels ranging from 8 to 20 mg/day. Urinary excretion means for subjects ranged from 9.4 to 16.9 mg I/day (Table 5.5-6). The variation in iodine intake between crewmembers was related to the individual volume of potable water consumed.

Following installation of the iodine removal device at the galley sink, the total iodine levels measured less than 0.05 mg/L in the drinking water but remained in full concentration in the shower and wash water. Urinary iodine levels decreased 5- to 10-fold after cessation of the water iodine exposure but remained above baseline values (Table 5.5-6 and Figure 5.5-4). By the end of the 91-day study, 56 days after cessation of drinking water iodine, the urinary values continued to remain above baseline values in three of the four subjects (Table 5.5-6, Figure 5.5-4). In three of the crewmembers, urine iodine levels fell to an average of 0.283 mg/24 hrs by three days after test completion. One crewmember (Subject 2) consumed a bundant iodine-rich seafood on multiple occasions after test completion and had a 24-hour urine iodine level of 1.2 mg/day two days after exiting the chamber (Table 5.5-6).

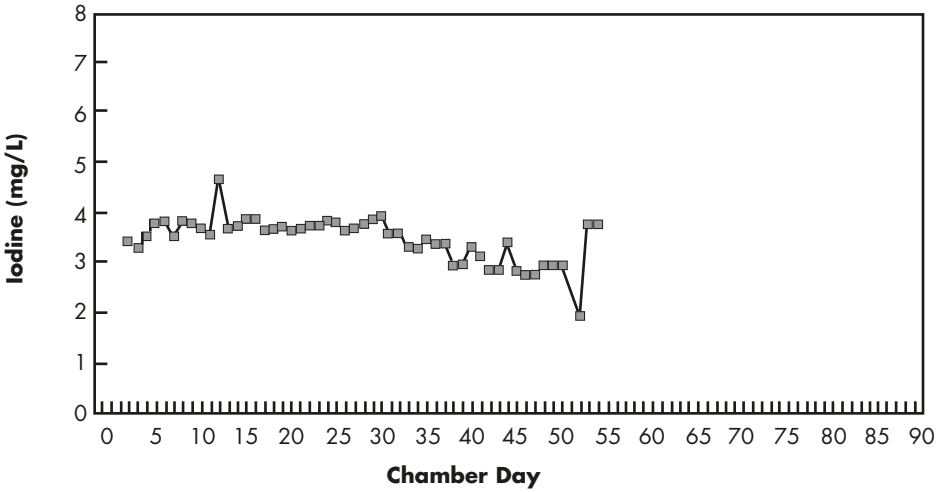

Figure 5.5-1 *Iodine levels in drinking water during Phase IIa by chamber day*

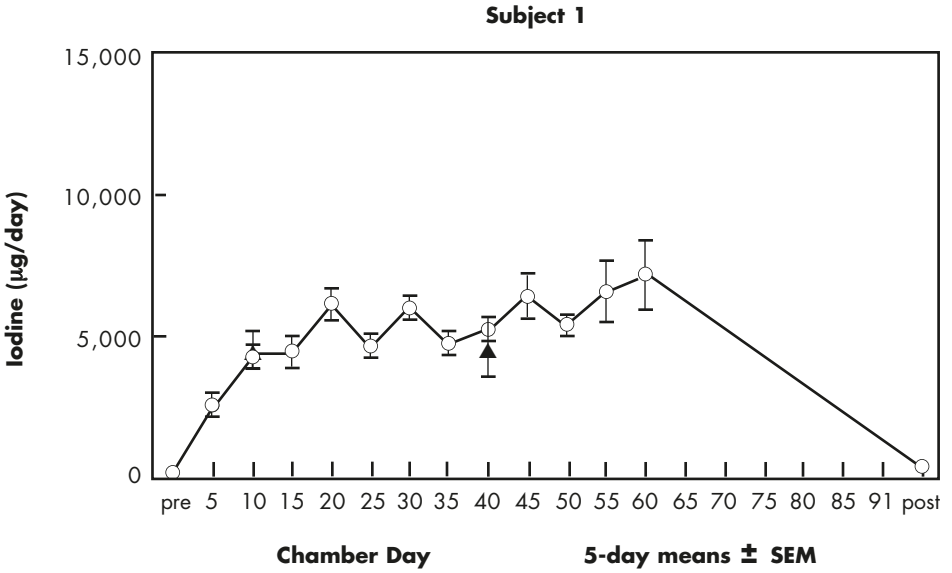

Figure 5.5-2 *Iodine intake from water (▲) and urinary iodine excretion (○) of crewmembers during Phase IIa*

