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Environmental Health Effects Research Series

DIETARY SUBACUTE TOXICITY OF ETHYLENE THIOUREA IN THE LABORATORY RAT

Health Effects Research Laboratory
Office of Research and Development
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DIETARY SUBACUTE TOXICITY OF ETHYLENE THIOUREA IN THE LABORATORY RAT

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory develops and revises air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is preparing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

The significance of the occurrence of residues of pesticides or metabolites of pesticides in or on plants destined for human consumption must be considered with respect to its ultimate impact on human health. The present study evaluates the effect of the presence of ethylenethiourea (ETU) in the diet of a mammalian model test system. ETU is the major metabolite of a class of fungicides (ethylenebisdithiocarbamates) and the toxicological hazard associated with this biologically active metabolite as a residue in food is under intensive investigation. An evaluation of the health hazards associated with the presence of ETU in food includes the primary effects on the thyroid and liver as well as several associated biochemical parameters in an effort to determine a dietary level which might be safe for man.

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ABSTRACT

Ethylene thiourea (ETU) was fed to groups of rats at 0, 1, 5, 25, 125 or 625 ppm for up to 90 days. Other groups of rats received either propylthiouracil (PTU; 125 ppm) or amitrole (50 ppm) in their diets as positive controls. Only those rats which received ETU at 125 or 625 ppm and those ingesting PTU or amitrole demonstrated a measurable toxic response. This toxicity was reflected as an alteration in thyroid function and a significant change in thyroid morphology.

Ingestion of 625 ppm ETU, or 125 ppm PTU resulted in very substantial decreases in serum triiodothyronine (T-3) and thyroxine (T-4). Marked increases in serum thyroid stimulating hormone (TSH) levels were found in the 625 and 125 ppm ETU rats, the 125 PTU rats and the rats receiving amitrole, at each time point this hormone was measured. A decrease in iodide uptake by the thyroid was also found in the rats which ingested 625 ppm ETU. While a statistically significant increase in serum T-4 and degree of thyroid hyperplasia was observed for the rats ingesting 25 ppm ETU for 60 days, normal thyroid hormone levels and thyroid morphology was found in the rats on 25 ppm ETU for either 30 or 90 days.

Based on biochemical and microscopic changes examined, the no-effect level for dietary ETU in this 90-day study is considered to be 25 ppm, equivalent to an average intake ranging from 19.5 mg/kg body weight at Week 1 to 12.5 mg/kg body weight at Week 12.

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INTRODUCTION

The salts of ethylenebisdithiocarbamic acid (EBDC) have been extensively used against a variety of pathogenic plant fungi. A principal impurity and degradation product of the EBDC fungicides is ethylene thiourea (2-imidazolidinethione; ETU). ETU has been identified as an impurity in commercial EBDC formulations (1, 2). It has been reported to occur as a result of metabolic (3, 4, 5) and chemical (6, 7, 8) alterations of the commercial fungicides. ETU has been identified on a number of different crops which had been field-sprayed with a commercial formulation of EBDC (9, 10). Cooking of foods containing EBDC residues also results in the formation of ETU (11, 12).

Early studies evaluating the toxicity of the EBDC fungicides reported a major effect to be thyroid hyperplasia and neoplasia (13, 14, 15). The toxicity of ETU has also been studied and found to be essentially similar to that of the parent fungicide, producing thyroid neoplasia in rats (16, 17) and liver tumors in mice (14). In these published reports, recorded parameters consisted of body weights, organ weights, food consumption, ^{131}I uptake, and terminal histopathology. In the ETU subacute toxicity study reported herein, thyroid hormone level measurements were also made to determine at what dietary dose level ETU causes thyroid hormone alterations and to establish a dietary concentration which does not induce thyroid changes leading to hyperplasia. In addition, it was hoped that a relationship between altered thyroid hormone levels and thyroid hyperplasia could be established.

EXPERIMENTAL

Materials

Sprague Dawley-derived rats were purchased from Charles River Laboratories (Wilmington, Massachusetts). ETU (estimated to be >95 percent pure) was obtained from the Aldrich Chemical Company (Milwaukee, Wisconsin), and propylthiouracil (PTU) and amitrole (3-amino-1,2,4-triazole) were purchased from the Sigma Chemical Company (St. Louis, Missouri). ^{125}I for the thyroid iodine uptake studies was obtained from New England Nuclear (Boston, Massachusetts). Commercial test kits for measuring serum thyroxine (T-4) and thyroid binding globulin (TBG) were purchased from Nuclear Medical Laboratories, Inc. (Dallas, Texas). Triiodothyronine (T-3) kits were obtained from Diagnostics Products Corporation (Los Angeles, California). Initial serum TSH measurements were performed with kits purchased from Beckman Instruments, Inc. (Fullerton, California). Shortly after this study began, the specificity of the antiserum for human TSH was changed and the measure of rat TSH was no longer accomplished.

TSH kits from ICN Medical, Pharmacia Diagnostics and Calbiochem were purchased and evaluated as possible substitutes for measuring rat TSH. Only the Calbiochem TSH RIA kit proved suitable, and it was used at the end of this study. TSH was not measured during most of the study.

ETU Purity Analysis

The ETU used in this study was analyzed by mass spectroscopy and nuclear magnetic resonance spectrometry (NMR). Direct probe high resolution mass spectroscopy showed a strong parent ion at m/e 103. This is shown in Figures 1 and 2. It was estimated through the use of both ^{13}C and ^{2}H NMR spectroscopy that ETU was 96.8 percent pure.

Thyroid Function and Control

Thyroid hormone is biosynthesized in the thyroid gland by the iodination of tyrosine. Iodotyrosines are coupled to form T-3 and T-4. These active hormones are released into the bloodstream and are distributed throughout the body where they regulate metabolic processes. Hormone synthesis and release is controlled by a peptide which originates in the anterior lobe of the pituitary, the thyroid stimulating hormone

(TSH). Pituitary secretion of TSH is, in turn, regulated by two factors, a hormone released by the hypothalamus called thyrotropin releasing hormone (TRH), and the concentration of free thyroid hormones (T-3 and T-4) in the interstitial fluid which bathes both the pituitary and hypothalamus.

Increased serum thyroid hormone concentrations suppress secretion of TSH while decreased hormone levels augment TSH release, providing for a steady-state thyroid hormone concentration. Recent studies indicate that thyroid hormone blocks pituitary response to TRH. As the serum levels of T-3 and T-4 fall below a threshold concentration, the TSH-secreting cells of the anterior pituitary become responsive to TRH and secrete TSH which, in turn, raises serum thyroid hormone levels. This feedback control system is designed to provide a constant supply of thyroid hormone to peripheral tissues, where it acts as a regulator of cellular metabolism.

Chemical substances that impair the synthesis or release of thyroid hormone cause hyperplasia of the thyroid gland. Continued exposure to antithyroid chemicals results in the transformation of the hyperplastic tissue to a malignant form. It is now well documented that chemicals altering thyroid function can initiate thyroid neoplasia (18, 19). Chemicals which impair the synthesis or release of TSH from the pituitary can severely affect the feedback control system which regulates serum T-3 and T-4 levels.

In summary, altered thyroid function can result from the action of a chemical on iodine uptake and incorporation, synthesis or release of thyroid hormones, synthesis or release of TSH, or inactivation of receptors activated by either TSH (at the level of the thyroid) or by thyroid hormone (at the pituitary level). Using commercially available test kits, the serum concentration of T-3, T-4, TBG and TSH can be measured. ^{125}I uptake can be measured directly. The Free Thyroxine Index (FTI) was calculated and is reported for each group. The FTI is a measurement of free serum T-4. While the T-4 level, measured by the T-4 radioimmunoassay kit, is influenced by TBG concentrations, the FTI is a measurement of the amount of T-4 free in the serum, independent of the serum TBG concentration. The formula used to calculate the FTI is shown below:

$$\text{FTI} = \frac{(\text{T-3 \% Bound})}{100} \times \text{T-4 } \mu\text{g\%}$$

Evaluation of Test Kits

We have previously shown that certain chemically induced alterations in thyroid function in rats could be measured using commercially available kits. We reported serum T-4 and TBG (T-3 binding) levels and ^{125}I uptake by the thyroid (20). Prior to the initiation of this ETU subacute toxicity bioassay, we evaluated a new T-3 kit produced by Diagnostic Products Corporation (Los Angeles, California), and a TSH kit from Beckman Instruments (Fullerton, California). The T-3 diagnostic kit quantitatively measures total serum T-3 by radioimmunoassay. One hundred microliters of each serum sample (or standard) is mixed with an equal volume of ^{125}I labeled T-3. Upon addition of the T-3 specific antibody, the endogenous serum T-3 and the radioactive T-3 compete for binding sites. This reaction takes place in the presence of ANS (anion-8-anilino-1-naphthaline sulfonic acid) which blocks the interaction of T-3 with other serum proteins. A second antibody, goat antirabbit gamma globulin, is added to separate the free serum T-3 from the bound T-3. This solution is well mixed and incubated at 37°C for 15 minutes. An ice cold solution of 6 percent polyethylene glycol is then added to help precipitate the antibody bound T-3. Following centrifugation (3,500xg; 20 min.), the supernatant containing the free T-3 is decanted and the antibody bound T-3 precipitant is counted. A five point standard curve is constructed and serum T-3 levels are determined from this curve.

The Beckman TSH diagnostic kit quantitatively measures total serum TSH by radioimmunoassay. The procedure is similar to that described above for the T-3 test. Serum from rats pretreated with amitrole was evaluated for T-3 and TSH levels and this was compared to values obtained from control serum.

Unfortunately, after the ETU subacute toxicity study began, Beckman switched to a new antiserum with increased specificity for human TSH. This kit would no longer measure rat TSH. Therefore, TSH kits from other commercial sources were purchased and evaluated as possible alternates. The kit produced by Calbiochem contains a relatively nonspecific TSH antiserum and will measure rat serum TSH levels. Unfortunately, this was not confirmed until near the end of the study and for this reason, TSH values are available for only very few groups.

Methods

ETU, PTU, or amitrole was added to corn oil and then incorporated into powdered rodent feed[(1)] using a twin shell tumble blender. The final corn-oil concentration in the blended feed was 1 percent. The test diets were prepared fresh weekly. The dietary levels of ETU were 625, 125, 25, 5 and 1 ppm, PTU was 125 ppm and amitrole, 50 ppm. These dietary levels of PTU and amitrole were previously shown to produce significant antithyroid effects (21, 22). A control group received powdered diet containing 1 percent corn oil. Each of the seven dosage groups contained 60 male and 60 female rats. The control group contained 72 male and 72 female rats. The animals were placed on study as outlined in Table 1.

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(1) Ralston Purina Company, Richmond, Indiana.

At 30-day intervals, 10 rats of each sex from each test group were sacrificed and serum T-3, T-4, TBG and TSH concentrations were measured. These rats were also used for necropsy. The remaining 10 rats of each sex per group were used for thyroid ^{125}I uptake studies. Each rat was individually caged throughout the study. Body weight and food consumption was determined weekly. Each rat was toe-punched at the start of the study for permanent identification.

The 10 tissues removed during necropsy are listed in Table 2. Due to excessive salivation and abnormal skin-hair coat development at the 625 ppm ETU level, skin and mandibular salivary glands were also removed during necropsy from the rats which received the high diet. The thyroid gland and liver were examined microscopically in all study groups. These two tissues were fixed in formalin imbedded in paraffin, sectioned (6 microns) and stained with Hematoxylin-Eosin. The remaining tissues were stored in 10 percent buffered formalin.

RESULTS

The rats which received 625 ppm ETU showed clinical signs of poisoning by the eighth day on study. Excessive salivation, loss of hair or failure to replace normal hair loss, rough and bristly hair coat, and scaly skin texture was observed. Ingestion of ETU was calculated and found to range from 11.7 to 15.2 mg/day in female rats to from 13.0 to 17.3 mg/day in male rats. Table 8 shows data on the weekly consumption of ETU and other chemicals by all animals on study. Fourteen of the 40 rats on the 625 ppm ETU 60-day study died between days 40 and 50 of the study. Only one rat from the 90-day group died.

