Comparison of the Effects of Iodine and Iodide on Thyroid Function in Humans

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INTRODUCTION

Iodine has been used successfully in the final disinfection of drinking water in the Space Shuttle Program. Since these flights are of relatively short duration and iodine has been widely accepted as a disinfectant that can be used in emergency situations, there has been little concern over health effects from this practice. As Space Station missions are extended in time, 90-180 days of exposure to iodine introduced in drinking water is envisioned. If the manned space program is to continue to Mars and beyond, even longer missions might be anticipated. To avoid the potentially disastrous results of outbreaks of infectious disease in the confined space available in either the Space Station or other spacecraft, it would be generally beneficial to maintain some minimal residual of iodine in the finished water as it is consumed. This would prevent outgrowth of organisms in the storage and dispensing units on Space Station. However, iodine has not been frequently employed in domestic water supplies because of fears of inducing some longer term health hazards that are associated with elevated intakes of iodine, most specifically congenital goiter (Wolff, 1969; Carswell, et al. 1970). These hazards remain rather speculative, and the question remains as to how much iodine can remain in the water that is consumed without resulting in a health hazard to the humans consuming the water.

Experiments conducted in rats found that administration of iodine as I^- vs. I_2 had opposite effects on plasma thyroid hormone levels (Sherer, et al., 1991). I_2 treated animals displayed elevated thyroxine (T_4) and thyroxine/triiodothyronine (T_4/T_3) ratios, whereas those treated with I^- displayed no change or reduced plasma concentrations of T_4 at concentrations in drinking water of 30 or 100 mg/L. Substantial differences were also observed in the uptake and distribution of

radiodine in the body depending upon whether it was administered as I^- or I_2 (Thrall and Bull, 1990; Thrall et al., 1992a). Further study revealed that this effect was attributable in large part to the reaction of I_2 with metabolites of T_4 in the gut of the rat to resynthesize T_4 (Thrall et al., 1992b). These data were in sharp contrast to the view that I_2 and I^- are essentially equivalent in their effects on thyroid function (Gilman, et al., 1990). These data also suggest that it may not be as necessary to control I_2 concentrations in iodine disinfected drinking water to the same levels as might be necessary to protect against the hypothyroid effects that arise from consuming excessive I^-.

The relative rate of thyroid hormone metabolism in humans and rats is known to be significantly different, primarily because of a greater degree of binding of the hormone to plasma proteins in humans. The turnover time of T_4 in humans varies between 5 and 9 days, whereas it is 12-24 hours in rats (Hayes, et al., 1989). This would mean that the concentrations of metabolites of thyroid hormones in the gut and available for reaction with I_2 should be significantly lower in humans than in rats.

Two experiments were designed to assess the hypothesis that similar effects would be seen in humans as were observed in rats. The first of these was a *rising dose tolerance study*, examining the thyroid status of male volunteers exposed to single doses of water containing I^- or I_2, up to a total dose of 1 mg/kg body weight. This was followed by a 14 day *repeated dose study* utilizing total doses of iodine in the two forms at either 0.3 or 1.0 mg/kg body weight.

To adequately protect astronauts from the effects of iodine, it is essential to establish a no-effect level for the residual forms of iodine left in the water as it is drunk. Therefore, these

observations must be extended to lower doses. Traditionally, a safety factor of 3 to 10 would be applied to a no-effect level to establish levels that would be safe. The possibility is still anticipated that the effects of I_2 and I^- might be different at lower doses (i.e., the resynthesis of thyroid hormone metabolites at low doses of I_2 in humans would be limited by the amount of metabolite present in the gastrointestinal tract, and could overcome the hypothyroid effects of somewhat smaller doses of total iodine). An ability to maintain a higher residual of I_2 in the Space Station drinking water would provide an additional level of protection against waterborne infectious disease in space.

METHODS AND MATERIALS

Study Population: Male students attending Washington State University (WSU), and qualifying for health care services at the WSU Student Health Center, were eligible for inclusion in the studies. Potential subjects were recruited through newspaper announcements and within selected classes. Each individual was required to complete a brief medical history using a standardized checklist. Any person reporting current, or a history of, any of the following conditions was excluded from further consideration as a study subject: thyroid disease/dysfunction; kidney problems/failure; heart disease/problems; malabsorption problems; porphyria; liver disease; anorexia; surgery within the prior six months; gallbladder tests within the prior two months; corticosteroid use within the prior two months; allergic reaction to iodine or shell fish.

Physical examinations were completed on the remaining potential subjects. The study physician carefully looked for any indication of thyroid dysfunction (i.e., nodules, goiters) and cardiovascular problems. Standard chemistry panels for blood (glucose, BUN, creatinine, uric acids, calcium, phosphorus, cholesterol, triglycerides, total protein, albumin, globulin, A/G ratio, total bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT, GGT/GGTP, LDH, sodium, potassium, and chloride) and urine were completed, as well as serum triiodothyronine (T_3), T_4, and thyroid stimulating hormone (TSH) levels to verify normal thyroid function. As an additional precaution, potential subjects were given a thyroid autoantibody titre test as a screening check for asymptomatic thyroid conditions/risks. After reviewing the screening and test results, if the study physician found no reason to suspect the individual would respond adversely to the iodine or iodide treatments proposed, he was admitted to the study.

Subject Requirements: Subjects were required to sign an informed consent form which detailed the procedures and restrictions for the study. To minimize potential confounding of study results, all subjects were required to eliminate alcohol, drugs (prescription, over-the-counter, and illegal drugs), and goitrogen vegetables (turnips, rutabagas, cabbage, cauliflower, brussels sprouts and broccoli) from their diet for two days prior to dosing, and throughout the experiment.

Sample Size and Group Assignment: Subjects, the study physician, and laboratory staff were blinded to treatment group status of each individual. In the *rising dose tolerance study*, 32 subjects were randomly assigned to one of three treatment groups: I_2 treatment, I^- treatment, or a control group. In the *repeated dose study*, 34 subjects were randomly assigned to one of five

treatment groups: a high or low dose I_2 treatment, a high or low dose I^- treatment, or a control group (dose amounts described below).

Procedures

Subject Dosing Amounts and Procedures:

Experiment 1, Rising dose tolerance study: All procedures were performed at the WSU Student Health Center under the supervision of the study physician and study coordinator. Subjects assigned to the I_2 treatment group received five rising doses of total iodine in phosphate buffer over a 15 day period on consecutive Mondays and Thursdays as follows: Dose 1, 0.01 mg/kg body weight; dose 2, 0.03 mg/kg; dose 3, 0.10 mg/kg; dose 4, 0.30 mg/kg; dose 5, 1.0 mg/kg. Matched dose amounts of I^- in phosphate buffer were administered to the I^- treatment group. The control group received distilled water with concentrations of NaCl matched to NaI and phosphate buffer concentrations as noted below. Each of the doses were made up using double-distilled/deionized water. To maintain a stable pH, doses for all treatment groups were prepared with the following amounts of phosphate buffer (pH=6.95): Dose 1, 0.00 mM phosphate buffer; dose 2, 0.10 mM phosphate buffer; dose 3, 0.33 mM phosphate buffer; dose 4, 1.00 mM phosphate buffer; dose 5, 3.33 mM phosphate buffer. Each dose was mixed 24 hours prior to dosing. To help ensure subjects were blinded to their treatment group status, all treatments were placed in brown pharmacy bottles, and treatments for the I^- and control groups were tinted with yellow food coloring to approximate the color of the I_2 treatments. Subjects were required to fast from 9:00 p.m. the night prior to each dose until the two hour blood draw following each dose. Fasting was not required prior to the 24 hour blood draws.

Experiment 2, repeated dose study: Dose types and amounts include:

Treatment Groups	Total Iodine Dose	Phosphate Buffer (pH=6.95)
Iodine (I_2) Low Dose	0.3 mg I_2/kg body weight	1.00 mM
Iodine (I_2) High Dose	1.0 mg I_2/kg body weight	3.33 mM
Iodide (I^-) Low Dose	0.3 mg I^-/kg body weight	1.00 mM
Iodide (I^-) High Dose	1.0 mg I^-/kg body weight	3.33 mM
Control	1.0 mg NaCl/kg body weight	3.33 mM

Subjects assigned to the I_2 treatment groups received 14 consecutive doses of I_2 in phosphate buffer over a 14 day period. Matched doses of I^- in phosphate buffer were administered to the I^- treatment groups. To help ensure subjects were blinded to their treatment group status, the control group received distilled water with concentrations of NaCl matched to the osmolar concentrations of NaI in the high dose group. Control and NaI solutions were tinted with yellow food coloring and put in brown pharmacy bottles so that all treatment group doses were approximately the same color.

A significant, but consistent amount (25%) of I_2 was converted to I^- in the preparation of the stock solutions. On each of the first two days of the study, subjects in the high dose I_2 group received I_2 doses equal to 1 mg/kg body weight (i.e., 1.3 mg total iodine/kg). Subsequently, the dose of I_2 administered on days 3 through 14 was adjusted to 0.75 mg/kg per day (i.e., dose of 1 mg total iodine/kg per day). The elevated dose in the first two days led to a slightly larger time weighted average dose in the high I_2 group (1.05 mg/kg per day) than in the high dose I^- group. The time weighted average for total iodine for the low dose I_2 group, however, was consistently greater (0.375 mg/kg/day) than in the iodide group (0.3 mg/kg/day). The data are provided as

total iodine doses in tables and graphs. Iodine concentrations were determined using the Leuco Crystal Violet method (Franson, 1985), and iodide was measured utilizing an iodide specific electrode. The dose was adjusted to the body weight of each individual by appropriate changes in the volume of the stock solutions (approximately 200 mg I_2/L for the high dose group, and 70 mg I_2/L for the low dose group.

Blood Collection: Student Health Services staff nurses and phlebotomists were responsible for all blood draws. Ten ml of blood was drawn from each subject 11 times in the *rising dose tolerance study*, and four times in the *repeated dose study*. Blood drawn immediately prior to dose one served as the baseline measure. The remaining draws in the *rising dose tolerance study* were taken at two hours and 24 hours following each of the five doses (day 0, 0.083, 1, 3,083, 4, 7.083, 8, 10.083, 11, 14.083, 15); the *repeated dose study* required two-hour post-dose draws on days 7 and 14, and the last draw was taken 24 hours following the final dose (day 0, 7.083, 14.083, 15.0).