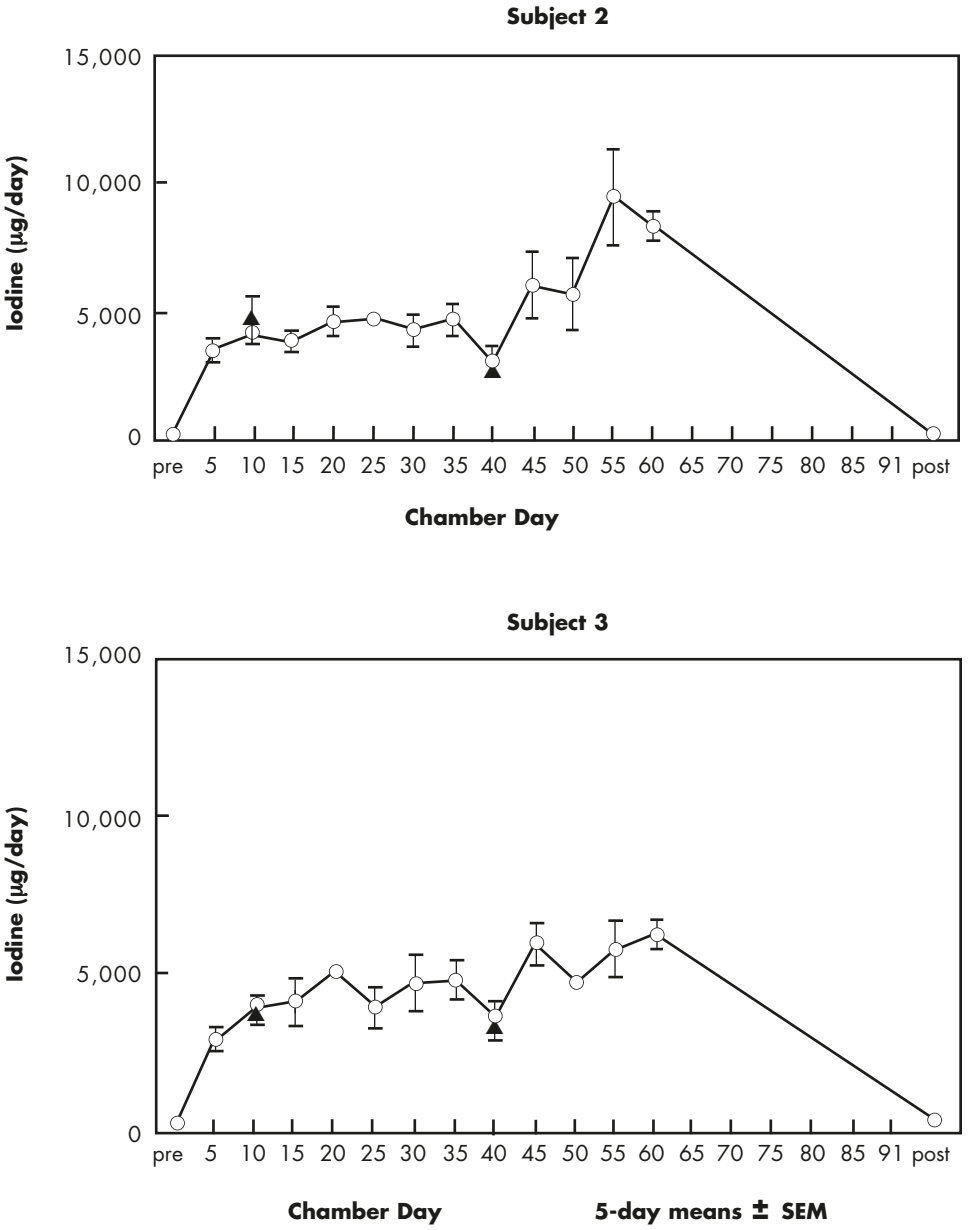

Figure 5.5-2 continued *Iodine intake from water (▲) and urinary iodine excretion (○) of crewmembers during Phase IIa*