The rats receiving 125, 25, 5 and 1 ppm ETU, control diet, 50 ppm amitrole or 125 ppm PTU showed no adverse clinical effects.

Consistent with the observable clinical changes, several biochemical changes were noted. Rats ingesting ETU at 625 ppm showed a significant decrease in iodine uptake. The percent T-3 bound to TBG was lower than normal at the 30- and 90-day evaluations. Serum concentrations of T-3 and T-4 were also very substantially lower than the levels obtained for the control rats. The serum TSH concentration for the 625 ppm rats, measured only at the time of the 30-day evaluation, was increased to more than twice the serum TSH concentration observed for the control rats. Significant differences in free T-4 were also found, as determined by the FTI.

The rate of iodine uptake, the percentage of T-3 bound to TBG, and the serum T-3 concentration in the rats receiving 125 ppm ETU were not significantly different from the control group. However, a statistically significant decrease in total serum T-4 concentration and in free serum

T-4 measured at the 30-, 60- and 90-day evaluations was observed. The serum TSH concentration in the 125 ppm ETU rats at 30 days was approximately three times the concentration measured in the control rats.

With one exception, there were no significant measurable differences in iodine uptake, T-3 binding to TBG or serum T-3, T-4 and TSH levels in the rats receiving ETU at either 25, 5 or 1 ppm for 30, 60 or 90 days. The rats ingesting 25 ppm ETU for 60 days showed a statistically significant increase in serum T-4 concentration. This was not evident at 30 or 90 days.

After 30 days of amitrole ingestion, very significantly decreased serum T-3 and T-4 levels were observed. The female rats from this group also had a decreased percent of T-3 bound to TBG. Both the male and female rats had an increased serum TSH concentration. In a previous report (EBIS toxicity study), we showed that ingestion of 50 ppm amitrole for four days resulted in a significant decrease in iodine uptake and T-4 serum concentrations. While the decreased T-4 levels are still found after 30 days of amitrole ingestion, iodine uptake appears to have returned to normal, probably as a result of biological compensation. At 60 and 90 days, normal values for all of the thyroid function measurements were noted.

The rats which received PTU had decreased serum T-3 and T-4 concentrations at 30, 60, and 90 days. The serum TBG level was affected only in the 60- and 90-day test groups. Since the PTU study was added after the ETU study had started, TSH values were obtainable for the 60- and 90-day PTU test groups. Both groups had markedly elevated serum TSH levels.

Tables 3, 4 and 5 list the percent iodine uptake, TBG, T-3 and T-4 concentrations after 30, 60 and 90 days on study, respectively. Also included in these tables are the values for the amitrole and PTU positive controls. TSH values are given for those test groups in which it was measured. The calculated FTI for each test group is shown in Table 6.

Diet consumption for all groups is shown in Figure 3. With the exception of those rats receiving 625 ppm ETU and those ingesting 125 PTU, there was no significant difference in feed consumption. A 30 percent to 40 percent reduction in food consumption was observed in the rats on the 625 ppm ETU and 125 ppm PTU test diets, compared to control animal consumption levels. The average weekly feed consumption for each test group with the standard deviation is listed in Table 7.

The amount of ETU, PTU or amitrole consumed per week is shown in Figure 4. The average amount of each test chemical consumed along with the standard deviation is listed in Table 8.

Individual body weights were recorded weekly throughout the study. Table 9 summarizes the body weight data (group mean ± S.D.). Figure 5 shows the weekly body weight gain for each dietary level. Only those rats which receive 625 ppm ETU or 125 ppm PTU test diets showed a marked decrease in body weight gain. No difference in body weight gain was observed for those rats which received ETU at 125, 25, 5 or 1 ppm, or amitrole, as compared to the control group.

At the conclusion of the study, gross necropsies were performed and certain organs were removed and weighed (see Table 2). Table 10 lists the mean organ weights and standard deviation for each group. There were no significant differences in organ weights in those rats fed 25, 5, 1 and 0 ppm ETU. However, thyroid hyperplasia was observed in all animals which received 625 and 125 ppm ETU, 125 ppm PTU or 50 ppm amitrole in their diet for 30, 60 or 90 days.

The organ-weight-to-body-weight ratios were calculated (Table 11). The spleen-to-body-weight ratio for the rats which ingested 625 ppm ETU is significantly decreased while the ratios for the thyroid, brain, kidneys, testicles and pituitary are significantly higher than the corresponding control values. Increased thyroid-to-body-weight ratios were also found for the rats which received 125 ppm PTU, 50 ppm amitrole or 125 ppm ETU (Table 11).

Organ-weight-to-brain-weight ratios were also calculated (Table 12). no significant differences were found between rats receiving 125, 25, 5, 1 and 0 ppm ETU. For those rats ingesting 625 ppm ETU, the ratio of heart, spleen, kidney, adrenals (female) and ovaries-to-brain-weight was significantly decreased and the thyroid-to-brain-weight ratio was significantly increased compared to control values. The thyroid-to-brain-weight ratios in the rats which received 125 ppm ETU were also significantly increased in size at 30, 60 and 90 days.

An increased thyroid-to-brain-weight ratio was the only significant organ-to-brain-weight ratio change found in the 50 ppm amitrole test animals. The animals which received 125 ppm PTU for 30, 60 or 90 days showed a very significant decrease in organ-to-brain-weight ratios for heart, spleen, kidney, ovary, liver and adrenals. These animals had a very significant increase in thyroid-to-brain-weight ratios compared to the control values. The organ-weight-to-brain-weight ratios for the rats which received amitrole and PTU are listed in Table 12.

Gross examinations revealed the majority of the rats which received ETU at 125 or 625 ppm, as well as those animals which received PTU or amitrole for 30, 60 or 90 days had enlarged red thyroids. Grossly visible patterns of centrilobular congestion were present in a few random rats fed amitrole or ETU. A summary of gross changes is presented in Table 13.

Microscopic examination of tissues was restricted to thyroid and liver. The thyroids were graded for degree of hyperplasia using a slight modification of the procedure of Astwood (23), and as defined in Table 14. Varying degrees of thyroid microfollicular hyperplasia resulted at feeding levels of ETU above 25 ppm (Table 15). Relatively mild changes were noted in animals fed 125 ppm ETU for 30 days as compared to the moderate changes observed in the rats fed 625 ppm ETU for the same time period. Marked thyroid microfollicular hyperplasia and reduced colloid formation were found in animals fed amitrole or PTU for 30 days. At 60 days, the rats receiving the three highest levels of ETU (625, 125 and 50 ppm) and the amitrole treatment group showed moderate thyroid hyperplasia as compared to the 60-day PTU group which was more marked in its thyroid hyperplastic response and reduced colloid production.

Ninety days of dietary exposure to 625 ppm ETU also resulted in microfollicular hyperplasia but not as severe as seen with PTU in the same time period. Numerous changes ranging from adenomatous hyperplasia of follicles to what appear to be true solid adenomas were present in the thyroids in the 625 ppm ETU group. Table 16 categorizes the hyperplastic thyroids from the 625 ppm ETU test group into either solid adenomas, cystic adenomas, adenomatous change or cystic-like follicles. No adenomas were observed in the thyroid sections taken from the other dietary groups. No liver tumors were observed in the rats at any dosage level of ETU or in those animals which received PTU or amitrole. The majority of the livers examined microscopically had mild centrilobular changes which can be described as follows. Portal triad areas have a smooth sheet of hepatocytes cut relatively across the nucleus and cytoplasm at about the same level giving well defined cell boundaries and cytoplasmic proportions. As one approaches the mid-zonal area and progresses into the centrilobular area of small central veins, the pattern changes to less distinct cell borders of swollen cytoplasmic material with fewer apparent nuclei. The chord pattern is less distinct and there is a mild increase in small polyploid nuclei. The general appearance is that of increased cytoplasm, fewer nuclei and less orderly hepatic chords.

The data presented in this report show no significant measurable adverse effects of dietary ETU at dosages of 5 ppm and below. Significant toxic responses, observed as altered thyroid function and changes in thyroid morphology, resulted from the ingestion of ETU at 125 ppm or 625 ppm for 30, 60 or 90 days. The observable effects at 25 ppm were noted only at the 60-day interval and were not seen at 30 or 90 days. Based on these data, a dietary no-effect level in rats might be expected to be 25 ppm over the 90-day study.

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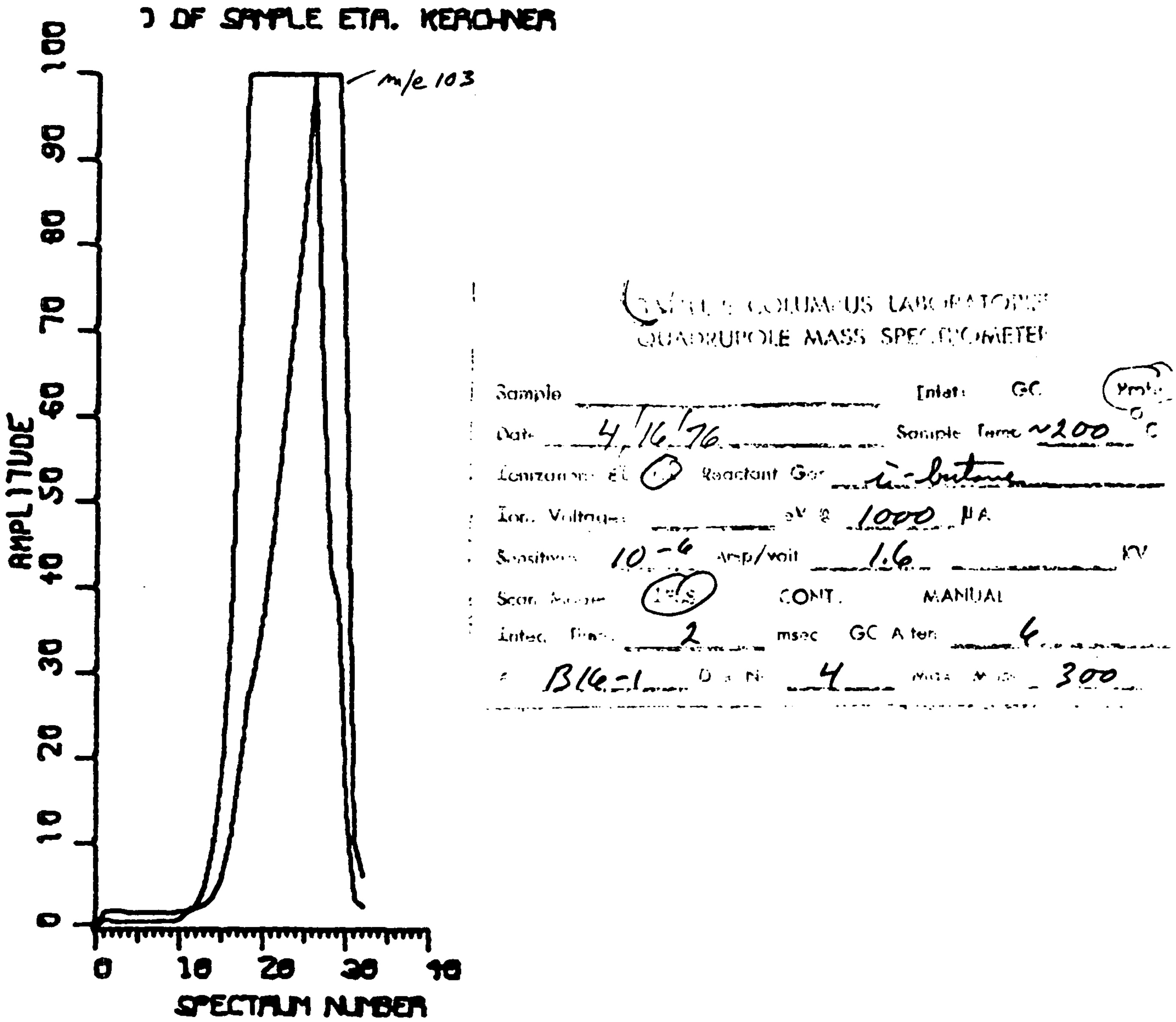