Urine Collection: Urine specimens were collected at the initial screening physical examination and the exit physical exam to assess iodide excretion levels in the *rising dose tolerance study*. In the *repeated dose study*, urine samples were collected at baseline, and at 2 hours, 24 hours, 48 hours, and 72 hours following the final dose (dose 14) to assess the excretion rate of iodide in the urine. Dietary salt intake was not restricted because the doses of iodine administered during this study rendered the amount derived from consuming iodized salt to insignificant amounts.

Physician Evaluation and Subject Follow-Up: The study physician and/or nursing staff examined all subjects two hours following each treatment dose during the *rising dose tolerance study*, and following dose 7 and dose 14 during the *repeated dose study*. Examinations included vital signs, weight, a thyroid examination, and an appraisal of general well-being. There was ongoing screening for adverse reactions and evidence of toxicity during each contact with the physician to determine if any subject should be withdrawn from the study.

A study exit physical examination was given to all subjects approximately 10 days following the final dose. This included a thyroid examination, vital signs, weight, and an overall appraisal of subject well-being. Standard chemistry panels for blood (CHEM 19 as previously described) and urine were again completed to verify that all values including T_3, T_4 and TSH approximated the values obtained during each subject's entrance physical examination.

Analyses

Iodine Stability: A stability study of each of the five dose levels of I_2 was conducted. The study involved preparing the five stock I_2 solutions in a manner identical to the procedure described above (see Subject Dosing and Amount Procedures - *rising dose tolerance study*). The I_2 content of each dose was then followed over an 18 day period using a modified Leuco Crystal Violet Method. Results of this analysis indicated the original concentrations were within 95 and 105% of the target concentrations and that the dosing solutions remained stable within $\pm$ 10% of the initial concentration during the course of both experiments.

Blood Analysis: ***Experiment 1, Repeated dose study***: Total plasma T_4 and T_3 concentrations were measured by RIA using the materials and methods provided in Amerlex kits

(Amersham Corp., Arlington Heights, IL). Percent free T_4 and free T_3 were measured by equilibrium dialysis of undiluted plasma at 37 C for 18 hr, as previously described by Young (Young, et al., 1979). The free thyroid hormone concentrations were calculated as the product of the total and percent free thyroid hormone.

Plasma TSH concentrations were measured by standard RIA double antibody procedures. Primary antibody, reference preparation and purified hormone for radiolabeling were kindly supplied by Dr. Salvatore Raiti of the NIDDK National Hormone and Pituitary Program, NIH (Bethesda, MD). The radiolabel was prepared with ^{125}I using a modified lactoperoxidase-glucose oxidase method and separated from free iodine on a Sephadex G-50 column.

Quality-control procedures were performed during every assay. Pooled plasma and a "blank" control sample were included in every assay run. A complete standard curve generated with each run of an assay was analyzed by computer utilizing log-logit data transformation methods. Intra-assay variability was calculated for the quality-control samples with every assay. In addition, inter-assay variance was analyzed by comparing quality-control samples from the present assay with those of previous assays and with the cumulative average value for that sample. Inter-assay standard deviation was calculated by an analysis of variance and was compared with the average result obtained on all previous assays. Standard curves were run in triplicate, whereas unknowns were assayed in duplicate.

Experiment 2, Repeated dose study: Total plasma T_4, T_3, TSH, and free T_4 levels were measured with chemiluminescence immunometric assay methods using the materials and methods provided in Nichols Institute Diagnostics kits (Nichols Institute Diagnostics, San Juan

Capistrano, CA 92675). This methodology greatly simplified the processing of the samples and ensured consistent results. Moreover, these are the highest quality clinically valid immunoassay tests available. These kits utilize the chemiluminescence of acridinium esters which emit light upon treatment with hydrogen peroxide and an alkaline solution. The luminometer is set up to automatically inject these solutions into the assay tubes. The oxidized acridinium ester is in an excited state. The subsequent return to ground state results in the emission of light which is quantified in two seconds, and is expressed in relative light units. These values are compared with a standard curve prepared with assay validated standard containing the particular hormone being measured. The concentration of the given hormone in the patient sample is determined directly from the standard curve (logit-log data calculations).

Quality control procedures were performed during every assay. To assure accurate and reliable results, included in each assay performed are validated controls with high, normal and low hormone levels. These immunoassay controls standards (Lyphochek) were obtained from BioRad ECS, (Anaheim CA). The values of these control standards values from each assay are then compared with expected values to ensure precision and reproducibility of the assay. Intra-assay variability was calculated for the quality control samples with every assay. In addition, inter-assay variability was analyzed by comparing quality control samples from the present assay with those of previous assays and with the cumulative average value for that sample. Inter-assay standard deviation was calculated by an analysis of variance and was compared with the average result obtained on all previous assays. Standard curves, control and unknown samples were run in duplicate.

Urinalysis: Excretion of iodide in the urine was determined indirectly by normalizing results with creatinine concentration of each subject's urine sample. Essentially this allows one to determine what fraction of the day's urinary output the subject's urine sample represented in a grab sample. Creatinine was measured using a diagnostic kit purchased from Sigma Chemical Co. (St. Louis, MO, 63178). Iodide concentration of the subject's urine sample was then determined using an I^- selective electrode in combination with a double junction reference electrode (Orion Research Co., Boston, MA 02129). Standard curves were prepared from samples contamining 0.1 to 10 μM iodide. Urine samples were diluted (usually 1:10) with double-distilled, deionized water and the signal obtained with the probe is compared to the standard curve. Combining the results of the creatinine study and I^- probe, a daily rate of I^- excretion was calculated. It was assumed from the clinical literature (Sigma Diagnostic Kit manual) that men excrete 1.95 g of creatinine over a 24 hour period.

Statistical Analysis: Statistical analyses were conducted using the Statistical Analysis Software (SAS) Package, version 6.04 (SAS Institute Inc., Cary, NC). The data were analyzed as a completely randomized design with a one-way treatment structure (treatment group) with repeated measures. Tests of least significance difference were used to test for differences among treatment group means if analysis of variance (ANOVA) P-values were ≤ 0.05. If time by group interaction was detected, group effects were analyzed at each time period. As previously described, in the *rising dose tolerance study*, repeated measures were taken over 11 time periods. Response was measured at baseline, and at two hours and 24 hours following each of the five

doses (day 0, 0.083, 1, 3.083, 4, 7.083, 8, 10.083, 11, 14.083, 15). The *repeated dose study* measured response at four points in time: baseline, two hours post-dose on day 7, two hours post-dose on day 14, and day 15 at exactly 24 hours following the final (14th) dose (day 0, 7.083, 14.083, 15.0).

RESULTS

Rising dose tolerance study: All subjects were male Caucasians, and ranged in age from 20 to 31 years old, with a mean of 22.9 years. There was no significant difference in age between the three treatment groups ($p=.79$). Thirty-one subjects completed the study yielding a 97% (31/32) completion rate. One subject was required by the study physician to drop out of the study at an early stage due to an ear infection which necessitated medication.

Figures 1a & b through 6a & b present the mean and standard error for T_4, free T_4, T_3, free T_3, TSH, and the T_4:T_3 ratio at two hours (panels A) and 24 hours (panels B) after administering each of the five doses of iodine as I_2 or I^-. Table 1 presents the ANOVA results for each thyroid hormone measured. Although time effects were observed, no time by group interaction was detected. The only overall statistically significant difference observed was the T_4:T_3 ratio. Table 2 presents the pairwise comparison for T_4:T_3 among treatment groups at each post-dose period. These differences reflect a larger ratio in the group receiving I^- relative to the controls, and to the I_2 group 24 hours after doses 1, 2, and 3 (Figure 6b). Although these differences were significant, no consistent findings were observed with increasing dose amounts. None of the values in the I_2 group were significantly different from the control group. A similar

pattern was observed for free T_4:T_3 although not statistically significant, therefore, these data have been omitted from the manuscript.

The mean excretion rates of iodide in the urine are provided in Figure 7. These data include measurements from urine collected in the pre-experiment physical examination and post-experiment physical examination for all groups. No significant differences were detected between the three groups in either the pre-experiment physical examination ($p = 0.78$) or the post-experiment physical examination ($p = 0.89$).

Repeated dose study: Thirty-three subjects completed the study yielding a 97% (33/34) completion rate. As in the *rising dose tolerance study*, the study physician ordered one subject to drop out because of an infection which required medication.

Significant effects did become apparent with repeated administration of these same doses (0.3 mg/kg, 1.0 mg/kg) for a 14 day period. Most of the effects relate to thyroid hormone status of the individuals, but there were also more non-specific effects of I_2 that became apparent in this experiment. Table 3 lists the frequency of responses to a questionnaire administered to the subjects at the conclusion of the study. Positive responses were unique to the high and low dose I_2 groups. Individuals from these groups complained of a burning sensation in the throat. This irritation was not evident on physical examination and, therefore, cannot technically be termed a chemical burn. However, it is a response over which there should be some concern. Clinical chemistries and physical examinations failed to identify any effects of either I_2 or I^- that were unrelated to thyroid function.

Figures 8a & b through 12a & b graphically depict the mean and standard error for T_4, free T_4, T_3, TSH and the T_4:T_3 ratio, respectively. Panel A of each figure compares the low and high dose I^- groups to the control group; likewise, panel B compares the I_2 groups to the control group. Table 4 presents the ANOVA results for each thyroid hormone measured. Although none of the overall group effects were statistically significant, interaction due to variation of treatment groups over time was detected within the T_3 and TSH measures necessitating univariate analysis of these two measures. A pairwise comparison for T_3 among treatment groups found no statistically significant effects at any of the individual time points. Table 5 presents the pairwise comparison for TSH among treatment groups at each post-dose period. Statistically significant increases are observed in both the high dose I_2 group and the high dose I^- group compared to the control group on day 15 (24 hours following the final dose administered on day 14). At the lower doses, neither form of iodine produced increases that were statistically significant. However, there was a consistent trend towards an increase with all doses which is difficult to ignore. As presented in Table 5, p-values consistently moved closer towards significance with each measurement: baseline, 0.58; day 7, 0.20, day 14, 0.08, day 15, 0.03. TSH levels did largely return to control levels 10 days after treatment was suspended.