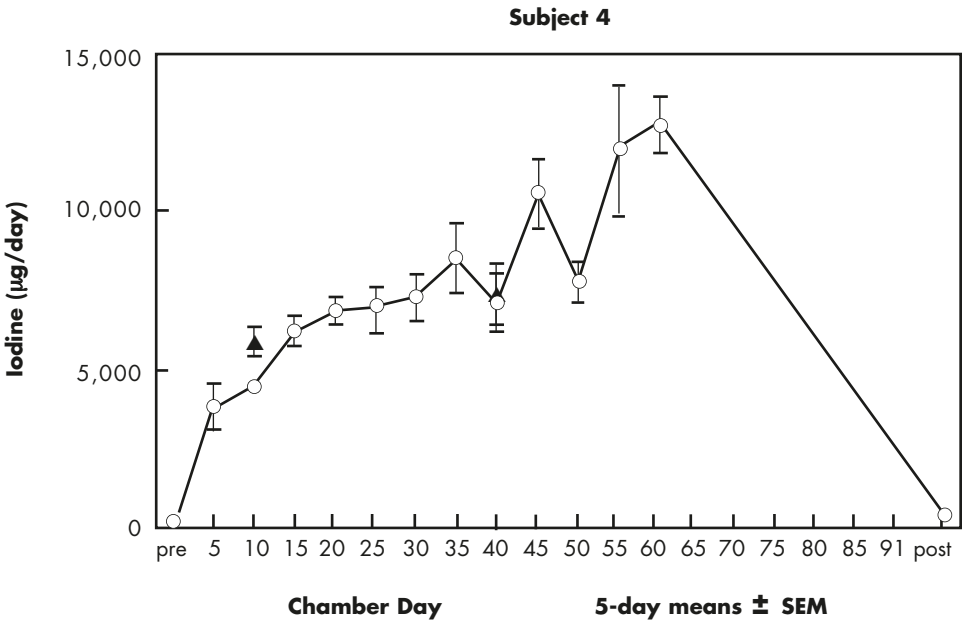

Figure 5.5-2 continued *Iodine intake from water (▲) and urinary iodine excretion (○) of crewmembers during Phase IIa*

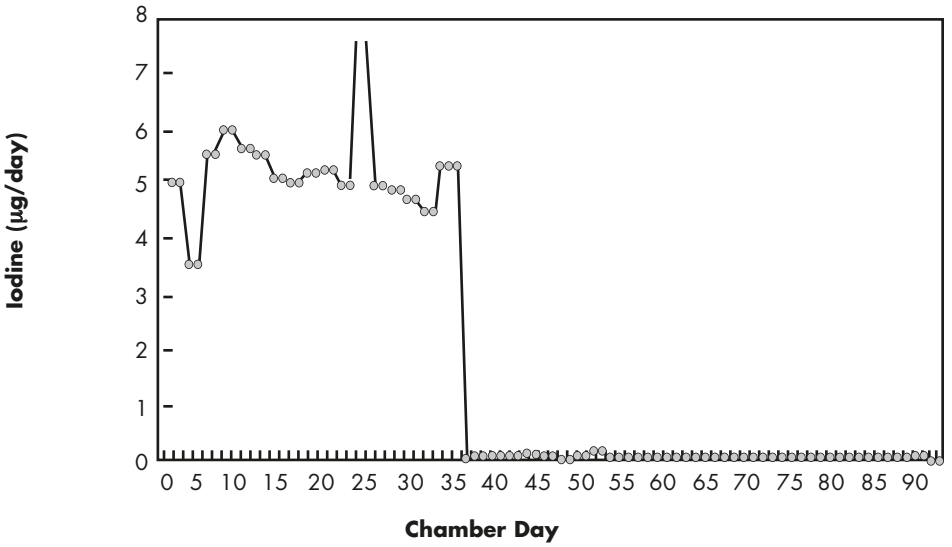

Figure 5.5-3 *Iodine levels in drinking water (mg/L) during Phase III by chamber day*