FIGURE 1. MS ANALYSIS OF THE ETU USED AS THE TEST CHEMICAL

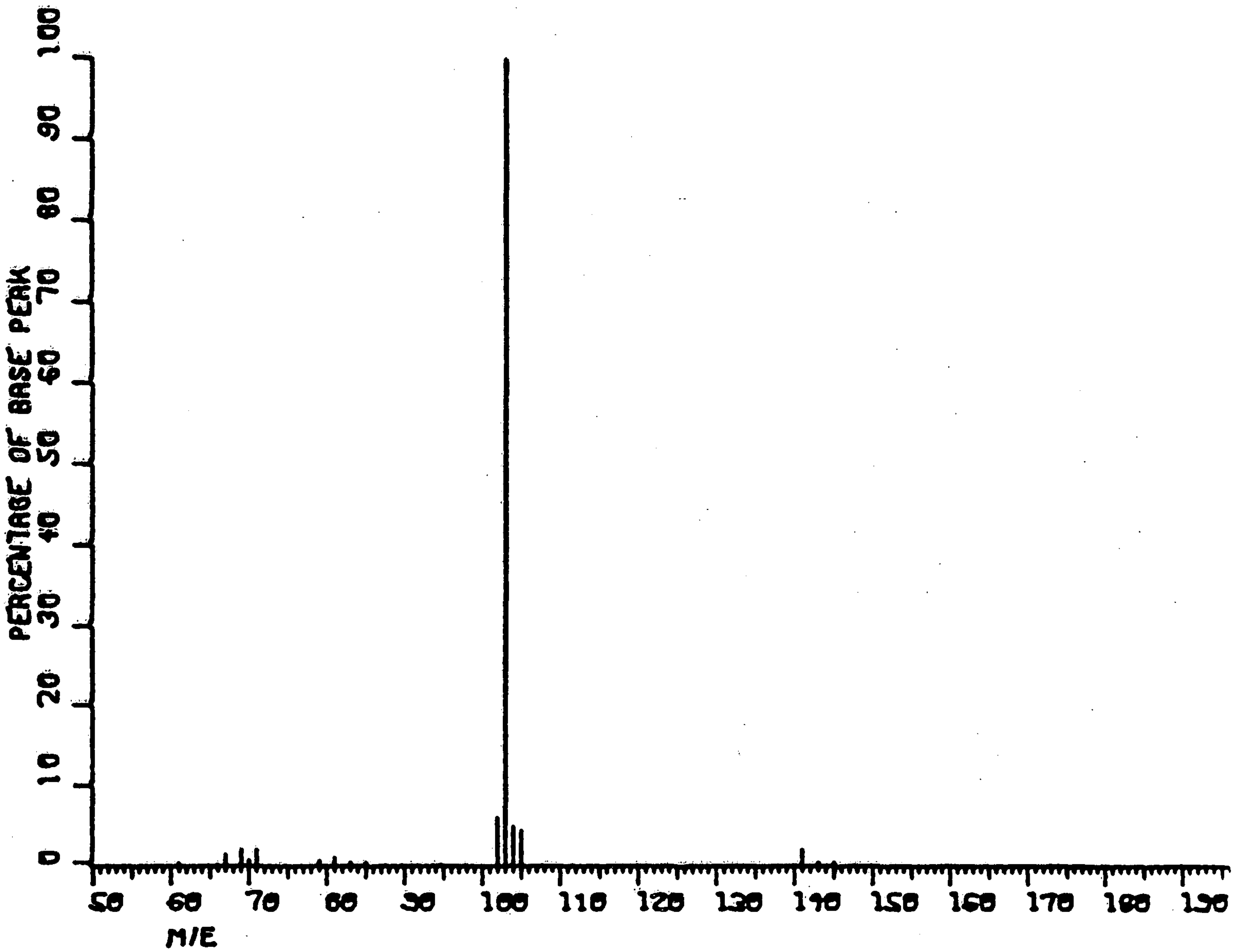

FIGURE 2. MS OF THE ETU USED AS THE TEST CHEMICAL

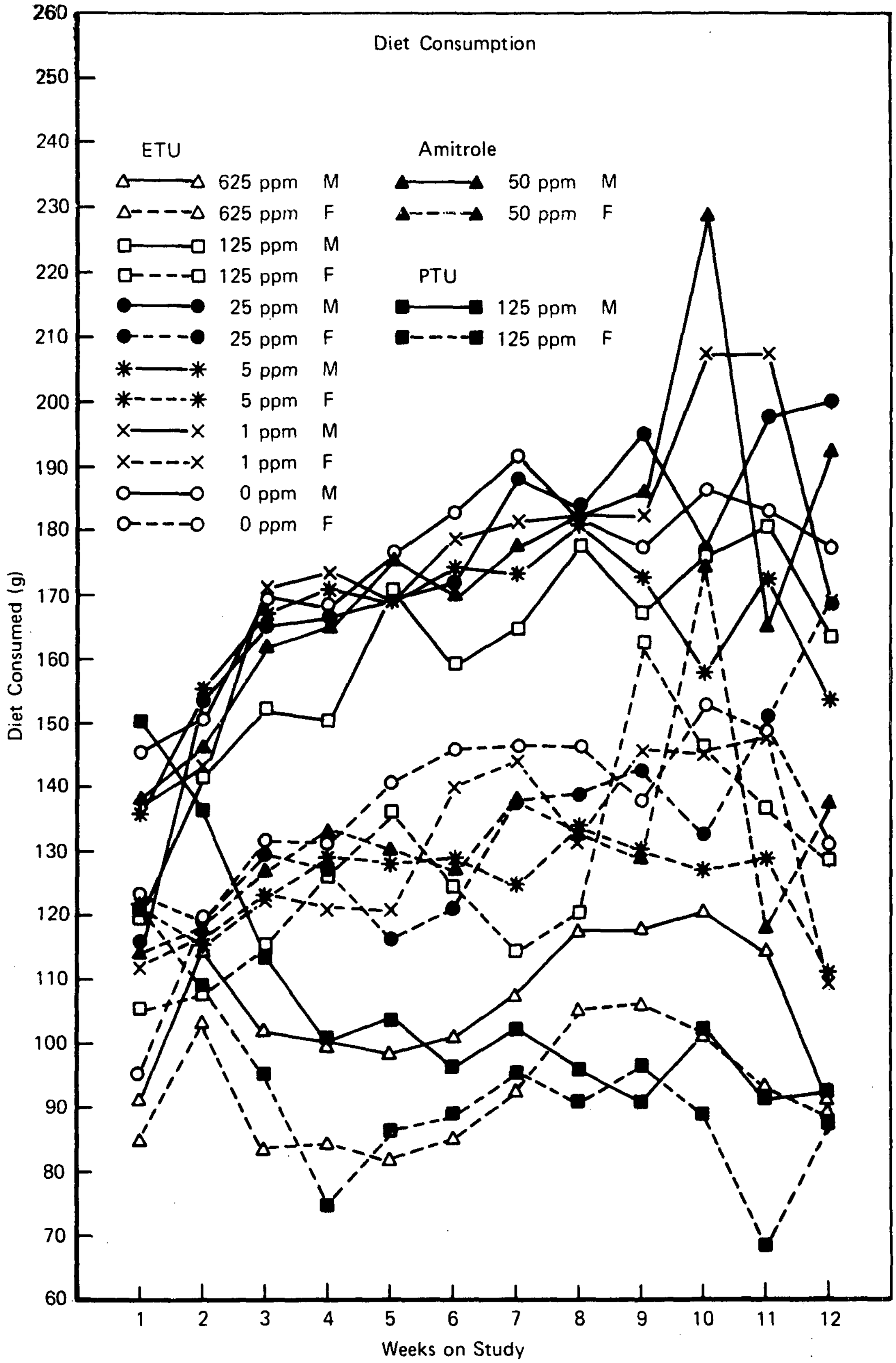

FIGURE 3. DIET CONSUMPTION

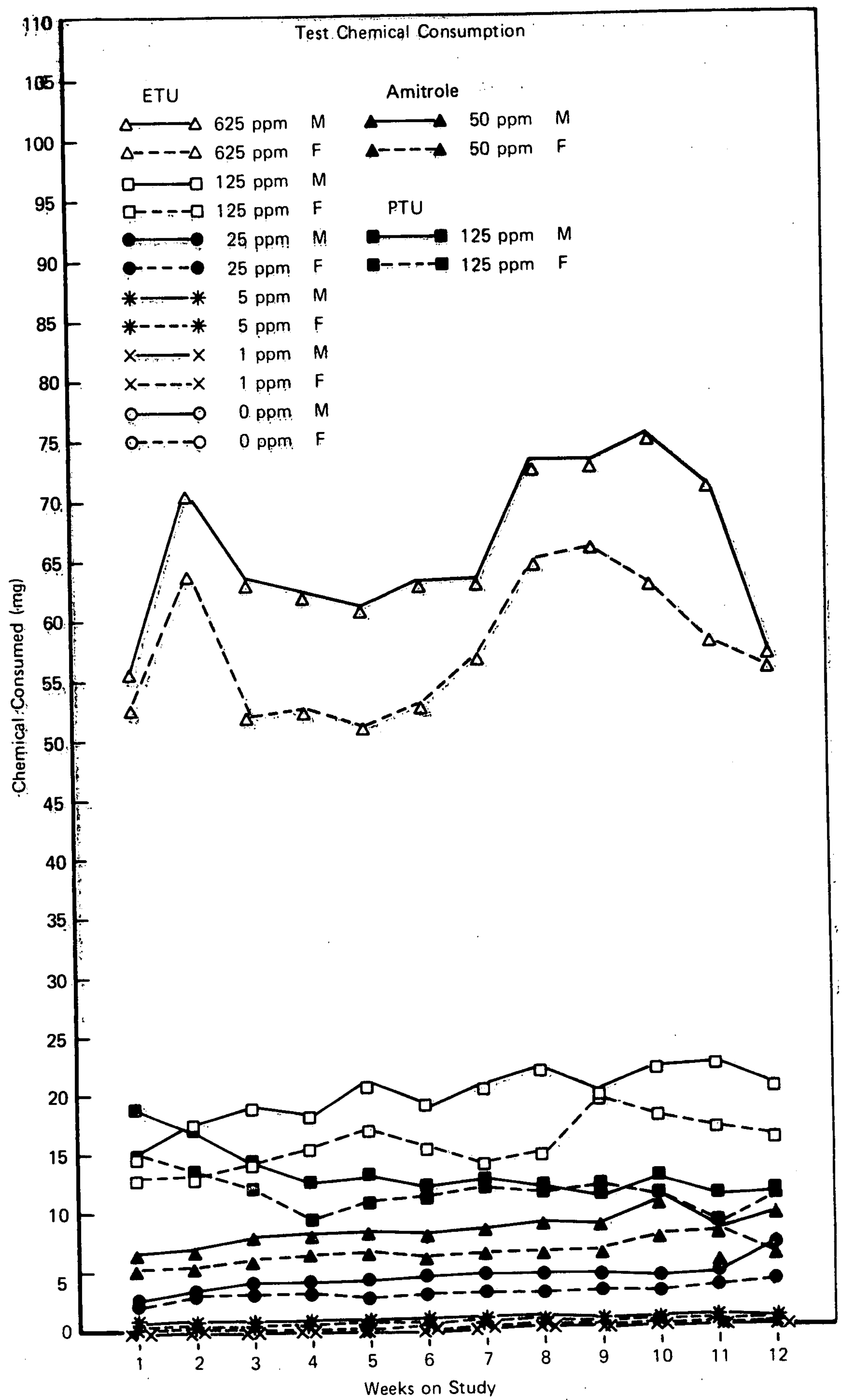

FIGURE 4. TEST CHEMICAL CONSUMPTION

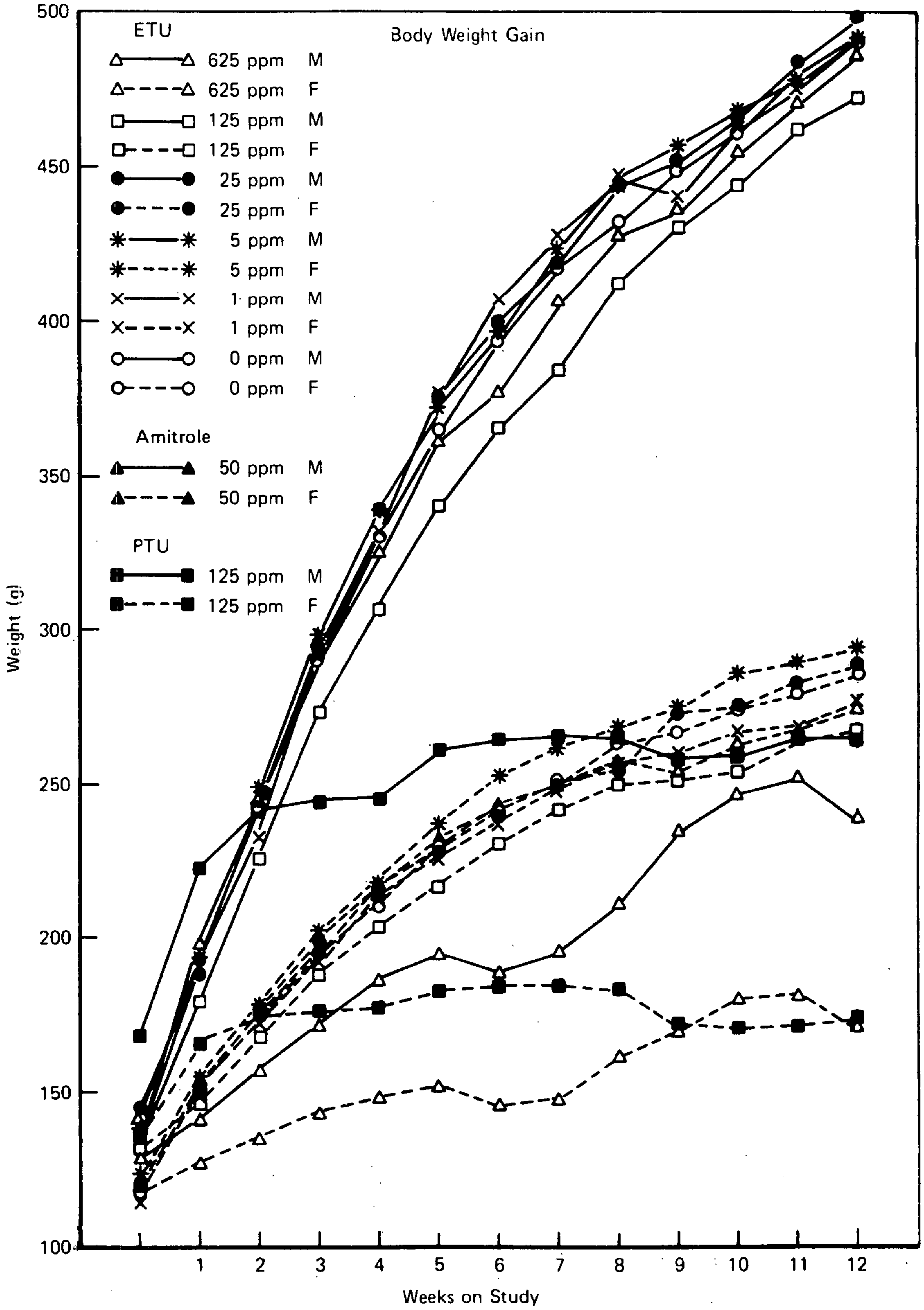

FIGURE 5. BODY WEIGHT GAIN

TABLE 1. ETU PROTOCOL DESIGN

ETU (ppm)	Sex	Number of Rats/Treatment Period 30 Days	60 Days	90 Days
625	M	20	20	20
625	F	20	20	20
125	M	20	20	20
125	F	20	20	20
25	M	20	20	20
25	F	20	20	20
5	M	20	20	20
5	F	20	20	20
1	M	20	20	20
1	F	20	20	20
0	M	24	24	24
0	F	24	24	24
Amitrole (ppm)				
50	M	20	20	20
50	F	20	20	20
PTU (ppm)				
125	M	20	20	20
125	F	20	20	20

TABLE 2. TISSUES REMOVED AND WEIGHED DURING NECROPSY

Heart	*Liver
Spleen	Pituitary
Kidney	*Thyroid (paired)
Ovary (paired)	Adrenal (paired)
Testicle (paired)	Brain

* Tissues processed for histopathologic evaluation.

TABLE 3. THYROID HORMONE LEVELS - AFTER 30 DAYS ON STUDY

ETU (ppm)	Sex	^{125}I (percent uptake)	TBG (percent T-3 bound)	T-3 (ng percent)	T-4 (µg percent)	TSH (µIU per ml)
625	M	1.2 ± 0.4*	60.3 ± 2.6*	57.3 ± 3.7*	0.9 ± 0.6*	14.3 ± 0.9*
625	F	2.1 ± 1.4*	60.6 ± 1.8*	58.4 ± 9.9*	1.1 ± 1.0*	14.6 ± 1.9*
125	M	3.6 ± 0.8	62.7 ± 1.3*	71.1 ± 11.8	2.6 ± 0.4*	23.3 ± 5.9*
125	F	4.0 ± 1.7	61.5 ± 1.3*	104.4 ± 16.3*	2.1 ± 0.5*	18.3 ± 4.0*
25	M	2.9 ± 0.6	65.7 ± 2.3	67.1 ± 15.9	5.6 ± 1.1	7.3 ± 1.5
25	F	3.2 ± 1.3	63.5 ± 2.0	86.3 ± 14.8	3.8 ± 0.8	5.1 ± 1.3
5	M	3.6 ± 0.6	69.3 ± 6.3	79.0 ± 8.1	4.7 ± 0.4	6.7 ± 1.4
5	F	3.8 ± 1.0	68.9 ± 1.3	88.1 ± 12.8	2.9 ± 0.9	4.9 ± 1.4
1	M	3.7 ± 0.7	64.5 ± 1.2	82.1 ± 13.0	5.1 ± 1.0	6.4 ± 0.8
1	F	3.0 ± 0.5	63.4 ± 1.3	90.9 ± 11.3	3.5 ± 1.0	4.5 ± 0.9
0	M	3.6 ± 0.9	68.0 ± 5.6	76.0 ± 11.8	5.0 ± 1.7	6.7 ± 2.5
0	F	3.5 ± 0.9	66.0 ± 5.2	83.2 ± 16.2	3.8 ± 1.4	6.0 ± 4.1
Amitrole (ppm)						
50	M	3.7 ± 2.1	63.0 ± 1.5	49.1 ± 19.5*	0.6 ± 0.8*	9.3 ± 0.6*
50	F	5.0 ± 3.5	61.4 ± 1.0*	55.2 ± 7.2*	0.3 ± 0.3*	8.9 ± 0.6*
PTU (ppm)						
125	M	2.9 ± 1.1	67.8 ± 2.0	58.9 ± 6.1*	0.9 ± 0.2*	- -
125	F	3.3 ± 0.7	69.5 ± 1.6	52.0 ± 8.0*	0.7 ± 0.1*	

*Significantly different ($p < 0.05$) from corresponding control. Student's t test was used to make comparison between the control and treated animals. All data reported as the mean, ± S.D.