Urinary excretion of iodide was utilized primarily to be certain that iodine was cleared from the system promptly after suspension of treatments. In Figure 13 it can be seen that the excretion of iodine in steady-state had approached within 70% or more of the theoretical maximum of the administered dose with all doses of iodine when examined 24 hours following the last dose of iodine. The major descrepancy in this analysis was at 2 hours after the last high

dose of iodide was administered, where the rate of urinary elimination averaged only about 1/2 that expected. However, this lower level is in large part due to a lower rate measured in one subject and there was a general trend towards a higher rate and a much tighter distribution in the 24 hour sample in this same group. Within an additional 48 hours (i.e., 72 hours after administration of iodine), the urinary excretion of iodide had essentially converged with the levels seen in control subjects. Therefore, within the limits imposed by the utilization of grab samples and correction of values to creatinine levels, rather than complete collections of urine, it was concluded that these data confirm the accuracy of the dosing schedule and demonstrate that the subjects complied with the dosing schedule.

DISCUSSION

No substantive effects were observed with either I_2 or I^- administration in the *rising dose tolerance study*. Throughout the study, the physician found no abnormalities that could be related to the treatments, and there were no significant changes in clinical chemistry measurements at exit physical examination. While the thyroid hormone levels in the blood of individuals varied significantly in time, the mean values of groups tracked well with one another and no interaction was detected. The day-to-day variation in thyroid hormone levels probably reflected small, systematic interassay variation and/or changes in environmental conditions that affected all subjects in an equivalent way. Thus, it may be concluded that single acute doses of I_2 or I^- up to 1 mg/kg of body weight have minimal effects on thyroid function in normal humans.

Both specific and non-specific effects of iodine were noted in the *repeated dose study*. I_2 produced the only non-specific effect of importance, the sensation of a "burned" throat. This effect might be expected from consumption of iodine since high concentrations are known to damage mucous membranes (Gosselin, et al., 1976). However, this effect was not reflected in clinical observations so it should not be considered a chemical burn as such. More than likely it reflects and significant degree of irritation to the mucous membranes that is more closely related to the concentrations of the solutions of iodine that were administered rather than the actual dose of iodine. High concentrations were used in this study primarily for the purpose of ensuring compliance by observing the actual consumption of the water. Nevertheless, it should be noted that 70 and 200 mg/L concentrations of iodine would never be achieved in Space Station water.

The daily administration of repeated doses of I_2 and I^- in the range of 0.3 to 1 mg total iodine/kg for a period of 14 days does induce changes in thyroid hormone status. Decreases in T_4 were observed with dose schedules with I^- and I_2, but none were statistically significant compared to each other, or compared to the control group (Figure 8a & b). TSH was significantly increased by the high dose of both I_2 and I^-, but in this case the effects of the high dose schedule of I_2 were substantively greater than that seen with I^-. It may well be that these differences do reflect some underlying differences between I_2 and I^-, but the statistical power of this experiment does not allow a clear conclusion in this area.

Depression of T_4 levels was not observed in either male or female rats with concentrations of I_2 or I^- of up to 100 mg/L for 100 days. There was, however, an increase in thyroid weights that approached statistical significance at the highest dose of I^- in male rats.

TSH was not measured in these experiments, but this latter result would be consistent with an increase in TSH levels. It was anticipated from the prior studies in rats (Sherer, et al., 1991; Thrall and Bull, 1990; Thrall, et al., 1992a & b) that there would be some divergence between the effects of iodine administered as I_2 vs I^-. It was predicted that at some low dose of iodine, administration of I_2 would preserve, or even increase the levels of circulating T_4, and increase the T_4 to T_3 ratio. There is no clear indication of such a differential effect in the present study. There may be several reasons for this divergence. First, it is quite clear that the rate of thyroid hormone turnover in humans is much less than that observed in rodents. This would result in lower concentrations of thyroid hormone metabolites that would be available in the gastrointestinal tract for reaction with administered I_2. Thus, the doses of iodine chosen may have been too high relative to the levels of available substrate. In this case, the effects of the actual doses of I_2 administered may have been simply swamped out by the overwhelming and well established effect of elevated consumption of total iodine. A second possibility is simply that there is inadequate amount of substrate available in the human gastrointestinal tract for this phenomena to have a substantive impact on thyroid hormone levels in humans.

There are trends in the data which suggest that such interaction could still play a little more important role at lower doses of I_2 and I^-. For example, the T_4 levels in I_2-treated volunteers are below that of control at the low dose when it was administered for 14 days, but they are still greater than the levels observed in I^- treated groups. However, this interpretation is considerably clouded by the fact that TSH levels were increased early and to a greater extent with I_2 than was observed with equivalent levels of I^-. Thus, the increases in T_4 levels could

result from higher TSH concentrations. Second, there is absolutely no hint of such an effect in the rising dose tolerance study. Therefore, the only conclusion that can be made from the present study is that there are insufficient T_4 precursors in the human intestine to allow for this mechanism to occur. In a formal sense, this issue can only be resolved by further investigation of the impact of chronic intake of lower levels of iodine than are employed in the present study on thyroid hormone status in humans.

The minor variations in plasma T_4 and T_3 levels observed in the present study have minimal implications for long-term adverse health effects in themselves. However, some problems might be associated with consistently elevated plasma TSH concentrations. This could have more serious long-term impacts on health that might be considered more fully in future studies. Health concerns that might arise from these effects would include goiter, and increased risk from cancer of the thyroid (Williams, et al., 1977; Hill, et al., 1989; Edmonds and Tellez, 1988), but there may also be other less well defined alterations in the function of other endocrine organs (Thomas, et al., 1987).

In addition to these traditionally recognized effects of elevated TSH, it is important to remember that nonphysiologic elevations of pituitary TSH secretion primarily results from the hypersecretion of the hypothalamic neurohormone thyrotropin-releasing-hormone (TRH) and this is associated with a number of pathological conditions in both men and women. An example of one of these conditions is hyperprolactinemia, which is characterized by numerous clinical manifestations including headaches, reproductive dysfunction, visual disorders and gynecomastia (Molitch and Reichlin, 1985).

In summary, the present experiment in humans failed to confirm the differential effect of I_2 on maintenance of serum T_4 concentrations relative to the effects of I^- that was observed in prior experiments in rats. The reaction of I_2 with metabolites of thyroid hormones in the intestine that appears responsible for this effect in rats probably also exists at some level in humans. The present results suggest that the concentrations of such metabolites in the human intestinal tract are too small to significantly affect circulating concentrations of T_4. However, based on the elevations in TSH, there should be some concern over the potential impacts of chronic consumption of iodine in drinking water.

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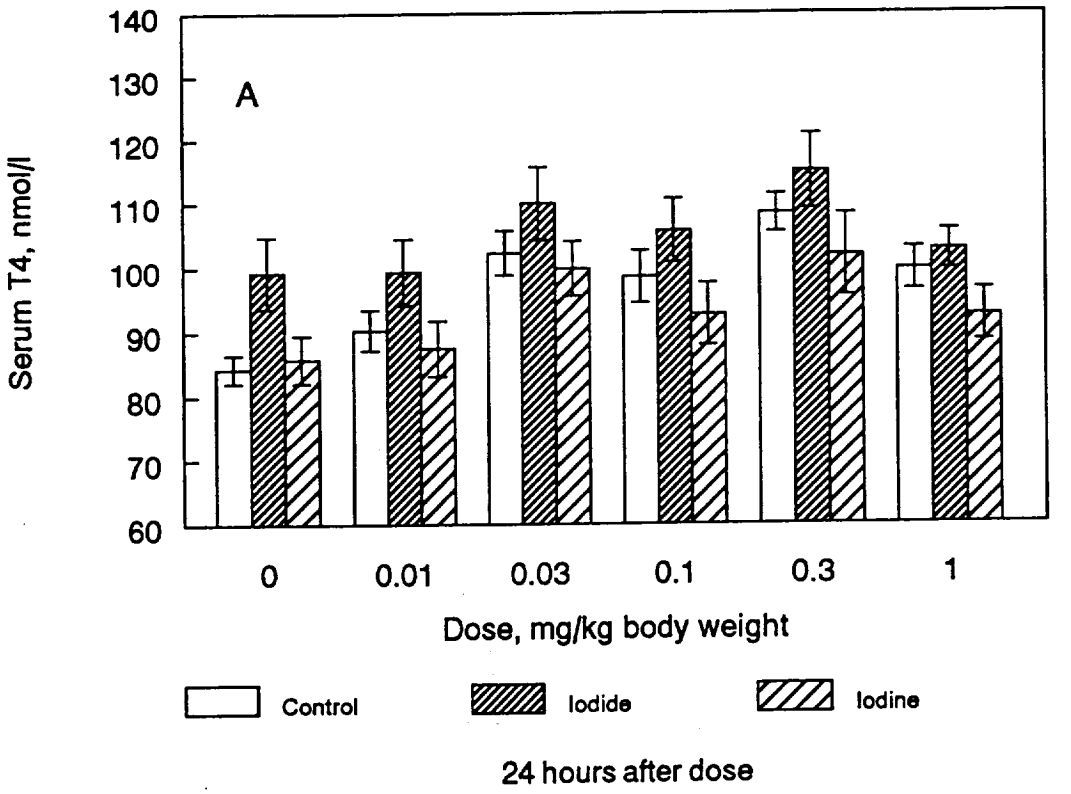
Figure 1. Effects of iodine treatments on serum T4 - 2 hours after dose