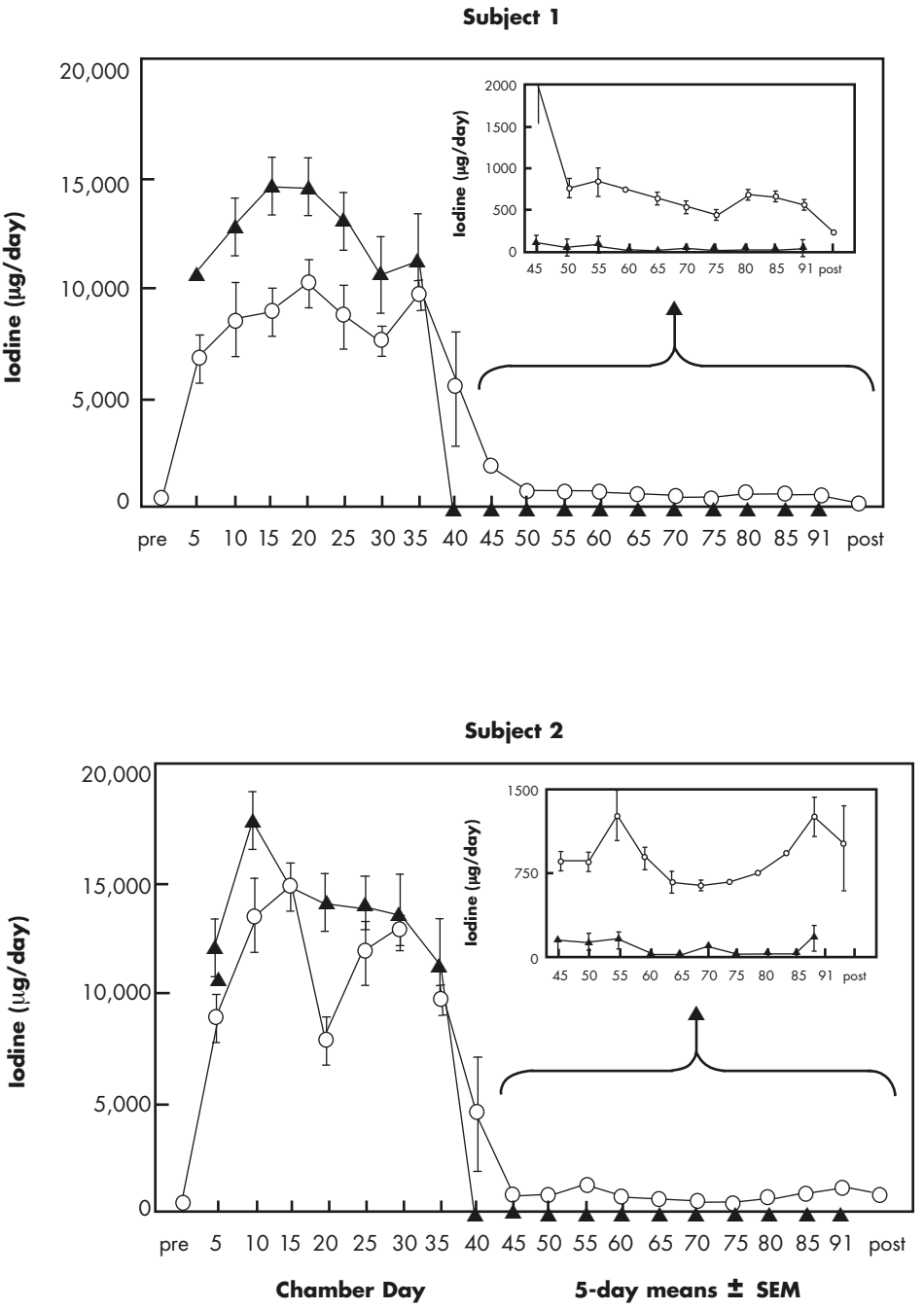

Figure 5.5-4 *Iodine intake from water (▲) and urinary iodine excretion (○) of crewmembers during Phase III*