TABLE 4. THYROID HORMONE LEVELS - AFTER 60 DAYS ON STUDY

ETU (ppm)	Sex	^{125}I (percent uptake)	TBG (percent T-3 bound)	T-3 (ng Percent)	T-4 (µg percent)	THS (µIU per ml)
625	M	1.9 ± 1.0*	79.0 ± 0.9	56.9 ± 10.3*	0.2 ± 0.1*	-
625	F	2.4 ± 1.8*	71.8 ± 1.4	56.8 ± 6.9*	0.2 ± 0.1*	-
125	M	3.6 ± 1.4	66.3 ± 1.3	79.8 ± 28.1	2.8 ± 0.5*	
125	F	3.3 ± 1.0	66.3 ± 2.1	78.5 ± 28.6*	2.0 ± 0.5*	-
25	M	3.2 ± 0.7	76.9 ± 1.6	86.4 ± 7.6	2.8 ± 0.5*	-
25	F	3.7 ± 1.3	74.7 ± 1.7	126.2 ± 15.1	2.6 ± 0.5*	-
5	M	3.5 ± 0.8	66.4 ± 1.2	85.4 ± 12.7	4.9 ± 0.5	-
5	F	4.0 ± 0.8	64.0 ± 1.8	118.5 ± 14.3	2.9 ± 0.9	-
1	M	2.7 ± 0.6	70.4 ± 1.2	80.3 ± 12.0	4.9 ± 0.7	-
1	F	3.2 ± 0.7	67.1 ± 1.3	93.3 ± 13.5	2.8 ± 0.8	-
0	M	4.3 ± 0.9	73.6 ± 4.9	77.3 ± 8.5	4.8 ± 0.7	5.8 ± 0.4**
0	F	3.5 ± 0.8	69.4 ± 4.3	103.8 ± 19.1	3.3 ± 0.5	6.4 ± 0.9**
Amitrole (ppm)						
50	M	4.0 ± 0.7	74.8 ± 1.6	83.4 ± 8.9	5.9 ± 0.8	-
50	F	4.8 ± 0.9	69.8 ± 1.3	111.6 ± 10.7	3.5 ± 0.6	-
PTU (ppm)						
125	M	3.9 ± 1.6	61.7 ± 2.6*	46.1 ± 3.9*	1.2 ± 0.2*	9.8 ± 1.0*
125	F	5.4 ± 1.7	62.2 ± 2.1*	50.9 ± 9.7*	0.8 ± 6.1*	10.8 ± 1.9*

* Significantly different ($p < 0.05$) from corresponding control.

** TSH values to be used as control for PTU group.

TABLE 5. THYROID HORMONE LEVELS - AFTER 90 DAYS ON STUDY

ETU (ppm)	Sex	^{125}I (percent uptake)	TBG (percent T-3 bound)	T-3 (ng percent)	T-4 (μg percent)	TSH (μIU per ml)
625	M	2.5 ± 0.8*	62.7 ± 2.0*	27.9 ± 13.3*	1.1 ± 0.6*	-
625	F	3.7 ± 1.8	62.7 ± 0.9*	35.2 ± 4.3*	1.1 ± 0.6*	-
125	M	2.8 ± 0.7	65.3 ± 1.1	86.1 ± 15.0	2.3 ± 0.6*	-
125	F	3.9 ± 1.1	64.3 ± 1.6	105.5 ± 16.0	1.6 ± 0.3*	-
25	M	3.3 ± 0.7	68.9 ± 1.5	79.4 ± 12.6	3.8 ± 1.0	-
25	F	3.4 ± 0.9	65.6 ± 2.3	108.7 ± 11.6	2.9 ± 0.7	-
5	M	3.7 ± 0.6	71.4 ± 0.8	76.1 ± 13.1	5.0 ± 1.0	-
5	F	4.2 ± 1.1	70.1 ± 2.2	105.2 ± 16.6	3.0 ± 0.7	-
1	M	3.5 ± 0.6	65.8 ± 1.1	68.7 ± 9.9	4.0 ± 1.0	-
1	F	3.2 ± 0.9	63.1 ± 1.4	116.7 ± 17.6	2.5 ± 0.7	-
0	M	3.8 ± 0.5	69.3 ± 2.7	72.0 ± 21.5	4.5 ± 0.8	5.8 ± 0.4**
0	F	4.1 ± 1.0	65.2 ± 2.9	106.8 ± 25.0	3.3 ± 0.8	6.4 ± 0.9**
Amitrole (ppm)						
50	M	5.8 ± 3.1	71.4 ± 1.5	67.3 ± 11.8	3.6 ± 1.3	-
50	F	4.8 ± 3.2	69.6 ± 2.1	94.8 ± 13.3	3.5 ± 1.1	-
PTU (ppm)						
125	M	4.7 ± 1.7	59.1 ± 1.3*	73.2 ± 9.9	0.6 ± 0.2*	9.4 ± 1.3*
125	F	5.6 ± 2.5	60.4 ± 1.7*	69.6 ± 9.4*	0.4 ± 0.2*	10.7 ± 2.1*

*Significantly different ($p < 0.05$) from corresponding control.