24 hours after dose

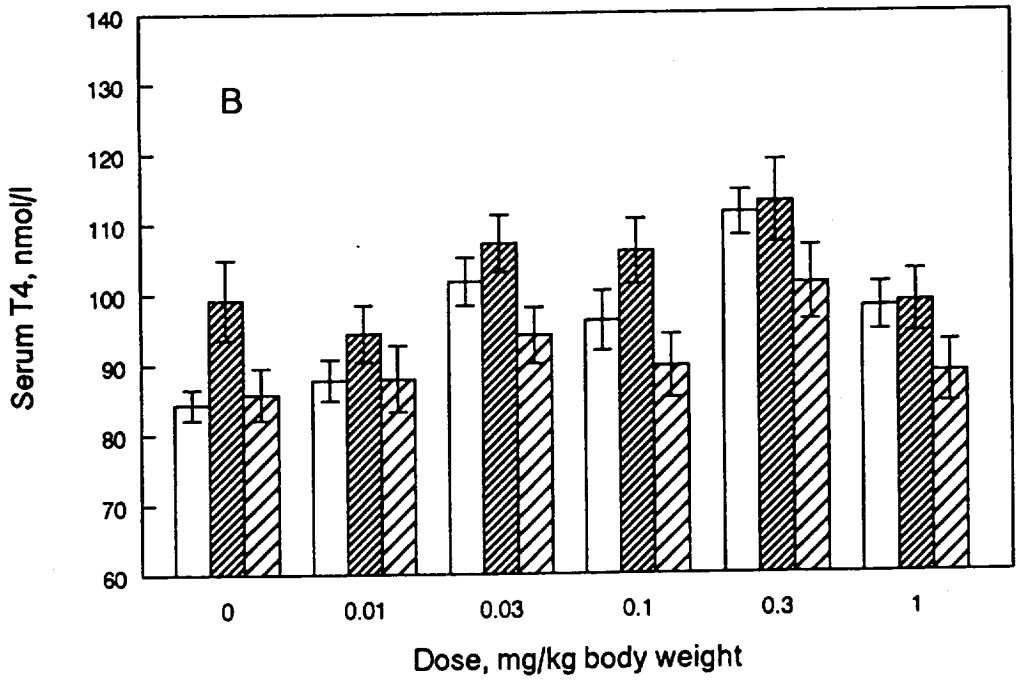
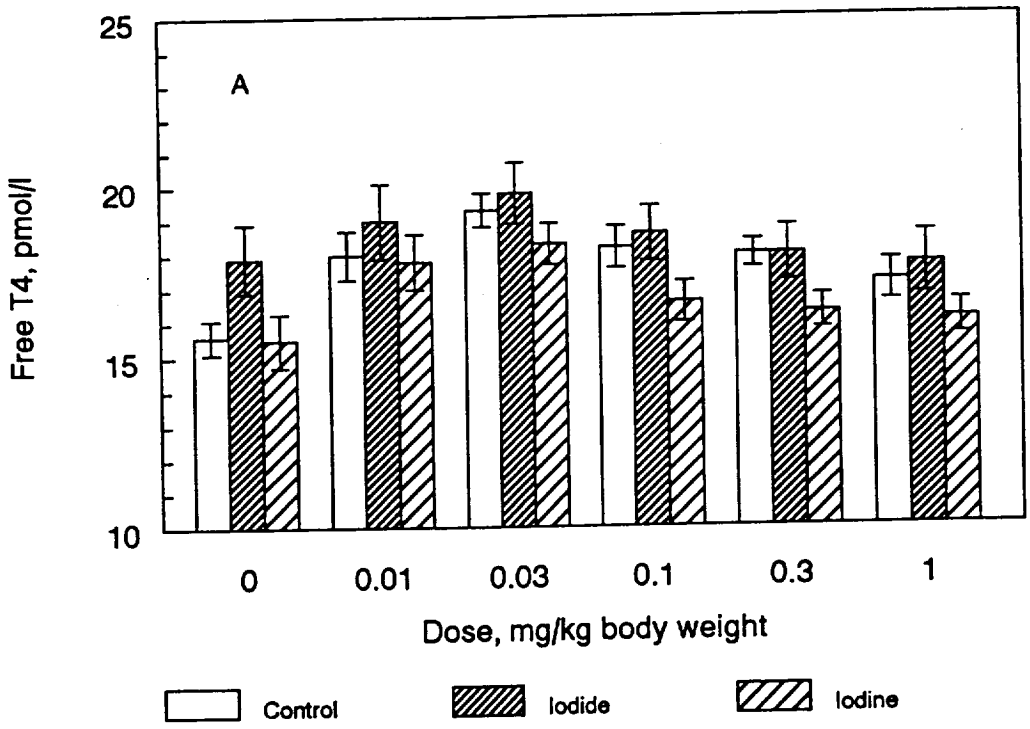


Figure 2. Effects of iodine treatments on serum free T4 - 2 hours after dose



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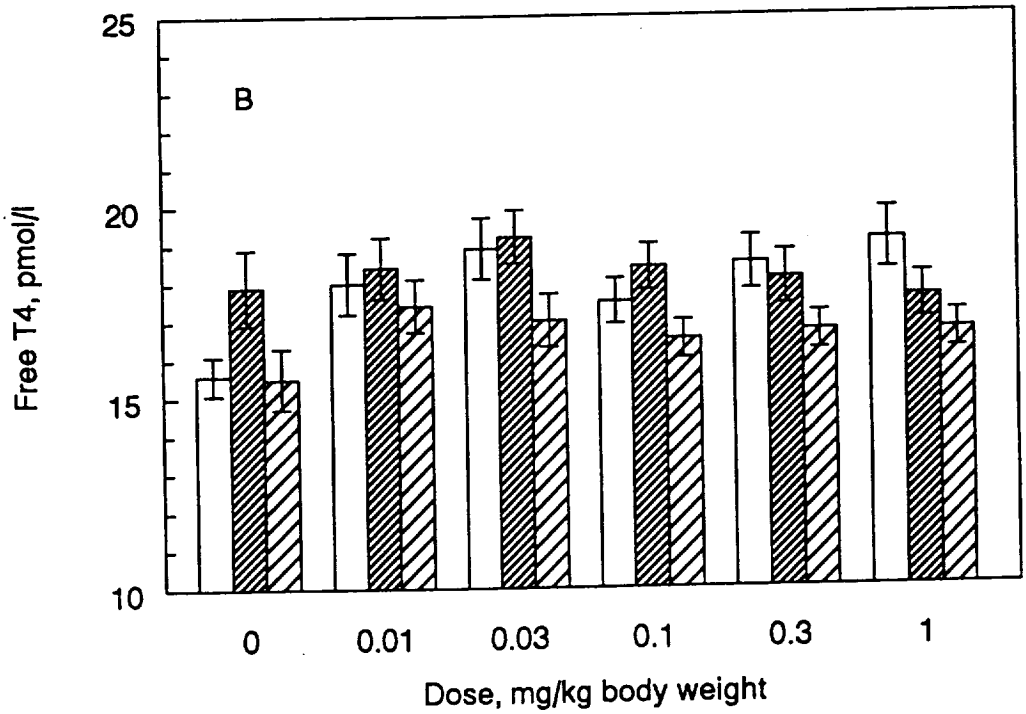
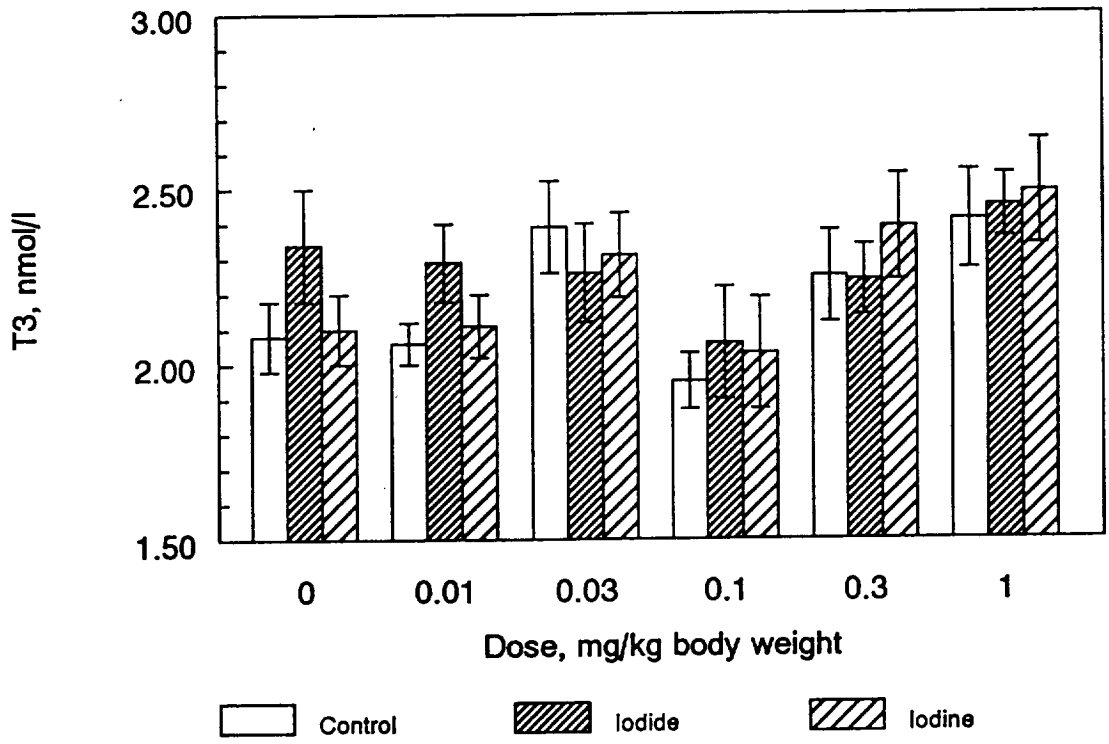