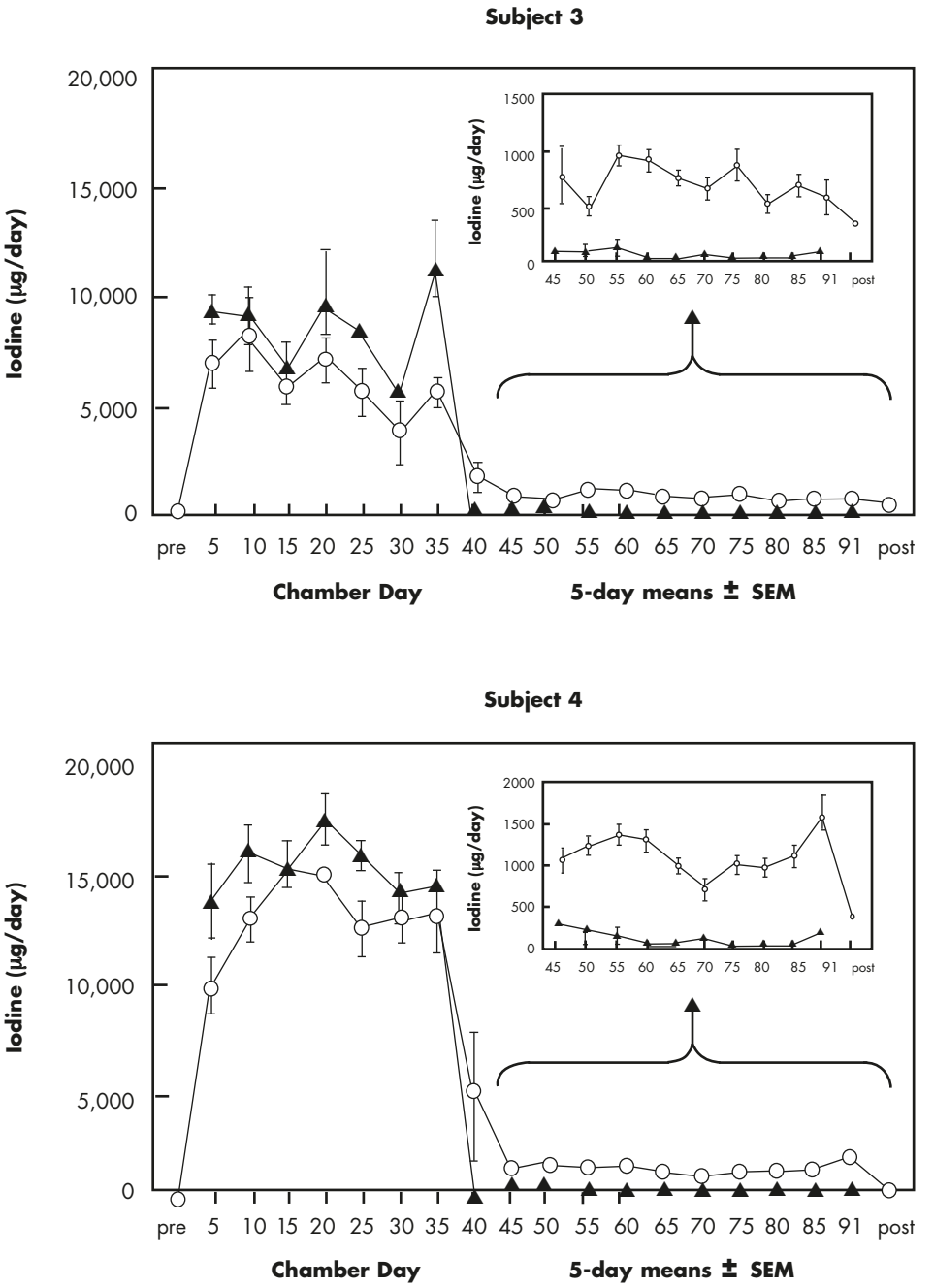

Figure 5.5-4 continued *Iodine intake from water (▲) and urinary iodine excretion (○) of crewmembers during Phase III*

Thyroid Function Assessment

Although mean TSH levels remained within normal range throughout the studies, there was a statistically significant increase in TSH levels in the Phase II and III studies (Tables 5.5-6 and 5.5-7). For the Phase II study, the values returned to baseline levels in all subjects within two weeks after the subjects exited the chamber. In the 60-day Phase IIa study, although not a statistically significant change, serum TSH in three of the four subjects had increased by the end of the study (Table 5.5-5). Subject 4, who had a baseline TSH value close to the upper limit, had a decreased TSH value below the baseline value at the end of the chamber study (Table 5.5-5). This subject had the highest iodine consumption and urinary levels (Figure 5.5-2) of the four subjects in the Phase IIa test. At day 62 postchamber, this subject had a very high TSH level and was referred for medical evaluation by an endocrinologist. There were no other biochemical or clinical signs of thyroid disease, and the TSH returned to near baseline value several months later (Table 5.5-5).

In the 91-day study, the mean serum TSH level in the four test subjects increased significantly above baseline values 30 days after entering the chamber (Table 5.5-6). After the iodine was removed from the drinking water on day 35 (concentration < 0.05 mg/L), the TSH values gradually decreased but did not completely return to baseline during the subsequent 56 days in the chamber (Table 5.5-7).