**TSH values to be used as control for PTU group.

TABLE 6. FREE THYROXINE INDEX

ETU (ppm)	Sex	Days on Study 30	60	90
625	M	0.52	0.15	0.68
625	F	0.67	0.12	0.70
125	M	1.62	1.86	1.48
125	F	1.27	1.35	1.05
25	M	3.69	2.12	2.64
25	F	2.42	1.91	1.90
5	M	3.24	3.27	3.53
5	F	2.00	1.88	2.12
1	M	3.28	3.49	2.64
1	F	2.22	1.86	1.52
0	M	3.37	3.52	3.12
0	F	2.52	2.31	2.14
Amitrole (ppm)				
50	M	0.35	4.37	2.53
50	F	0.15	2.42	2.41
PTU (ppm)				
125	M	0.64	0.74	0.33
125	F	0.49	0.48	0.23

TABLE 7. WEEKLY DIET CONSUMPTION*

ETU (ppm)	Sex	Week No. 1	Week No. 2	Week No. 3	Week No.4	Week No. 5	Week No. 6
625	M	91.2 ± 14.1	114.6 ± 29.5	102.0 ± 14.8	100.7 ± 16.3	98.5 ± 17.2	101.0 ± 20.8
625	F	85.0 ± 14.9	103.8 ± 30.7	83.9 ± 24.3	84.0 ± 17.2	82.2 ± 24.1	85.2 ± 23.9
125	M	120.3 ± 27.0	141.9 ± 19.5	152.7 ± 20.6	150.6 ± 27.3	171.3 ± 35.2	159.6 ± 22.1
125	F	105.8 ± 33.5	107.7 ± 18.7	115.8 ± 22.9	126.8 ± 42.2	136.8 ± 58.3	124.5 ± 31.4
25	M	114.7 ± 27.0	153.6 ± 17.0	165.3 ± 23.6	166.6 ± 18.7	169.2 ± 13.6	172.1 ± 24.9
25	F	95.0 ± 20.8	119.8 ± 22.9	129.8 ± 37.9	127.1 ± 27.6	116.6 ± 17.5	121.1 ± 25.1
5	M	136.2 ± 18.9	155.4 ± 20.5	167.9 ± 26.8	171.2 ± 36.1	169.0 ± 21.1	174.3 ± 19.8
5	F	121.6 ± 24.8	115.4 ± 23.2	123.1 ± 19.9	129.3 ± 38.7	128.7 ± 29.3	128.8 ± 20.7
1	M	137.0 ± 18.0	143.5 ± 26.0	171.1 ± 28.1	173.9 ± 41.5	168.8 ± 13.4	179.0 ± 27.3
1	F	112.3 ± 13.6	116.5 ± 23.2	123.1 ± 27.9	121.2 ± 29.3	120.9 ± 23.3	140.3 ± 43.4
0	M	145.5 ± 35.2	151.1 ± 20.4	169.9 ± 21.5	168.0 ± 20.3	176.7 ± 35.0	182.9 ± 47.7
0	F	123.3 ± 43.3	119.1 ± 22.8	131.7 ± 43.2	131.6 ± 39.1	140.9 ± 39.7	146.3 ± 59.2
Amitrole (ppm)							
50	M	138.4 ± 16.4	146.1 ± 17.6	162.3 ± 19.8	165.6 ± 19.9	175.8 ± 26.0	169.9 ± 30.9
50	F	114.0 ± 19.2	118.8 ± 20.8	127.3 ± 31.7	133.3 ± 32.9	130.2 ± 26.9	127.1 ± 26.8
PTU (ppm)							
125	M	150.6 ± 17.7	136.7 ± 17.5	113.6 ± 23.4	100.1 ± 17.2	104.1 ± 14.5	96.8 ± 18.7
125	F	120.7 ± 13.8	108.6 ± 16.6	95.5 ± 23.7	74.4 ± 13.3	86.7 ± 27.6	89.1 ± 21.2

TABLE 7. (Continued)

ETU (ppm)	Sex	Week No. 7	Week No. 8	Week No. 9	Week No. 10	Week No. 11	Week No. 12
625	M	107.8 ± 17.9	117.9 ± 15.3	117.8 ± 20.7	121.0 ± 20.1	114.8 ± 17.2	91.6 ± 18.7
625	F	92.6 ± 24.8	105.2 ± 20.8	106.1 ± 27.1	101.8 ± 20.8	93.8 ± 13.5	89.8 ± 30.2
125	M	165.0 ± 13.7	178.2 ± 43.2	167.6 ± 38.4	176.7 ± 29.5	181.2 ± 46.8	164.3 ± 27.9
125	F	114.7 ± 11.9	120.5 ± 21.2	163.1 ± 83.1	146.6 ± 54.8	137.1 ± 50.9	129.6 ± 56.9
25	M	188.7 ± 43.9	183.5 ± 23.1	195.3 ± 34.4	176.8 ± 16.3	198.2 ± 51.7	200.7 ± 59.8
25	F	138.3 ± 32.9	139.0 ± 43.3	143.3 ± 36.9	133.0 ± 26.1	151.4 ± 63.1	170.0 ± 69.4
5	M	173.6 ± 27.7	181.0 ± 37.4	173.2 ± 31.2	158.6 ± 35.3	172.9 ± 38.3	154.2 ± 18.0
5	F	125.2 ± 26.9	133.9 ± 51.9	130.7 ± 25.4	127.6 ± 47.0	129.7 ± 24.3	111.1 ± 16.5
1	M	181.9 ± 45.9	182.9 ± 33.2	182.7 ± 27.9	207.8 ± 56.2	207.9 ± 54.2	168.8 ± 18.0
1	F	144.6 ± 53.2	131.9 ± 34.3	146.0 ± 46.7	145.8 ± 49.1	148.1 ± 61.5	109.6 ± 14.9
0	M	191.6 ± 48.7	181.8 ± 48.7	177.8 ± 30.5	186.5 ± 40.4	183.4 ± 45.0	177.8 ± 46.2
0	F	146.8 ± 48.7	146.6 ± 55.8	138.1 ± 36.2	153.2 ± 66.6	149.0 ± 66.8	131.7 ± 50.9
Amitrole (ppm)							
50	M	177.6 ± 40.8	182.1 ± 38.0	185.9 ± 39.9	229.1 ± 75.6	165.8 ± 22.0	192.5 ± 32.1
50	F	138.0 ± 51.6	132.9 ± 48.4	129.2 ± 40.8	174.6 ± 79.8	118.4 ± 25.7	138.1 ± 59.0
PTU (ppm)							
125	M	102.7 ± 19.0	96.4 ± 18.9	91.0 ± 19.4	101.9 ± 16.5	91.5 ± 18.1	92.0 ± 14.1
125	F	95.5 ± 19.5	91.3 ± 28.1	96.5 ± 28.3	89.1 ± 20.8	68.5 ± 9.9	88.2 ± 15.4

* Mean, ± S.D.; presented in grams.

TABLE 8. WEEKLY TEST CHEMICAL INGESTION*

ETU (ppm)	Sex	Week No. 1	Week No. 2	Week No. 3	Week No. 4	Week No. 5	Week No. 6	Week No. 7	Week No. 8	Week No. 9	Week No. 10	Week No. 11	Week No. 12
625	M	57.0	71.6	63.7	62.9	61.6	63.1	67.4	73.7	73.6	75.6	71.7	57.3
625	F	53.1	64.9	52.4	52.5	51.4	53.3	57.9	65.7	66.3	63.6	58.6	56.1
125	M	15.0	17.7	19.1	18.8	21.4	19.9	20.6	22.3	21.0	22.1	22.7	20.5
125	F	13.2	13.5	14.5	15.9	17.1	15.6	14.3	15.1	20.4	18.3	17.1	16.2
25	M	2.9	3.8	4.1	4.2	4.2	4.3	4.7	4.6	4.9	4.4	5.0	5.0
25	F	2.4	3.0	3.3	3.2	2.9	3.0	3.5	3.5	3.6	3.3	3.8	4.3
5	M	0.7	0.8	0.8	0.9	0.9	0.9	0.9	0.9	0.9	0.8	0.9	0.8
5	F	0.6	0.6	0.6	0.7	0.6	0.6	0.6	0.7	0.7	0.6	0.7	0.6
1	M	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
1	F	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1
0	M	0	0	0	0	0	0	0	0	0	0	0	0
0	F	0	0	0	0	0	0	0	0	0	0	0	0
Amitrole (ppm)													
50	M	6.9	7.3	8.1	8.3	8.8	8.5	8.9	9.1	9.3	11.5	8.3	9.6
50	F	5.7	5.9	6.4	6.7	6.5	6.4	6.9	6.7	6.5	8.7	5.9	6.9
PTU (ppm)													
125	M	18.8	17.1	14.2	12.5	13.0	12.1	12.8	12.1	11.4	12.7	11.4	11.5
125	F	15.1	13.6	11.9	9.3	10.8	11.1	11.9	11.4	12.1	11.1	8.6	11.0

* Mean, ± S. D.; presented in grams.

TABLE 9. WEEKLY BODY WEIGHT GAIN*

ETU, ppm	Sex	Weeks on Study 0	1	2	3	4	5	6
625	M	129.4 ± 14.2	141.4 ± 15.0	157.7 ± 17.8	172.1 ± 24.3	187.2 ± 25.3	195.1 ± 21.1	189.6 ± 26.5
625	F	117.5 ± 12.0	127.2 ± 12.6	135.5 ± 12.6	143.6 ± 15.8	148.6 ± 17.5	152.6 ± 16.2	145.7 ± 21.5
125	M	132.1 ± 17.5	180.3 ± 22.7	226.7 ± 24.4	274.0 ± 27.0	306.6 ± 37.3	341.3 ± 38.2	365.7 ± 38.0
125	F	116.6 ± 14.6	146.3 ± 13.1	168.2 ± 15.1	188.9 ± 16.0	204.1 ± 20.8	217.3 ± 25.8	230.7 ± 23.0
25	M	145.0 ± 11.3	188.6 ± 18.1	242.1 ± 15.2	295.0 ± 20.0	335.9 ± 21.9	376.9 ± 22.9	401.3 ± 21.3
25	F	127.2 ± 12.1	152.1 ± 13.3	176.5 ± 14.8	199.7 ± 16.8	217.4 ± 18.4	228.8 ± 20.6	241.0 ± 23.8
5	M	140.5 ± 13.9	195.3 ± 14.4	248.9 ± 21.5	299.8 ± 22.9	340.1 ± 28.8	373.9 ± 30.4	398.5 ± 36.3
5	F	124.0 ± 12.4	155.1 ± 11.4	179.4 ± 23.9	201.6 ± 19.6	218.2 ± 21.5	238.5 ± 22.8	254.1 ± 22.0
1	M	131.0 ± 16.6	191.5 ± 22.1	234.0 ± 29.9	292.7 ± 32.7	332.3 ± 35.2	377.5 ± 37.6	408.6 ± 40.9
1	F	115.2 ± 13.7	151.6 ± 13.9	173.4 ± 14.7	193.8 ± 17.3	213.3 ± 20.2	227.4 ± 17.8	238.1 ± 18.4
0	M	141.0 ± 27.6	193.8 ± 29.4	242.8 ± 30.1	290.5 ± 36.9	331.9 ± 35.8	366.4 ± 35.3	394.5 ± 33.6
0	F	119.0 ± 21.1	151.6 ± 18.0	174.9 ± 22.2	194.5 ± 21.5	211.0 ± 20.1	228.9 ± 21.6	242.3 ± 23.7
Amitrole								
50	M	139.1 ± 18.7	199.5 ± 20.8	245.3 ± 25.7	291.5 ± 27.5	328.6 ± 27.2	361.6 ± 30.5	378.3 ± 37.5
50	F	120.2 ± 13.7	155.5 ± 16.2	176.7 ± 19.0	195.1 ± 23.7	216.5 ± 21.6	232.6 ± 24.8	243.4 ± 23.9
PTU								
125	M	168.5 ± 39.8	224.3 ± 35.2	241.9 ± 37.0	245.3 ± 34.9	247.4 ± 32.1	261.7 ± 30.2	265.0 ± 29.3
125	F	136.4 ± 26.6	167.8 ± 22.5	174.1 ± 24.3	176.3 ± 25.8	178.1 ± 24.2	183.5 ± 26.9	185.0 ± 26.7