Figure 3. Effects of iodine treatments on serum T3 - 2 hours after dose



24 hours after dose

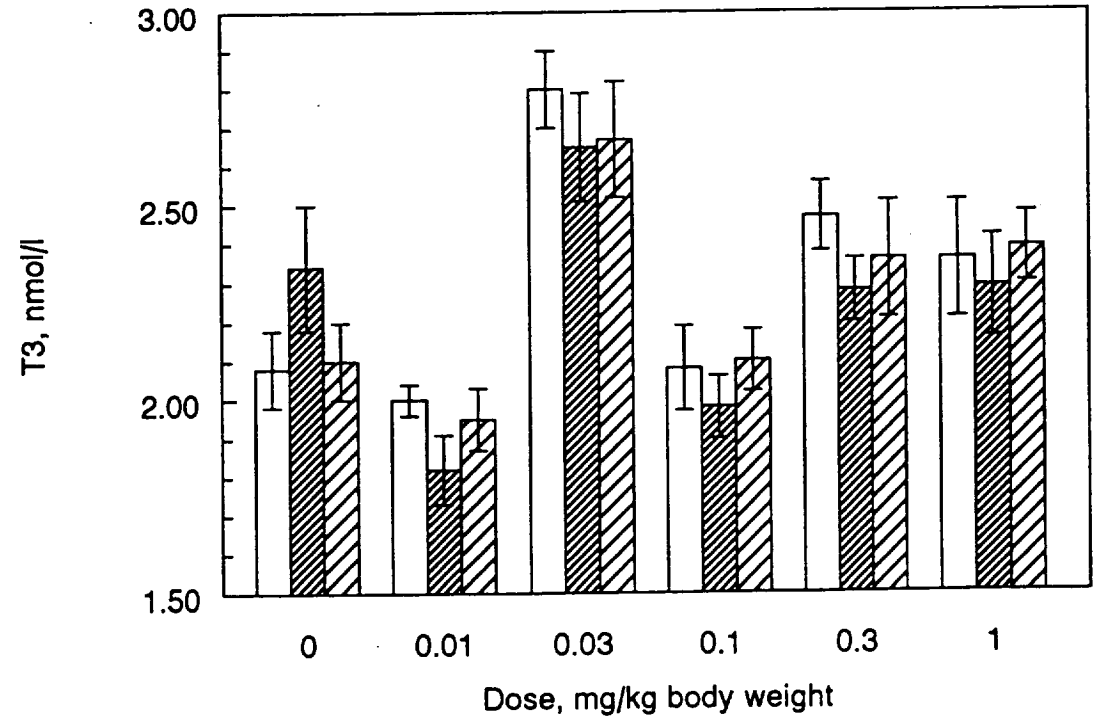
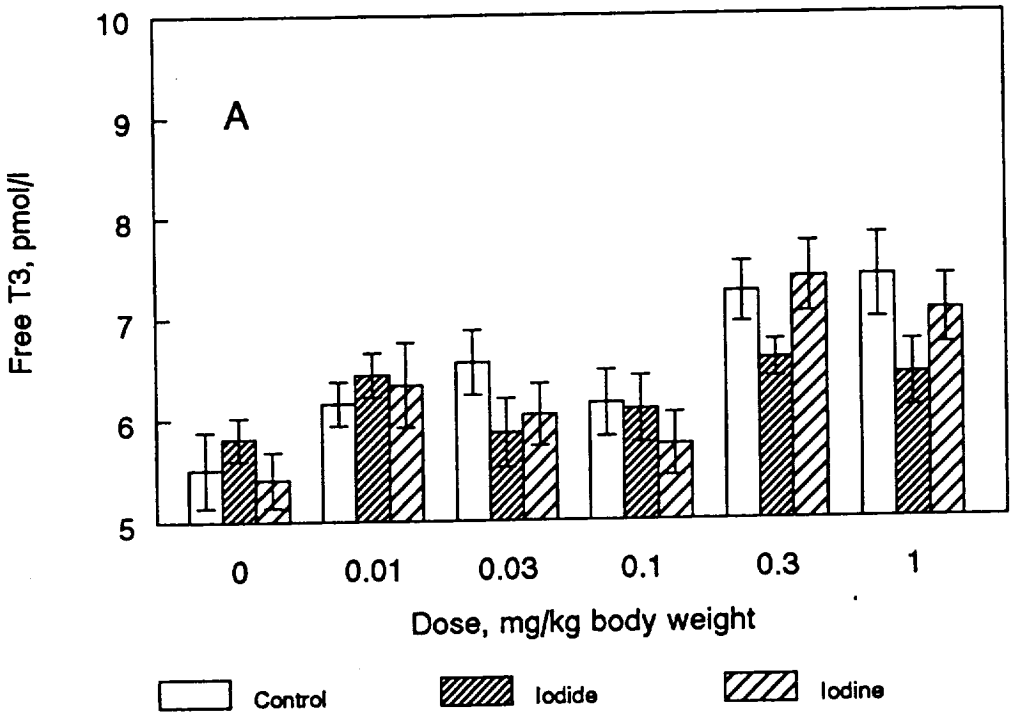


Figure 4. Effects of iodine treatments on serum free T3 - 2 hours after dose



24 hours after dose

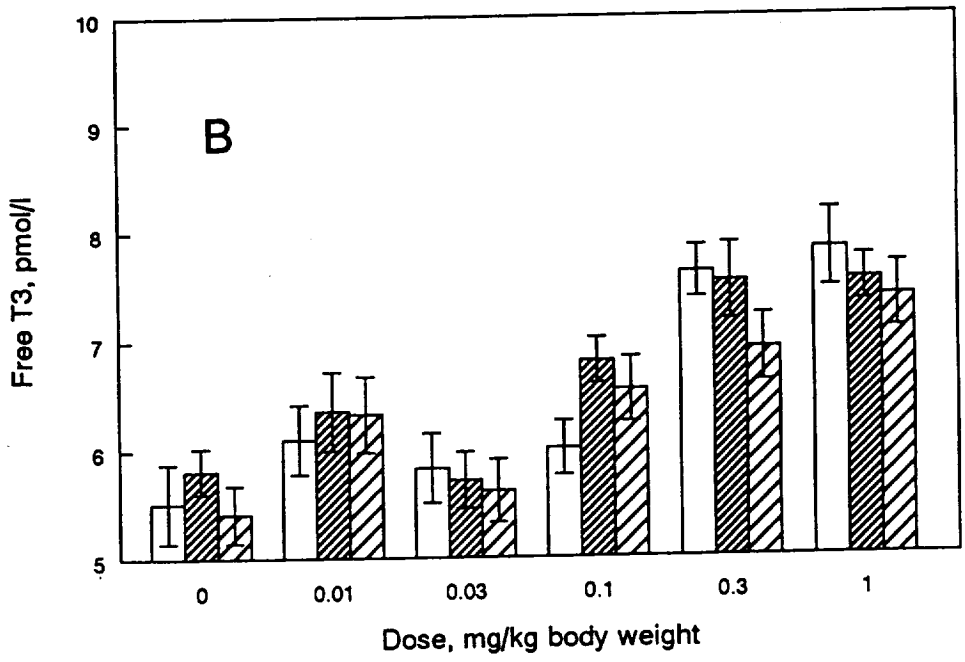
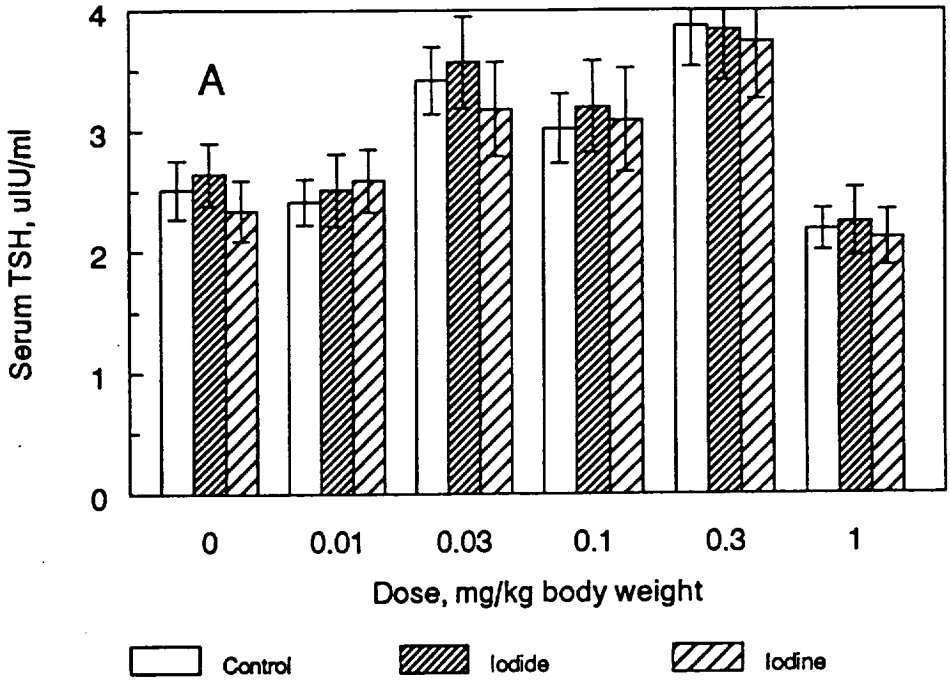