For Subject 4 in the Phase III study, the TSH remained higher than the baseline value but within the normal reference range (Table 5.5-6) throughout the chamber study period with no decrease in the level after removal of iodine from the drinking water. Figure 5.5-4 shows that the iodine consumption of this individual crewmember was highest of any of the Phase III crewmembers, between 15 and 23 mg/day throughout the 35 days. Elevated urinary iodine levels reflected this high consumption level. This crewmember had no detectable levels of TSH at 7 and 8 months after cessation of iodine consumption. The TSH levels remained low for a year after completion of the chamber study. After one year the TSH levels returned to prechamber baseline levels. All other measures of thyroid function remained within normal ranges. The consulting endocrinologist found no other biochemical changes or clinical signs indicative of thyroid disease and diagnosed the crewmember with iodine-induced subclinical hyperthyroidism.

Table 5.5-7 *Thyroid-stimulating hormone (TSH) levels for the Phases II, IIa, and III tests as mean ± standard deviation*[a]

Test Duration (days)	Phase	Iodine Exposure (days)	Prechamber	Postchamber[b]
			TSH[c] (μIU/L)	TSH[c] μIU/L)
30	II	30	1.4 ± 0.4	2.0[d] ± 0.6
60	IIa	60	2.6 ± 1.7	2.3 ± 1.2
91	III	30	1.3 ± 0.5	3.2[d] ± 0.7

[a]Each phase had four subjects

[b]Phases II and IIa reflect values from last day of the chamber test, but Phase III reflects values obtained on day 30 of the 91-day chamber study. Phase III drinking water contained iodine until day 35

[c]Normal ranges for TSH were 0.47-5.01 μIU/L

[d]After 30 days of iodine exposure there was a significant increase in TSH. Student's paired t-test, $p < 0.05$

Urinary Iodine Contamination Study

For the Phase III study, urinary iodine levels remained at approximately 1 mg/day after iodine removal from drinking water at day 35 (Figure 5.5-4), but returned to baseline levels within three days of exiting the chamber. One potential source of contamination involved the methods for collection, volume measurement and aliquoting procedures for the urine voids, and void volume determinations. A study (for details see Appendix) was completed to determine if this was the cause of the persistence of urinary iodine levels above baseline. The data demonstrated that contamination during urine collection and processing was not the source of the continued elevated urine iodine levels.

Other potential sources of iodine contamination were discussed and considered, however, no plausible explanation was identified. A few of the possibilities included release of iodine into the atmosphere from the clothes dryer (which vented into the chamber), ingestion of water from brushing teeth, showering, or residual iodine from washing of dishes (glasses, pots, pans, etc.) with iodinated water. There is a small potential for increased content of iodine in the crops grown in situ. While none of these seem to have major implications in iodine contamination, it is possible that there were multiple sources, and that small contributions from each contributed to the elevated level of excretion.

Discussion

The results from the three chamber tests demonstrated that the levels of iodine in the potable water system proposed for the ISS were too high. Since these studies were concluded, the Food and Nutrition Board (10) has established an upper limit for iodine intakes from all sources as 1.1 mg/day. The subjects in the chamber studies exceeded this level and consequently, for two subjects, TSH levels were significantly changed by the end of the chamber test. Chronic daily intake at the initially proposed levels of iodine to be provided by the U.S. ISS water system was determined to exceed these guidelines (7, 10, 17). Nutritional recommendations for the astronauts and the chamber test subjects are a minimum water intake of 2 L/day from food and fluids. Approximately 50 to 80% of that water is provided by the spacecraft water with the remainder from food sources. Thus, 1 to 2 L of iodinated water would be consumed and this would exceed the Food and Nutrition Board recommendations for daily iodine intake (10). Like the subjects in these chamber studies, astronauts will be required to participate in an intensive exercise program requiring water consumption for hydration. Thus, total iodine must be well within the 1.0 mg/day for 2 to 4 L of water consumed per day. Since food consumption provides about 0.25 mg/day, the requirement was set at a maximum of 0.25 mg of iodine/L in U.S.-supplied ISS water. This would limit water consumption to a maximum of 3 L/day to maintain daily intake levels from all sources at less than the limit established by NASA of less than 1.0 mg/day of iodine. Consequently, there remains concern that the maximum level of 0.25 mg/L of iodine in the spacecraft water will not provide sufficient microbial control thus increasing the risk to ISS crewmembers.

Thyroid dysfunction is more likely to appear with prolonged consumption of pharmacological doses of iodine, as evidenced by the transient subclinical hypothyroidism and subclinical hyperthyroidism states exhibited in some subjects and by the fluctuation of TSH levels (first high and then low) in the 60- and 91-day studies. TSH levels follow circadian rhythms that must be addressed in these types of evaluations. For the chamber studies, blood samples were collected in the morning to reduce the circadian effects as the crew was on a normal schedule. However, similar to the findings by Allan and Czeisler (1), these chamber subjects had periods of sleep deprivation and reported significant reduction of sleep time during their chamber stay. Changes in circadian patterns occur with sleep deprivation, and TSH peak levels and nadirs may occur at different times during such periods. Such changes can complicate the interpretation of TSH levels during iodine exposure.