TABLE 9. (Continued)

		Weeks on Study					
ETU, ppm	Sex	7	8	9	10	11	12
625	M	195.7 ± 36.0	210.7 ± 34.6	234.8 ± 29.8	246.6 ± 34.8	251.2 ± 38.2	239.4 ± 40.3
625	F	148.8 ± 25.0	161.9 ± 21.6	170.3 ± 25.7	180.7 ± 23.1	181.3 ± 23.9	171.5 ± 28.3
125	M	385.3 ± 40.5	413.4 ± 32.3	431.4 ± 36.7	444.6 ± 40.2	462.5 ± 40.9	472.1 ± 43.3
125	F	242.1 ± 23.4	249.9 ± 26.6	250.8 ± 22.0	254.5 ± 25.5	265.7 ± 24.4	268.1 ± 23.4
25	M	420.1 ± 29.0	443.0 ± 26.0	451.9 ± 29.2	466.4 ± 26.1	483.5 ± 33.1	497.5 ± 33.8
25	F	250.9 ± 22.9	254.3 ± 25.6	273.6 ± 25.0	275.2 ± 23.1	283.3 ± 23.3	288.8 ± 26.9
5	M	425.1 ± 39.4	447.8 ± 42.2	457.7 ± 38.4	468.7 ± 35.4	478.8 ± 38.5	491.9 ± 39.2
5	F	263.3 ± 24.1	269.6 ± 25.4	274.9 ± 26.5	286.7 ± 25.8	290.2 ± 23.4	295.2 ± 26.8
1	M	428.6 ± 44.4	446.7 ± 49.7	442.0 ± 49.0	462.0 ± 49.4	476.0 ± 52.9	492.3 ± 55.3
1	F	249.1 ± 19.6	256.5 ± 19.1	260.0 ± 20.8	267.5 ± 20.1	269.8 ± 24.0	276.3 ± 22.2
0	M	417.9 ± 36.0	432.9 ± 39.7	448.9 ± 35.7	461.1 ± 38.8	478.4 ± 33.7	492.1 ± 35.2
0	F	251.1 ± 22.0	263.3 ± 30.6	266.6 ± 30.5	275.2 ± 26.6	280.5 ± 28.0	285.9 ± 30.7
Amitrole							
50	M	407.4 ± 37.0	428.8 ± 44.2	437.5 ± 44.4	456.4 ± 40.1	471.1 ± 40.0	487.7 ± 40.4
50	F	249.8 ± 22.7	258.2 ± 25.8	254.9 ± 32.8	263.8 ± 31.2	269.0 ± 32.2	275.5 ± 32.6
PTU							
125	M	265.5 ± 30.4	265.7 ± 31.0	259.0 ± 33.0	259.3 ± 35.5	265.3 ± 35.7	265.6 ± 37.2
125	F	184.9 ± 27.5	183.7 ± 27.8	171.8 ± 28.0	171.1 ± 28.9	172.4 ± 27.6	174.5 ± 29.0

* Mean, ± S.D.; presented in grams.

TABLE 10. ORGAN WEIGHTS OBTAINED AT NECROPSY

ETU (ppm)	Days on Study	Sex	Heart (g)	Spleen (g)	Rt. Kidney (g)	Left Kidney (g)	Ovary (paired; g)	Testicle (paired; g)	Liver (g)	Pituitary (mg)	Thyroid (mg)	Adrenal (paired; mg)	Brain (g)
625	90	M	0.77 ± 0.16	0.28 ± 0.11	0.85 ± 0.11	0.83 ± 0.14		4.37 ± 0.60	7.56 ± 1.54	10.10 ± 3.63	48.20 ± 24.34	40.70 ± 6.15	1.80 ± 0.08
625	90	F	0.58 ± 0.11	0.24 ± 0.07	0.65 ± 0.06	0.63 ± 0.05	0.08 ± 0.02		6.51 ± 0.83	13.25 ± 4.40	45.88 ± 12.98	43.13 ± 8.64	1.66 ± 0.08
125	90	M	1.37 ± 0.13	0.83 ± 0.13	1.69 ± 0.29	1.65 ± 0.31		5.17 ± 0.45	19.06 ± 2.40	10.80 ± 2.10	37.30 ± 8.21	48.20 ± 10.02	2.05 ± 0.14
125	90	F	0.88 ± 0.07	0.53 ± 0.12	0.93 ± 0.10	0.92 ± 0.08	0.09 ± 0.02		9.78 ± 0.99	12.80 ± 2.94	23.70 ± 3.53	52.10 ± 7.80	1.81 ± 0.09
25	90	M	1.41 ± 0.14	0.84 ± 0.12	1.59 ± 0.17	1.61 ± 0.17		5.33 ± 0.73	17.62 ± 1.93	10.38 ± 2.33	29.50 ± 9.88	51.30 ± 8.38	2.06 ± 0.06
25	90	F	0.97 ± 0.13	0.53 ± 0.09	1.00 ± 0.10	0.98 ± 0.11	0.10 ± 0.14		10.92 ± 1.01	1470 ± 2.75	20.20 ± 6.05	59.60 ± 8.19	1.90 ± 0.08
5	90	M	1.41 ± 0.22	0.88 ± 0.11	1.49 ± 0.19	1.49 ± 0.18		5.29 ± 0.55	16.62 ± 2.14	11.00 ± 3.27	25.70 ± 4.97	48.90 ± 9.40	2.05 ± 0.12
5	90	F	0.90 ± 0.09	0.54 ± 0.09	1.00 ± 0.09	0.97 ± 0.10	0.11 ± 0.01		10.72 ± 1.67	14.20 ± 3.68	18.90 ± 6.06	63.60 ± 8.51	1.89 ± 0.81
1	90	M	1.39 ± 0.15	0.80 ± 0.15	1.55 ± 0.22	1.55 ± 0.22		5.11 ± 0.30	17.98 ± 3.04	9.80 ± 4.37	27.50 ± 4.77	49.80 ± 7.13	2.04 ± 0.13
1	90	F	0.84 ± 0.06	0.52 ± 0.09	0.94 ± 0.08	0.94 ± 0.09	0.10 ± 0.02		10.57 ± 1.28	13.90 ± 4.15	21.10 ± 4.47	64.40 ± 10.27	1.80 ± 0.18
0	90	M	1.43 ± 0.19	0.90 ± 0.10	1.62 ± 0.20	1.60 ± 0.18		5.67 ± 0.55	17.33 ± 1.92	11.42 ± 3.09	30.42 ± 8.64	51.33 ± 6.30	2.08 ± 0.09
0	90	F	0.93 ± 0.09	0.55 ± 0.11	1.01 ± 0.11	0.97 ± 0.10	0.10 ± 0.02		10.21 ± 1.22	14.83 ± 6.44	25.00 ± 4.45	66.08 ± 11.85	1.83 ± 0.10
625	60	M	0.77 ± 0.31	0.31 ± 0.19	0.86 ± 0.19	0.88 ± 0.21		3.17 ± 1.14	8.00 ± 1.13	10.20 ± 3.11	57.60 ± 19.09	41.40 ± 11.02	1.76 ± 0.07
625	60	F	0.57 ± 0.06	0.21 ± 0.03	0.67 ± 0.03	0.65 ± 0.03	0.08 ± 0.02		7.57 ± 0.66	9.11 ± 2.32	38.11 ± 18.40	41.00 ± 7.48	1.65 ± 0.10
125	60	M	1.37 ± 0.23	0.76 ± 0.13	1.46 ± 0.08	1.45 ± 0.11		4.59 ± 0.51	17.42 ± 1.37	13.70 ± 2.79	37.10 ± 10.93	55.90 ± 9.64	2.00 ± 0.13
125	60	F	0.95 ± 0.33	0.54 ± 0.08	0.94 ± 0.06	0.93 ± 0.08	0.13 ± 0.01		10.12 ± 1.31	12.10 ± 2.18	27.30 ± 7.01	63.00 ± 10.74	1.85 ± 0.11
25	60	M	1.38 ± 0.09	0.80 ± 0.10	1.64 ± 0.21	1.63 ± 0.21		5.35 ± 0.53	20.82 ± 3.22	10.40 ± 1.58	34.50 ± 7.37	48.50 ± 6.17	2.04 ± 0.07
25	60	F	0.88 ± 0.11	0.53 ± 0.04	0.99 ± 0.14	0.99 ± 0.12	0.10 ± 0.02		10.32 ± 1.55	8.80 ± 3.08	23.00 ± 5.79	59.40 ± 15.28	1.88 ± 0.07
5	60	M	1.43 ± 0.18	0.84 ± 0.10	1.65 ± 0.21	1.59 ± 0.22		5.04 ± 0.60	17.86 ± 3.09	8.60 ± 2.07	20.40 ± 4.40	47.60 ± 9.08	1.95 ± 0.15
5	60	F	0.92 ± 0.13	0.54 ± 0.07	0.96 ± 0.07	0.93 ± 0.09	0.10 ± 0.02		10.53 ± 1.03	11.20 ± 2.30	18.10 ± 4.12	63.40 ± 8.06	1.88 ± 0.10
1	60	M	1.29 ± 0.16	0.72 ± 0.09	1.55 ± 0.19	1.57 ± 0.18		4.99 ± 0.55	16.69 ± 2.10	9.20 ± 1.99	27.00 ± 6.38	50.00 ± 8.99	1.99 ± 0.14
1	60	F	0.83 ± 0.10	0.55 ± 0.07	0.99 ± 0.17	0.94 ± 0.09	0.10 ± 0.02		9.49 ± 0.96	12.40 ± 3.81	21.80 ± 6.14	57.10 ± 14.91	1.84 ± 0.13
0	60	M	1.35 ± 0.21	0.74 ± 0.12	1.64 ± 0.25	1.62 ± 0.22		4.90 ± 0.72	17.23 ± 2.58	10.08 ± 3.61	29.17 ± 13.72	52.25 ± 9.96	2.06 ± 0.13
0	60	F	0.90 ± 0.09	0.56 ± 0.10	1.05 ± 0.26	0.94 ± 0.15	0.12 ± 0.03		10.33 ± 2.24	16.75 ± 6.82	23.25 ± 9.66	65.00 ± 14.57	1.90 ± 0.07
625	30	M	0.61 ± 0.08	0.34 ± 0.07	0.30 ± 0.12	0.79 ± 0.12		3.83 ± 0.36	8.36 ± 0.88	12.30 ± 2.64	29.30 ± 8.04	38.00 ± 7.60	1.71 ± 0.11
625	30	F	0.52 ± 0.08	0.28 ± 0.06	0.64 ± 0.09	0.65 ± 0.10	0.09 ± 0.03		7.92 ± 1.25	7.30 ± 2.63	28.80 ± 6.84	37.20 ± 8.01	1.68 ± 0.09
125	30	M	1.05 ± 0.09	0.74 ± 0.11	1.26 ± 0.09	1.25 ± 0.09		4.08 ± 0.24	15.72 ± 1.35	10.40 ± 3.78	33.20 ± 12.70	45.40 ± 6.82	1.88 ± 0.07
125	30	F	0.83 ± 0.08	0.51 ± 0.64	0.90 ± 0.09	0.86 ± 0.10	0.12 ± 0.02		9.44 ± 0.95	10.60 ± 2.72	23.80 ± 7.24	58.20 ± 9.00	1.78 ± 0.07
25	30	M	1.15 ± 0.12	0.79 ± 0.11	1.29 ± 0.09	1.28 ± 0.07		4.23 ± 0.45	14.88 ± 1.11	8.70 ± 1.77	26.00 ± 6.62	48.40 ± 11.61	1.88 ± 0.09
25	30	F	0.82 ± 0.07	0.54 ± 0.10	0.92 ± 0.09	0.91 ± 0.09	0.12 ± 0.02		9.75 ± 0.72	8.40 ± 3.86	21.90 ± 4.38	61.30 ± 6.62	1.79 ± 0.07
5	30	M	1.11 ± 0.09	0.79 ± 0.08	1.33 ± 0.15	1.35 ± 0.13		4.33 ± 0.27	16.08 ± 2.41	8.90 ± 1.45	20.10 ± 4.04	49.70 ± 8.72	1.97 ± 0.12
5	30	F	0.77 ± 0.10	0.52 ± 0.06	0.83 ± 0.09	0.82 ± 0.08	0.11 ± 0.01		8.83 ± 1.15	8.20 ± 2.15	16.50 ± 3.66	55.50 ± 5.87	1.76 ± 0.07
1	30	M	1.16 ± 0.12	0.72 ± 0.11	1.26 ± 0.08	1.24 ± 0.08		3.96 ± 0.41	14.18 ± 1.33	7.70 ± 1.89	19.40 ± 3.24	45.30 ± 7.66	1.92 ± 0.11
1	30	F	0.74 ± 0.05	0.51 ± 0.08	0.81 ± 0.05	0.81 ± 0.06	0.12 ± 0.02		8.64 ± 0.97	7.70 ± 2.58	14.80 ± 2.90	61.30 ± 11.56	1.79 ± 0.06
0	30	M	1.23 ± 0.26	0.77 ± 0.10	1.39 ± 0.18	1.38 ± 0.19		4.23 ± 0.47	15.24 ± 1.21	9.58 ± 5.93	24.17 ± 8.13	45.50 ± 6.57	1.91 ± 0.08
0	30	F	0.86 ± 0.17	0.53 ± 0.06	0.85 ± 0.07	0.85 ± 0.09	0.12 ± 0.02		9.92 ± 1.29	11.50 ± 3.06	16.00 ± 3.52	57.75 ± 6.21	1.81 ± 0.08