Figure 5. Effects of iodine treatments
on serum TSH - 2 hours after dose



24 hours after dose

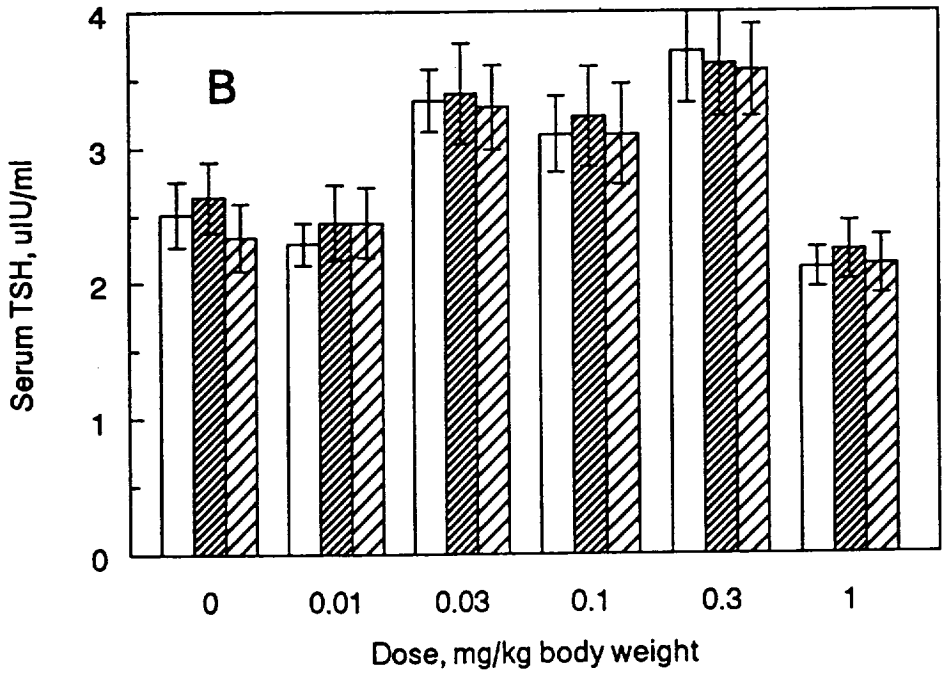
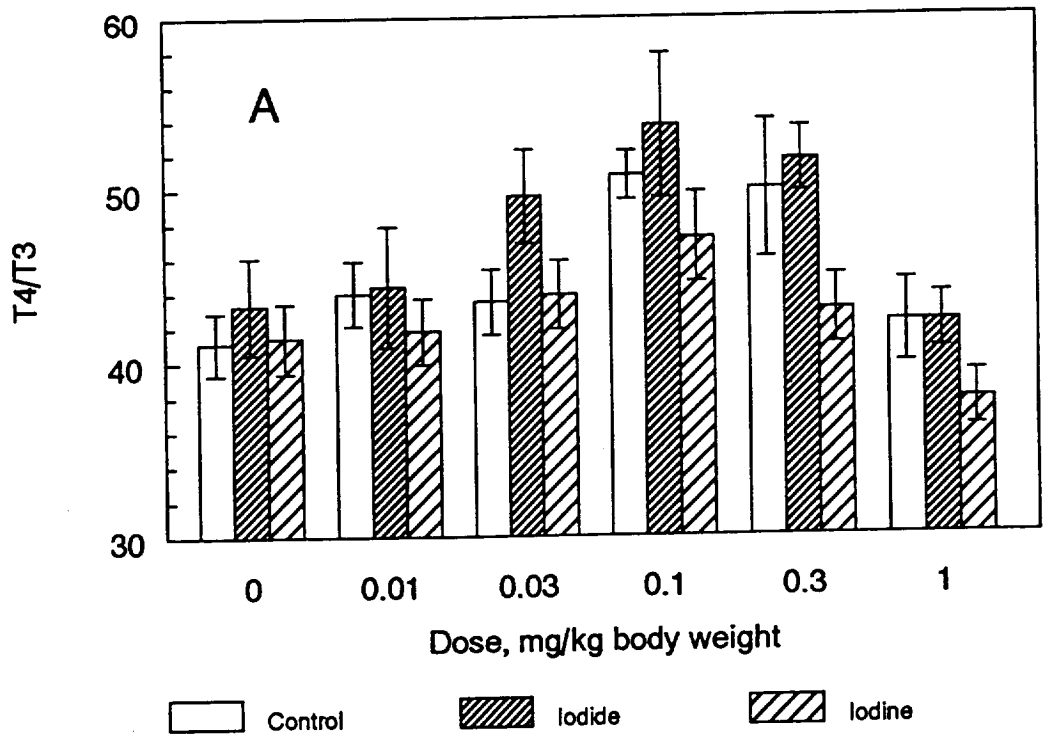


Figure 6. Effects of iodine treatments
on T4/T3 ratio - 2 hours after dose



24 hours after dose

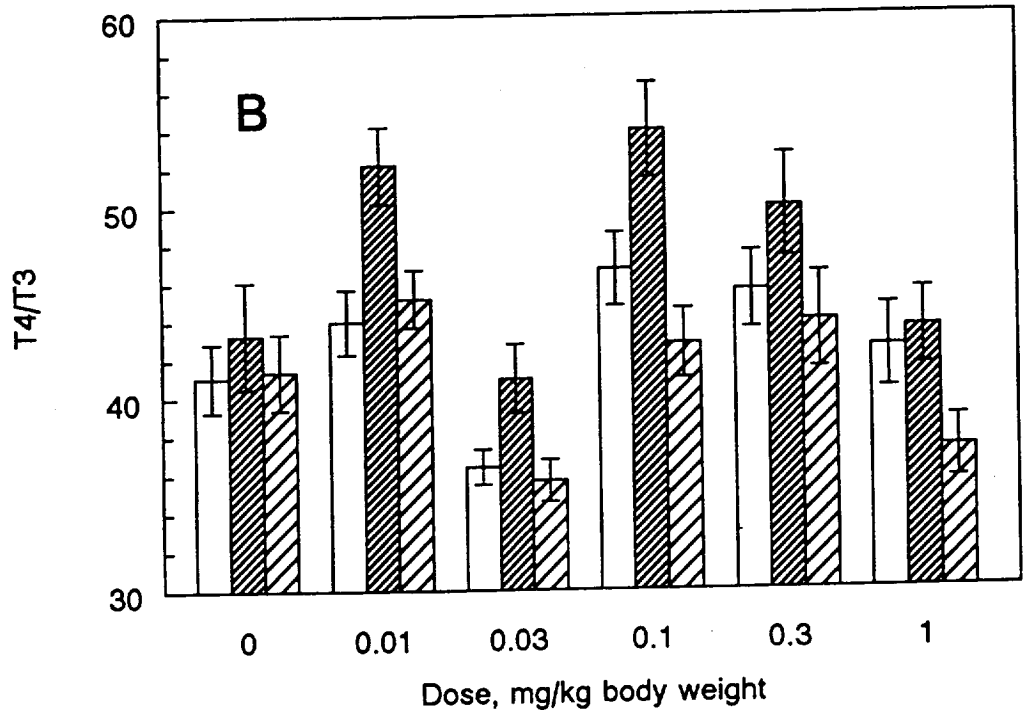


Table 1

Experiment 1, *Rising Dose Tolerance Study*
Analysis of Variance for Repeated Measures: P-Values
(n=31)

Thyroid Hormone	Time Effect	Time by Group Effect	Group Effect
T_4	0.0001	0.7142	0.1000
Free T_4	0.0001	0.0893	0.0709
T_3	0.0001	0.5729	0.9754
Free T_3	0.0001	0.1120	0.7966
TSH	0.0001	0.4610	0.9536
T_4:T_3	0.0001	0.1932	**0.0372**
Free T_4:Free T_3	0.0001	0.4655	0.2935

Table 2

Experiment 1, *Rising Dose Tolerance Study*
T_4:T_3 Univariate ANOVA with Least Significant Differences
(n=31)

T_4:T_3	P-Value	Group Differences		
		Iodine to Control	Iodide to Control	Iodine to Iodide
Baseline	0.7703	-	-	-
Dose 1, 0.01 mg/kg body wt				
2 hours post-dose	0.7251	-	-	-
24 hours post-dose	0.0054	-	+	+
Dose 2, 0.03 mg/kg body wt				
2 hours post-dose	0.1148	-	-	-
24 hours post-dose	0.0156	-	+	+
Dose 3, 0.1 mg/kg body wt				
2 hours post-dose	0.2995	-	-	-
24 hours post-dose	0.0028	-	+	+
Dose 4, 0.3 mg/kg body wt				
2 hours post-dose	0.0771	-	-	-
24 hours post-dose	0.2116	-	-	-
Dose 5, 1.0 mg/kg body wt				
2 hours post-dose	0.1537	-	-	-
24 hours post-dose	0.0598	-	-	-