Another concern was the persistently elevated urinary iodine in all crewmembers after the removal of the iodine from the drinking water. Because iodine excretion levels returned promptly to the normal range after leaving the chamber, it appears that the iodine within the chamber may have served as a source of contamination that maintained urinary iodine above baseline levels. It is highly improbable that the

source of urinary iodine was from the thyroid gland or other storage depots because thyroid iodine turnover is slow and would not decrease abruptly with exit from the chamber. Since the source of the contamination remains unknown, future chamber studies need to carefully review procedures and monitor crew iodine levels.

COMMENTARY

Upon recognition that the initially proposed water iodine levels for the ISS were excessive and because of the subsequent Food and Nutrition Board recommendation of the upper limit of 1.1 mg iodine/day, NASA established a limit for drinking water iodine levels with a requirement for concurrent maintenance of the microbiological standards. To achieve these requirements, NASA reduced the maximum concentration of water iodine significantly by the removal of iodine at the water port to the galley (point of use). These changes led to modification of the spacecraft water system. An iodine removal cartridge containing an anion-exchange resin was installed to remove the iodine from the drinking water prior to consumption. To obtain the levels for a maximum consumption of 3 L of water/day, and assuming the food iodine at 0.25 mg/day, the total water iodine concentration must be below 0.25 mg/L of water. Iodine containing supplements are not allowed for flight crewmembers.

Although there has been no epidemiological association between space crews' consumption of iodine in spacecraft drinking water and thyroid disease, NASA has instituted a surveillance program for thyroid health including periodic monitoring for thyroid autoantibodies and other measures of ensuring thyroid health.

Ongoing research continues in an effort to determine the most effective and safe means of disinfecting the potable water. Solutions to disinfecting the potable water in spacecraft and closed chambers may also lead to development of more effective community water systems in developing countries, military field deployment use, and wilderness and expedition water treatment systems and facilities.

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APPENDIX

Iodine Analysis

Urinary iodine determinations were conducted using an Elan 6000 Inductively Coupled Plasma Mass Spectrometer (ICP-MS; Perkin-Elmer, Inc., Norwalk, CT) equipped with the Perkin-Elmer AS90 autosampler. Prior to each day of analysis, the ICP-MS was adjusted to achieve optimal operating conditions.

All solutions were prepared with redistilled nitric acid and with reagent-grade deionized water. Single element calibrators of iodide and indium, at concentrations of 1000 mg/L each, were obtained from High Purity Standards, Inc. (Charleston, SC). The iodine calibration standards were prepared in 0.1% HNO_3 with concentrations of 0.1, 1.0, 2.5, 5.0, and 10 μg/dL. Urine samples were diluted in 0.1% HNO_3 at various dilution factors (range 1:20 to 1:200) in order to read within the calibration curve. An internal standard (indium) was used to correct for nonspectral interferences and for signal shifts. Indium was chosen because it is close to the mass of iodine, it is not present in significant amounts in urine, and it is free from spectral interference. A 100 μg/dL stock solution of indium was prepared in 0.1% HNO_3 and added to the blank, calibration standards, and urine sample dilutions for a final concentration of 5 μg/dL.

A comparative study was conducted by preparing three aliquots of 16 samples with iodine concentrations to cover the range of the standard curve (specifically, ~20-900 μg/dL). One set of the 16 samples was sent to a commercial reference laboratory, another set was sent to a research laboratory, and a third set was analyzed by the Nutritional Biochemistry Laboratory at NASA Johnson Space Center. Results demonstrated excellent correlation (NASA vs. Research Lab, $R^2 = 0.98$; NASA vs. reference laboratory, $R^2 = 0.97$), indicating acceptable agreement between methods.

Reproducibility was assessed by using three urine pools with concentrations covering the range of the standard curve (iodine concentrations = 0.60, 4.76, and 9.04 μg/dL). The within-assay precision was assessed by analyzing five replicates of the controls in a single assay, repeated for five consecutive assays. For the three control pools, the within-assay CVs were 1.4%, 1.0%, and 0.7%, respectively. The between-assay CVs, from separate assays (n = 5), were 3.6%, 3.7%, and 3.4%, respectively.