TABLE 10. (Continued)

Amitrole (ppm)	Days on Study	Sex	Heart (g)	Spleen (g)	Rt. Kidney (g)	Left Kidney (g)	Ovary (paired; g)	Testicle (paired; g)	Liver (g)	Pituitary (mg)	Thyroid (paired; mg)	Adrenal (paired; mg)	Brain (g)
50	90	M	1.29 ± 0.15	0.80 ± 0.11	1.49 ± 0.20	1.51 ± 0.19	--	5.15 ± 0.45	17.25 ± 2.70	12.44 ± 2.40	64.80 ± 15.34	48.10 ± 8.35	2.01 ± 0.08
50	90	F	0.89 ± 0.09	0.61 ± 0.09	1.01 ± 0.11	1.00 ± 0.11	0.10 ± 0.01	--	10.48 ± 0.76	17.30 ± 5.00	41.60 ± 9.77	61.10 ± 7.20	1.90 ± 0.05
50	60	M	1.27 ± 0.21	0.75 ± 0.08	1.58 ± 0.21	1.56 ± 0.20	--	5.02 ± 0.54	17.33 ± 2.79	10.40 ± 2.67	36.30 ± 11.27	44.80 ± 7.22	2.03 ± 0.15
50	60	F	0.92 ± 0.12	0.57 ± 0.06	1.01 ± 0.08	0.99 ± 0.11	0.10 ± 0.02	--	10.53 ± 1.27	14.60 ± 4.99	24.30 ± 6.18	67.20 ± 10.59	1.87 ± 0.05
50	30	M	0.89 ± 0.07	0.55 ± 0.06	1.09 ± 0.08	1.11 ± 0.08	--	4.10 ± 0.43	13.73 ± 2.30	7.80 ± 2.90	71.90 ± 12.31	35.60 ± 8.02	1.89 ± 0.07
50	30	F	0.72 ± 0.11	0.54 ± 0.11	0.80 ± 0.06	0.80 ± 0.06	0.13 ± 0.03	--	10.70 ± 1.85	7.60 ± 1.78	53.80 ± 9.20	52.80 ± 7.90	1.72 ± 0.04
PTU (ppm)													
125	90	M	0.71 ± 0.11	0.25 ± 0.05	0.77 ± 0.06	0.76 ± 0.07	--	4.47 ± 0.34	8.39 ± 0.89	8.11 ± 3.02	113.40 ± 44.90	28.67 ± 6.67	1.85 ± 0.13
125	90	F	0.54 ± 0.07	0.20 ± 0.03	0.60 ± 0.10	0.59 ± 0.11	0.07 ± 0.01	--	6.53 ± 1.19	9.90 ± 2.47	86.10 ± 31.56	26.60 ± 3.63	1.77 ± 0.11
125	60	M	0.73 ± 0.09	0.35 ± 0.07	0.94 ± 0.10	0.94 ± 0.11	--	4.84 ± 0.62	9.54 ± 1.31	7.90 ± 2.02	101.80 ± 33.68	28.70 ± 5.96	1.92 ± 0.13
125	60	F	0.62 ± 0.12	0.28 ± 0.05	0.69 ± 0.06	0.70 ± 0.09	0.09 ± 0.02	--	7.48 ± 0.97	8.90 ± 3.25	90.20 ± 26.64	34.20 ± 5.41	1.80 ± 0.11
125	30	M	0.60 ± C 08	0.31 ± 0.05	0.78 ± 0.10	0.77 ± 0.09	--	3.86 ± 0.18	8.01 ± 1.40	7.30 ± 3.86	55.60 ± 12.77	23.50 ± 2.07	1.80 ± 0.08
125	30	F	0.52 ± 0.07	0.25 ± 0.04	0.61 ± 0.07	0.59 ± 0.05	0.09 ± 0.02	--	6.92 ± 0.84	7.20 ± 2.70	62.20 ± 17.94	27.70 ± 5.72	1.71 ± 0.05
Control (ppm)													
0	90	M	1.43 ± 0.19	0.90 ± 0.10	1.62 ± 0.20	1.62 0.18	--	5.67 ± 0.55	17.33 ± 1.92	11.42 ± 3.09	30.42 ± 8.64	51.33 ± 6.30	2.08 ± 0.09
0	90	F	0.93 ± 0.09	0.55 ± 0.11	1.01 ± 0.11	0.97 0.10	0.10 ± 0.02	--	10.21 ± 1.22	14.83 ± 6.44	25.00 ± 4.45	66.08 ± 11.85	1.83 ± 0.10
0	60	M	1.35 ± 0.21	0.74 ± 0.12	1.64 ± 0.25	1.62 0.22	--	4.90 ± 0.72	17.23 ± 2.58	10.08 ± 3.63	29.17 ± 13.72	52.20 ± 9.96	2.06 ± 0.13
0	60	F	0.90 ± 0.09	0.56 ± 0.10	1.05 ± 0.26	0.94 0.15	0.12 ± 0.03	--	10.33 ± 2.24	16.75 ± 6.62	23.25 ± 9.66	65.00 ± 14.57	1.90 ± 0.07
0	30	M	1.23 ± 0.26	0.77 ± 0.12	1.39 ± 0.18	1.38 0.19	--	4.23 ± 0.47	15.24 ± 1.21	9.58 ± 5.93	24.17 ± 8.13	45.50 ± 6.57	1.91 ± 0.08
0	30	F	0.86 ± 0.17	0.53 ± 0.06	0.88 ± 0.07	0.85 0.09	0.12 ± 0.02	--	9.92 ± 1.29	11.50 ± 3.06	16.00 ± 3.52	57.75 ± 6.21	1.81 ± 0.08

TABLE 11. ORGAN WEIGHT:BODY WEIGHT RATIO

ETU (ppm)	Days on Study	Sex	Heart (g)	Spleen (g)	Rt. Kidney (g)	Ovary (paired, g)	Testicle (paired, g)
625	90	M	3.63×10^{-3}	1.34×10^{-3}	3.99×10^{-3}	--	2.07×10^{-2}
625	90	F	3.44×10^{-3}	1.41×10^{-3}	3.81×10^{-3}	4.60×10^{-4}	--
125	90	M	2.82×10^{-3}	1.70×10^{-3}	3.41×10^{-3}	--	1.06×10^{-2}
125	90	F	3.25×10^{-3}	1.93×10^{-3}	3.41×10^{-3}	3.43×10^{-4}	--
25	90	M	2.78×10^{-3}	1.66×10^{-3}	3.12×10^{-3}	--	1.05×10^{-2}
25	90	F	3.29×10^{-3}	1.79×10^{-3}	3.42×10^{-3}	3.31×10^{-4}	--
5	90	M	2.85×10^{-3}	1.78×10^{-3}	3.01×10^{-3}	--	1.07×10^{-2}
5	90	F	3.13×10^{-3}	1.85×10^{-3}	3.48×10^{-3}	3.71×10^{-4}	--
1	90	M	2.73×10^{-3}	1.56×10^{-3}	3.04×10^{-3}	--	1.01×10^{-2}
1	90	F	2.99×10^{-3}	1.84×10^{-3}	3.34×10^{-3}	3.70×10^{-4}	--
0	90	M	2.72×10^{-3}	1.71×10^{-3}	3.09×10^{-3}	--	1.08×10^{-2}
0	90	F	3.28×10^{-3}	1.95×10^{-3}	3.56×10^{-3}	3.56×10^{-4}	--
625	60	M	3.79×10^{-3}	1.53×10^{-3}	4.26×10^{-3}	--	2.06×10^{-2}
625	60	F	3.68×10^{-3}	1.35×10^{-3}	4.34×10^{-3}	5.25×10^{-4}	--
125	60	M	3.29×10^{-3}	1.81×10^{-3}	3.51×10^{-3}	--	1.10×10^{-2}
125	60	F	3.76×10^{-3}	2.13×10^{-3}	3.75×10^{-3}	5.21×10^{-4}	--
25	60	M	2.94×10^{-3}	1.70×10^{-3}	3.50×10^{-3}	--	1.14×10^{-2}
25	60	F	3.46×10^{-3}	2.09×10^{-3}	3.92×10^{-3}	3.80×10^{-4}	--
5	60	M	3.05×10^{-3}	1.79×10^{-3}	3.51×10^{-3}	--	1.88×10^{-2}
5	60	F	3.43×10^{-3}	2.02×10^{-3}	3.57×10^{-3}	3.85×10^{-4}	--
1	60	M	2.79×10^{-3}	1.56×10^{-3}	3.37×10^{-3}	--	1.09×10^{-2}
1	60	F	3.19×10^{-3}	2.12×10^{-3}	3.78×10^{-3}	3.99×10^{-4}	--
0	60	M	2.97×10^{-3}	1.63×10^{-3}	3.60×10^{-3}	--	1.08×10^{-2}
0	60	F	3.33×10^{-3}	2.07×10^{-3}	3.87×10^{-3}	4.40×10^{-4}	--
625	30	M	3.28×10^{-3}	1.80×10^{-3}	4.29×10^{-3}	--	2.06×10^{-2}
625	30	F	3.39×10^{-3}	1.81×10^{-3}	4.21×10^{-3}	5.79×10^{-4}	--
125	30	M	3.24×10^{-3}	2.48×10^{-3}	3.89×10^{-3}	--	1.26×10^{-2}
125	30	F	3.87×10^{-3}	2.39×10^{-3}	4.20×10^{-3}	5.44×10^{-4}	--
25	30	M	3.43×10^{-3}	2.35×10^{-3}	3.84×10^{-3}	--	1.26×10^{-2}
25	30	F	3.72×10^{-3}	2.44×10^{-3}	4.14×10^{-3}	5.33×10^{-4}	--
5	30	M	3.18×10^{-3}	2.27×10^{-3}	3.82×10^{-3}	--	1.24×10^{-2}
5	30	F	3.71×10^{-3}	2.51×10^{-3}	3.97×10^{-3}	5.38×10^{-4}	--
1	30	M	3.58×10^{-3}	2.24×10^{-3}	3.89×10^{-3}	--	1.23×10^{-2}
1	30	F	3.52×10^{-3}	2.41×10^{-3}	3.85×10^{-3}	5.82×10^{-4}	--
0	30	M	3.39×10^{-3}	2.12×10^{-3}	3.84×10^{-3}	--	1.17×10^{-2}
0	30	F	3.84×10^{-3}	2.38×10^{-3}	3.77×10^{-3}	5.40×10^{-4}	--