Figure 7. Exp. 1: Rising dose tolerance study - urinary iodide excretion

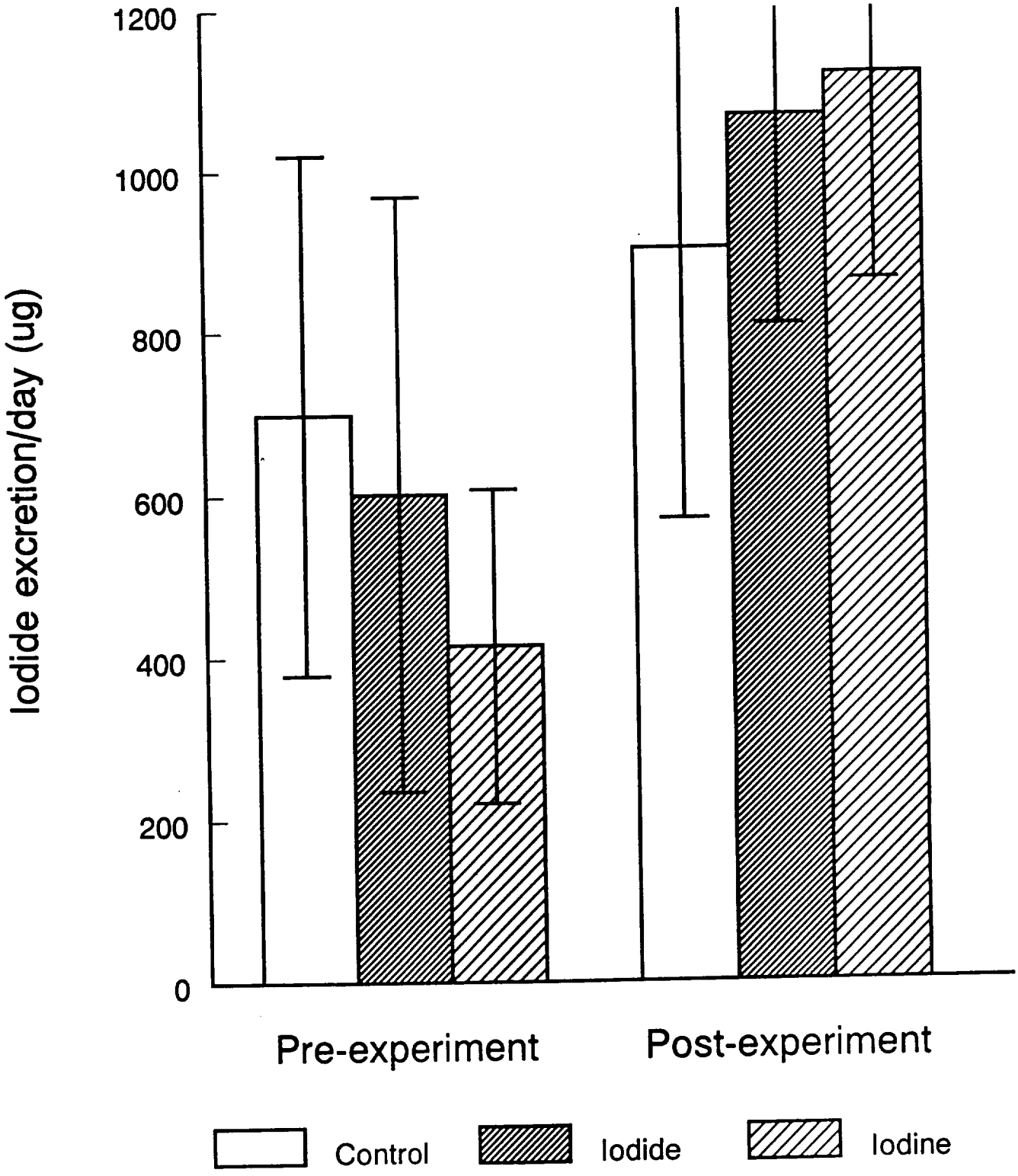


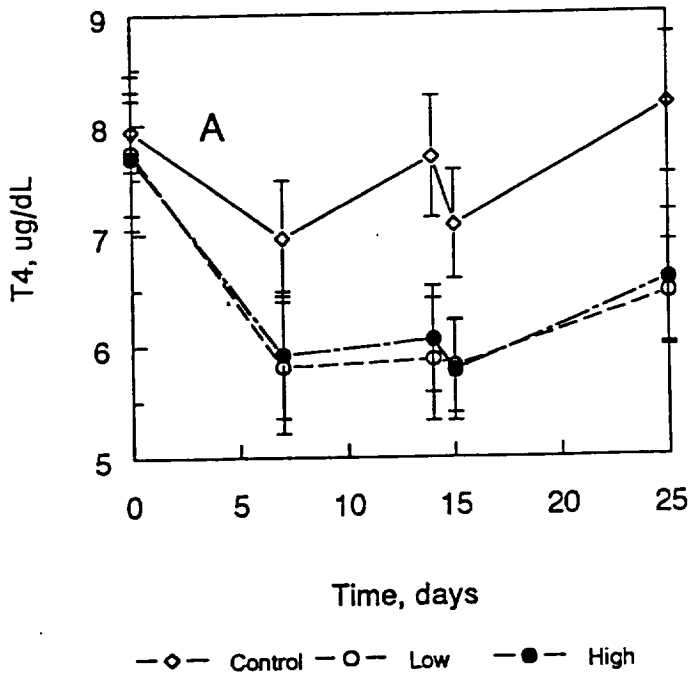
Table 3

Experiment 2, *Repeated Dose Study*
Adverse Reactions Unique to the Iodine (I_2) Treatment Groups

Adverse Reaction	Treatment Group*	
	Low Dose I_2 (n=6)	High Dose I_2 (n=7)
	Yes	Yes
Burned lips	0	1
Burned throat	**4**	**5**
Burned esophagus	2	1
Hoarseness	0	1
Light-headed after any dose	1	2
Flushed	0	1
Upset stomach	0	2
Abdominal pain	0	2
Tachycardia	1	0
Dizziness	1	0
Nausea	0	1
Excessive drooling	0	1
Colder than usual	1	1
Hotter than usual	0	1
Constipation	0	1
Irritated nasal passage	1	0

* Low dose = 0.3 mg/kg body weight
High dose = 1.0 mg/kg body weight

Figure 8. Effect of iodine treatments on serum T4 - Iodide X 14 days



Iodine X 14 days

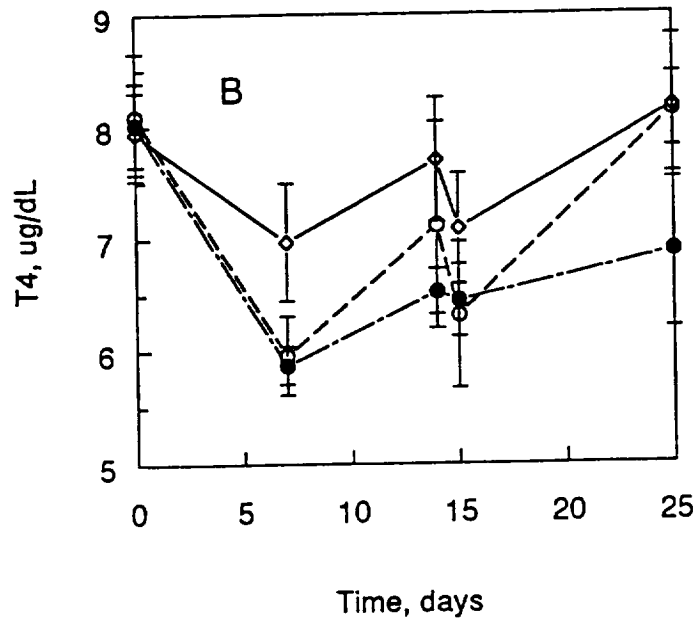
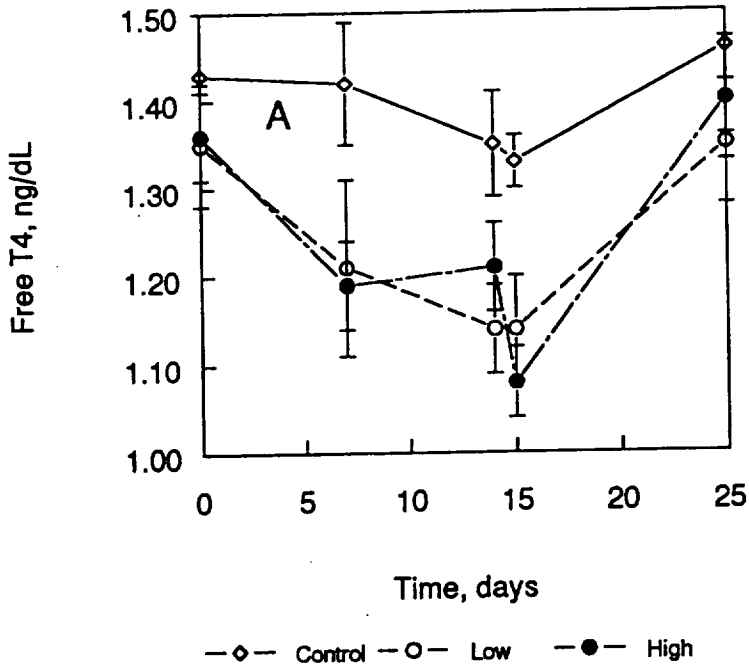


Figure 9. Effect of iodine treatments on free T4 - Iodide X 14 days



Iodine X 14 days

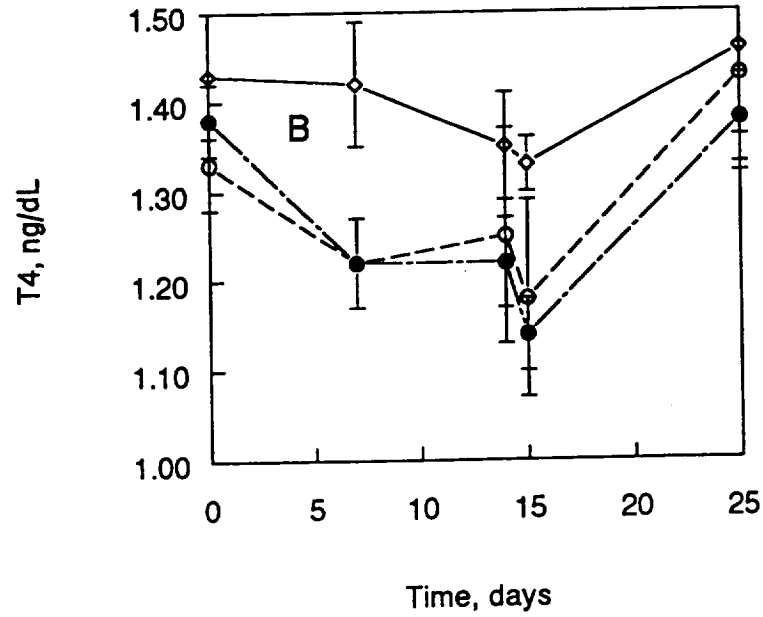
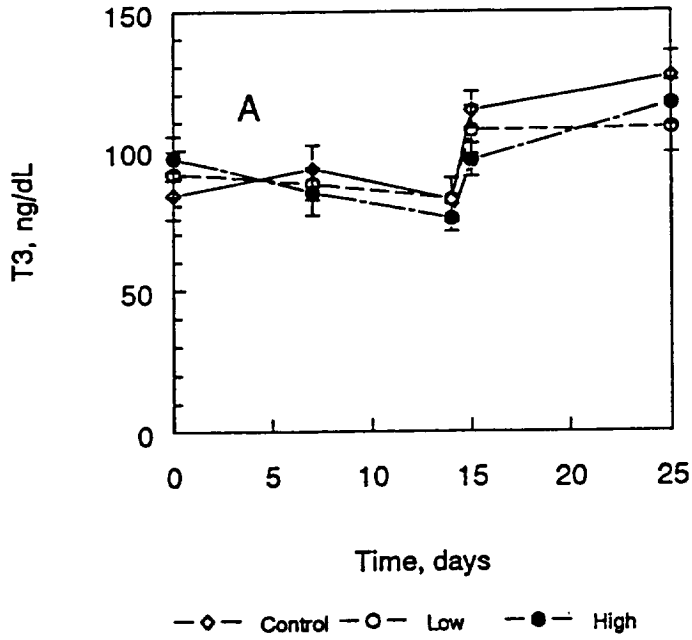