Contamination Study

For the Phase III study, urine was collected in graduated cylinders, an aliquot was removed, and the samples were stored frozen until analysis. After each collection the cylinders were rinsed with 225 ml iodinated water (approximately 3.5 or 5.2 mg iodine/L in the 60-day and 91-day studies, respectively). Cylinders were placed upright until the next collection. Estimates of micturition rate, void volume, and iodine content indicated that it would take approximately 25 ml of this water to raise the urinary iodine content to the level seen in the urine of subjects drinking iodinated water. Nonetheless, a contamination study was designed to determine if washing the collection cylinder with water containing iodine might cause iodine contamination of the next collected urine sample.

Two urine pools were prepared, along with an iodinated rinse water. Aliquots were removed from both urine pools and the iodinated rinse water at the start of the study for later analysis. Aliquots of rinse water were collected each time it was used. Every hour for eight hours, 350 ml of urine was poured into a graduated cylinder (one for each pool), and an aliquot was removed. The cylinders were rinsed with 225 ml of iodinated water, placed upright, and allowed to stand until the next collection. To test different collection techniques, collections 1 through 4 included the residual rinse water which had pooled in the bottom of the cylinder while remaining upright. Collections 5 through 8 had the excess rinse water poured out of the cylinder before addition of the urine. Results (Figure 5.5-5) indicate that any iodine contamination from rinsing the cylinder had little effect on the urinary iodine concentration.

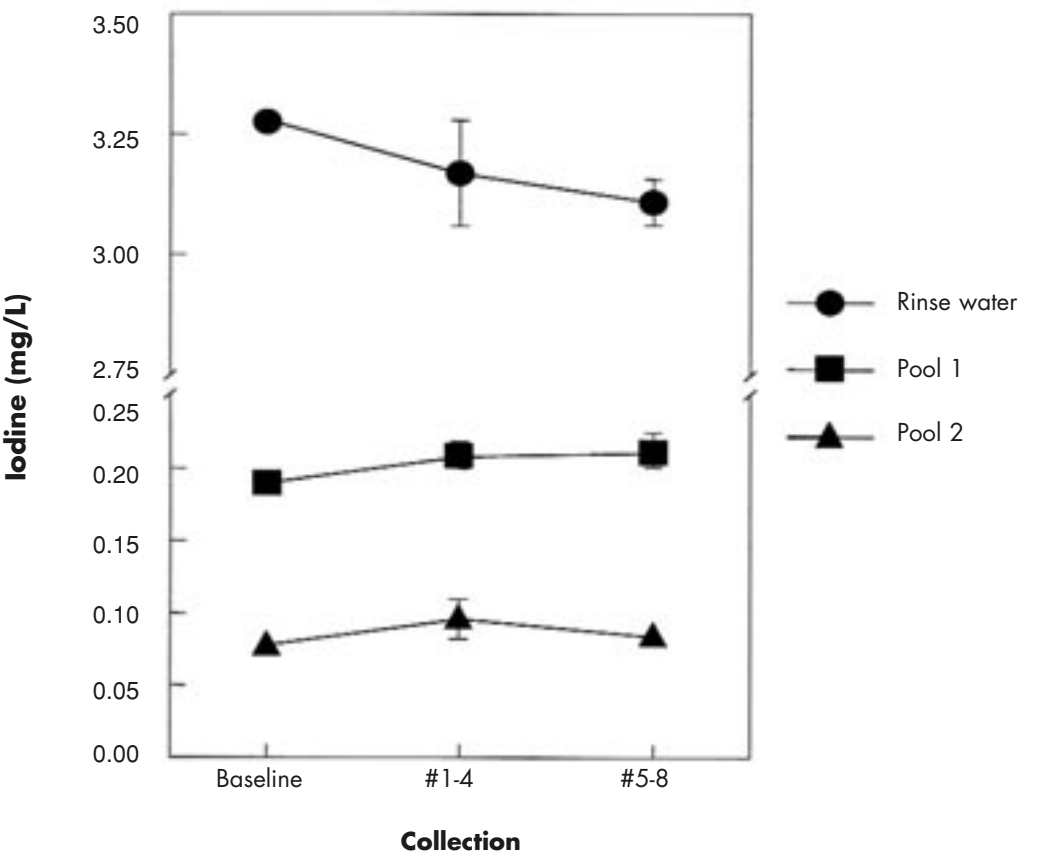

Figure 5.5-5 *Levels of urine contamination with different cylinder washings*