Figure 10. Effect of iodine treatments on T3 - Iodide X 14 days



Iodine X 14 days

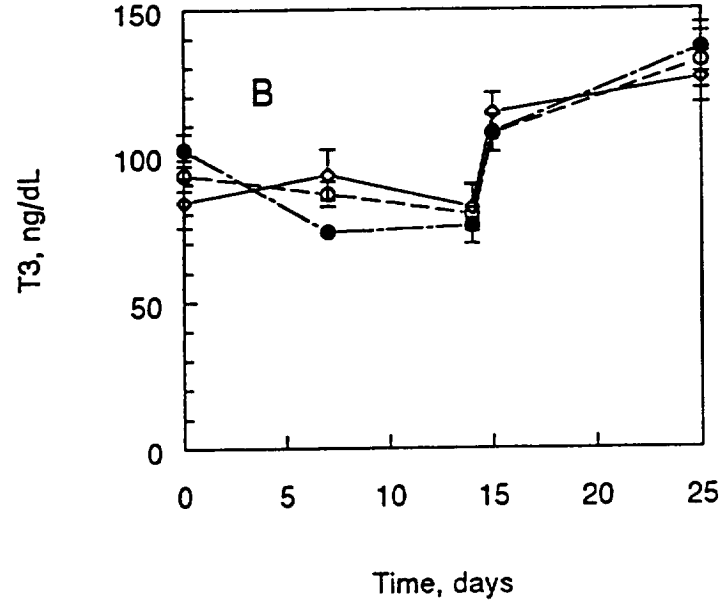
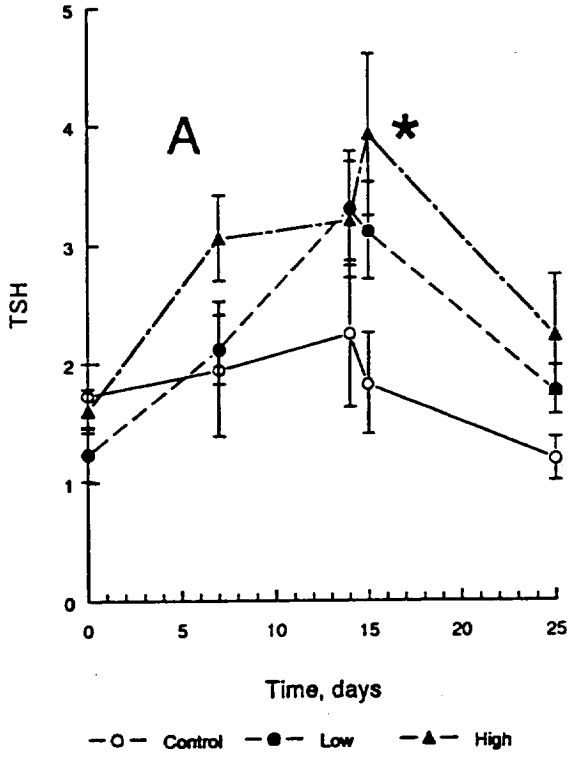


Figure 11. Effect of iodine treatments
on serum TSH - Iodide X 14 days



Iodine X 14 days

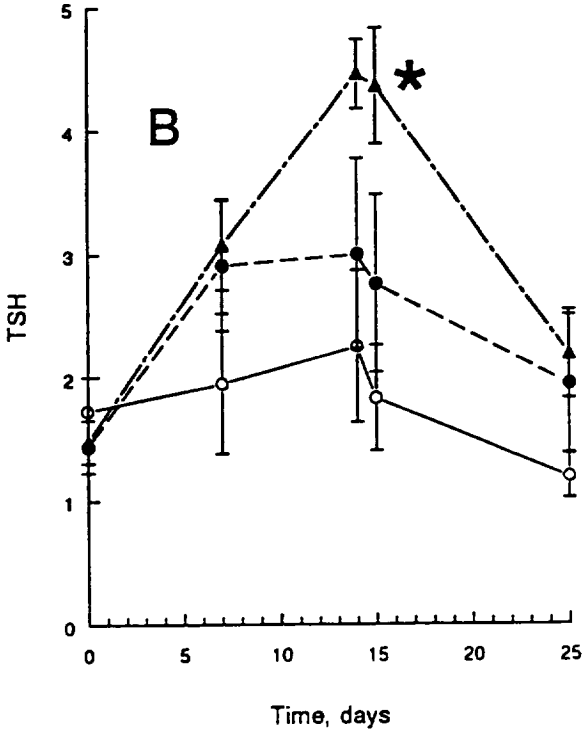
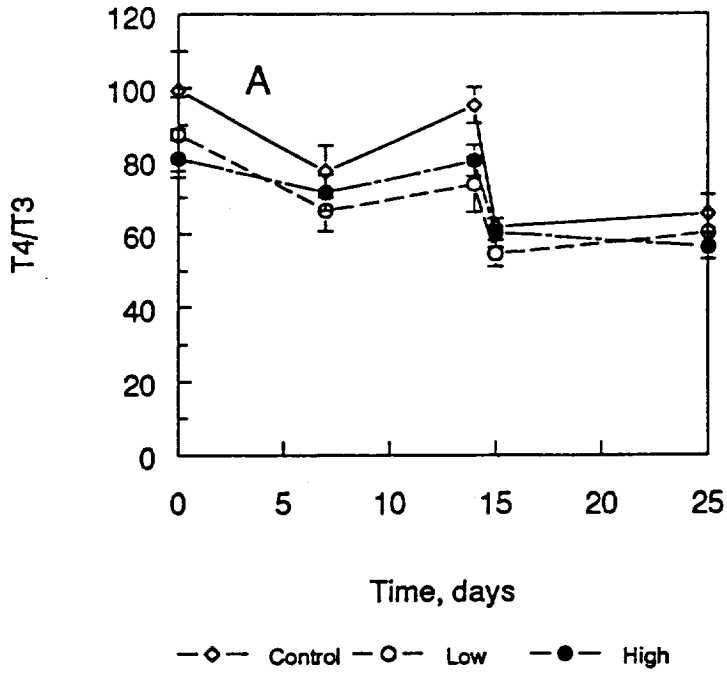


Figure 12. Effect of Repeated Doses of iodine on T4/T3 ratio - Iodide X 14 days



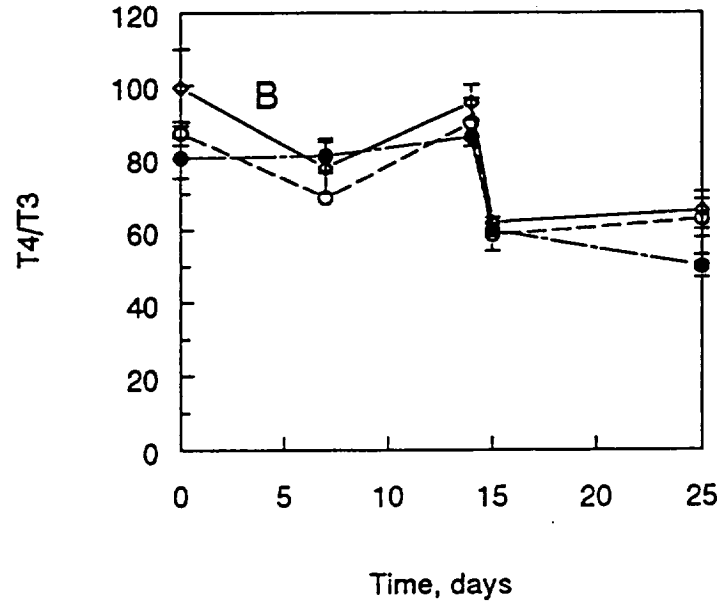


Table 4

Experiment 2, *Repeated Dose Study*
Analysis of Variance for Repeated Measures: P-Values
(n=32)

Thyroid Hormone	Time Effect	Time by Group Effect	Group Effect
T_4	0.0001	0.1622	0.4332
Free T_4	0.0001	0.4394	0.1534
T_3	0.0001	**0.0031**	0.9742
TSH	0.0001	**0.0008**	0.1255
T_4:T_3	0.0001	0.1133	0.3040

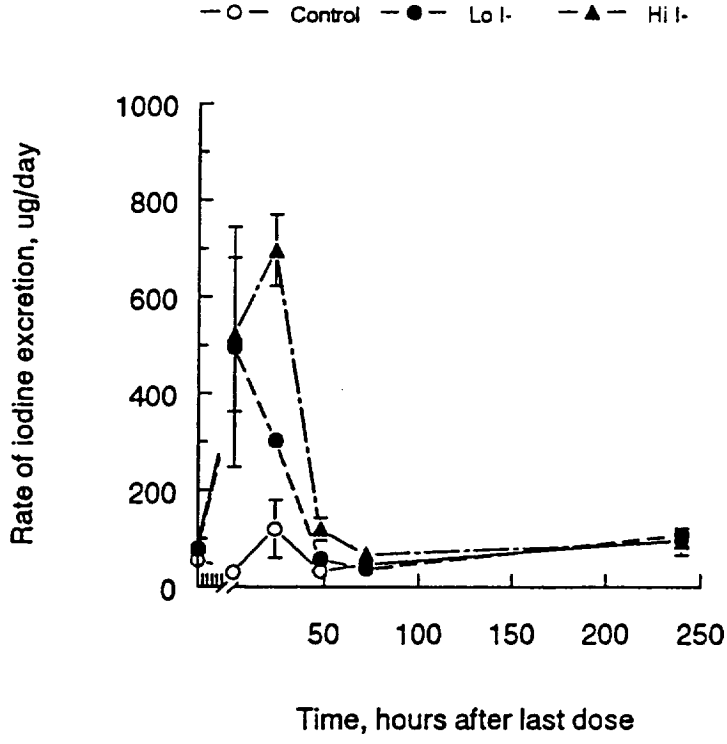
Table 5

Experiment 2, *Repeated Dose Study*
TSH Univariate ANOVA with Least Significant Differences
(n=32)

		Group Differences									
TSH	P-Value	↓ I_2 to Control[a]	↑ I_2 to Control[b]	↓ I^- to Control	↑ I^- to Control	↓ I_2 to ↑ I^-	↑ I_2 to ↑ I^-	↓ I^- to ↑ I^-	↓ I_2 to ↑ I_2	↓ I^- to ↑ I_2	↓ I^- to ↓ I_2
Baseline	0.5858	-	-	-	-	-	-	-	-	-	-
Day 7	0.2034	-	-	-	-	-	-	-	-	-	-
Day 14	0.0880	-	-	-	-	-	-	-	-	-	-
Day 15	0.0309	-	+	-	+	-	-	-	-	-	-

[a] ↓ = Low dose group, 0.3 mg/kg body weight
[b] ↑ = High dose group, 1.0 mg/kg body weight

Figure 13. Urinary excretion of iodine in repeated dose study - Iodide X 14 d



Iodine X 14 d