TABLE 11. (Continued)

ETU (ppm)	Days on Study	Sex	Liver (g)	Pituitary (g)	Thyroid (paired; g)	Adrenal (mg)	Brain (g)
625	90	M	3.59×10^{-2}	4.79×10^{-5}	22.91×10^{-5}	1.93×10^{-4}	8.53×10^{-3}
625	90	F	3.84×10^{-2}	7.82×10^{-5}	27.10×10^{-5}	2.54×10^{-4}	9.79×10^{-3}
125	90	M	3.91×10^{-2}	2.22×10^{-5}	7.66×10^{-5}	0.99×10^{-4}	4.21×10^{-3}
125	90	F	3.59×10^{-2}	4.71×10^{-5}	8.73×10^{-5}	1.92×10^{-4}	6.66×10^{-3}
25	90	M	3.46×10^{-2}	2.04×10^{-5}	5.80×10^{-5}	1.01×10^{-4}	4.04×10^{-3}
25	90	F	3.72×10^{-2}	5.01×10^{-5}	6.88×10^{-5}	2.03×10^{-4}	6.49×10^{-3}
5	90	M	3.37×10^{-2}	2.23×10^{-5}	5.21×10^{-5}	0.99×10^{-4}	4.16×10^{-3}
5	90	F	3.72×10^{-2}	4.92×10^{-5}	6.55×10^{-5}	2.20×10^{-4}	6.54×10^{-3}
1	90	M	3.54×10^{-2}	1.93×10^{-5}	5.41×10^{-5}	0.98×10^{-4}	4.02×10^{-3}
1	90	F	3.76×10^{-2}	4.94×10^{-5}	7.14×10^{-5}	2.29×10^{-4}	6.41×10^{-3}
0	90	M	3.31×10^{-2}	2.18×10^{-5}	5.80×10^{-5}	0.98×10^{-4}	3.96×10^{-3}
0	90	F	3.60×10^{-2}	5.23×10^{-5}	8.81×10^{-5}	2.33×10^{-4}	6.46×10^{-3}
625	60	M	3.91×10^{-2}	5.03×10^{-5}	5.03×10^{-5}	2.04×10^{-4}	8.66×10^{-3}
625	60	F	4.91×10^{-2}	5.90×10^{-5}	5.90×10^{-5}	2.66×10^{-4}	10.70×10^{-3}
125	60	M	4.17×10^{-2}	3.28×10^{-5}	3.28×10^{-5}	1.34×10^{-4}	4.78×10^{-3}
125	60	F	4.03×10^{-2}	4.81×10^{-5}	4.81×10^{-5}	2.51×10^{-4}	7.35×10^{-3}
25	60	M	4.44×10^{-2}	2.22×10^{-5}	2.22×10^{-5}	1.03×10^{-4}	4.35×10^{-3}
25	60	F	4.05×10^{-2}	3.45×10^{-5}	3.45×10^{-5}	2.33×10^{-4}	7.38×10^{-3}
5	60	M	3.80×10^{-2}	1.84×10^{-5}	1.84×10^{-5}	1.02×10^{-4}	4.16×10^{-3}
5	60	F	3.93×10^{-2}	4.18×10^{-5}	4.18×10^{-5}	2.37×10^{-4}	7.03×10^{-3}
1	60	M	3.63×10^{-2}	2.00×10^{-5}	2.00×10^{-5}	1.09×10^{-4}	4.32×10^{-3}
1	60	F	3.64×10^{-2}	4.75×10^{-5}	4.75×10^{-5}	2.19×10^{-4}	7.04×10^{-3}
0	60	M	3.79×10^{-2}	2.22×10^{-5}	2.22×10^{-5}	1.15×10^{-4}	4.54×10^{-3}
0	60	F	3.82×10^{-2}	6.19×10^{-5}	4.19×10^{-5}	2.40×10^{-4}	7.04×10^{-3}
625	30	M	4.50×10^{-2}	6.82×10^{-5}	15.82×10^{-5}	2.05×10^{-4}	9.19×10^{-3}
625	30	F	5.21×10^{-2}	4.80×10^{-5}	18.90×10^{-5}	2.45×10^{-4}	11.10×10^{-3}
125	30	M	4.84×10^{-2}	3.20×10^{-5}	10.20×10^{-5}	1.40×10^{-4}	5.79×10^{-3}
125	30	F	4.43×10^{-2}	4.97×10^{-5}	11.20×10^{-5}	2.73×10^{-4}	8.34×10^{-3}
25	30	M	4.42×10^{-2}	2.58×10^{-5}	7.72×10^{-5}	1.44×10^{-4}	5.59×10^{-3}
25	30	F	4.40×10^{-2}	3.79×10^{-5}	9.89×10^{-5}	2.70×10^{-4}	8.09×10^{-3}
5	30	M	4.62×10^{-2}	2.55×10^{-5}	5.77×10^{-5}	1.43×10^{-4}	5.65×10^{-3}
5	30	F	4.24×10^{-2}	3.94×10^{-5}	7.93×10^{-5}	2.67×10^{-4}	8.46×10^{-3}
1	30	M	4.40×10^{-2}	2.39×10^{-5}	6.02×10^{-5}	1.40×10^{-4}	5.96×10^{-3}
1	30	F	4.02×10^{-2}	3.67×10^{-5}	7.06×10^{-5}	2.92×10^{-4}	8.53×10^{-3}
0	30	M	4.22×10^{-2}	2.65×10^{-5}	6.20×10^{-5}	1.26×10^{-4}	5.30×10^{-3}
0	30	F	4.43×10^{-2}	5.13×10^{-5}	7.14×10^{-5}	2.58×10^{-4}	8.11×10^{-3}

TABLE 11. (Continued)

Amitrole (ppm)	Days on Study	Sex	Heart (g)	Spleen (g)	Right Kidney (g)	Ovary (paired) (g)	Testicle (paired) (g)
50	90	M	2.66×10^{-3}	1.65×10^{-3}	3.08×10^{-3}	-	1.07×10^{-2}
50	90	F	3.04×10^{-3}	2.08×10^{-3}	3.47×10^{-3}	3.42×10^{-4}	
50	60	M	2.83×10^{-3}	1.67×10^{-3}	3.52×10^{-3}	-	1.12×10^{-2}
50	60	F	3.45×10^{-3}	2.15×10^{-3}	3.77×10^{-3}	3.86×10^{-4}	-
50	30	M	2.83×10^{-3}	1.74×10^{-3}	3.49×10^{-3}	-	1.31×10^{-2}
50	30	F	3.32×10^{-3}	2.48×10^{-3}	3.71×10^{-3}	6.20×10^{-4}	
PTU (ppm)							
125	90	M	2.66×10^{-3}	0.93×10^{-3}	2.89×10^{-3}	-	1.69×10^{-2}
125	90	F	2.82×10^{-3}	1.03×10^{-3}	3.16×10^{-3}	3.08×10^{-4}	-
125	60	M	2.58×10^{-3}	1.24×10^{-3}	3.30×10^{-3}	-	1.71×10^{-2}
125	60	F	3.05×10^{-3}	1.40×10^{-3}	3.38×10^{-3}	4.48×10^{-4}	-
125	30	M	2.76×10^{-3}	1.43×10^{-3}	3.58×10^{-3}	-	1.77×10^{-2}
125	30	F	3.10×10^{-3}	1.45×10^{-3}	3.60×10^{-3}	5.39×10^{-4}	-
Control							
0	90	M	2.72×10^{-3}	1.71×10^{-3}	3.09×10^{-3}	-	1.08×10^{-2}
0	90	F	3.26×10^{-3}	1.95×10^{-3}	3.56×10^{-3}	3.56×10^{-4}	-
0	60	M	2.58×10^{-3}	1.24×10^{-3}	3.30×10^{-3}	-	1.71×10^{-2}
0	60	F	3.05×10^{-3}	1.40×10^{-3}	3.38×10^{-3}	4.48×10^{-4}	-
0	30	M	3.39×10^{-3}	2.12×10^{-3}	3.84×10^{-3}	-	1.31×10^{-2}
0	30	F	3.84×10^{-3}	2.38×10^{-3}	3.77×10^{-3}	6.20×10^{-4}	-

TABLE 11. (Continued)

Amitrole (ppm)	Days on Study	Sex	Liver (g)	Pituitary (g)	Thyroid (paired) (g)	Adrenal (mg)
50	90	M	3.56×10^{-2}	2.56×10^{-5}	13.43×10^{-5}	0.99×10^{-4}
50	90	F	3.59×10^{-2}	5.92×10^{-5}	14.23×10^{-5}	2.09×10^{-4}
50	60	M	3.88×10^{-2}	2.33×10^{-5}	8.12×10^{-5}	1.00×10^{-4}
50	60	F	3.95×10^{-2}	5.48×10^{-5}	9.11×10^{-5}	2.52×10^{-4}
50	30	M	4.38×10^{-2}	2.49×10^{-5}	22.91×10^{-5}	1.14×10^{-5}
50	30	F	4.95×10^{-2}	3.52×10^{-5}	22.80×10^{-5}	2.44×10^{-5}
PTU (ppm)						
125	90	M	3.17×10^{-2}	3.02×10^{-5}	42.90×10^{-5}	1.08×10^{-4}
125	90	F	3.42×10^{-2}	5.19×10^{-5}	45.20×10^{-5}	1.40×10^{-4}
125	60	M	3.37×10^{-2}	2.79×10^{-5}	35.90×10^{-5}	1.01×10^{-4}
125	60	F	3.68×10^{-5}	4.38×10^{-5}	44.43×10^{-5}	1.68×10^{-4}
125	30	M	3.67×10^{-5}	3.35×10^{-5}	25.53×10^{-5}	1.08×10^{-4}
125	30	F	4.10×10^{-5}	4.27×10^{-5}	36.81×10^{-5}	1.64×10^{-4}
Control (ppm)						
0	90	M	3.31×10^{-2}	2.18×10^{-2}	5.80×10^{-5}	0.98×10^{-4}
0	90	F	3.60×10^{-2}	5.23×10^{-2}	8.81×10^{-5}	2.33×10^{-4}
0	60	M	3.79×10^{-2}	2.22×10^{-2}	6.42×10^{-5}	1.15×10^{-4}
0	60	F	3.82×10^{-2}	6.19×10^{-2}	8.59×10^{-5}	2.40×10^{-4}
0	30	M	4.22×10^{-2}	2.65×10^{-2}	6.70×10^{-5}	1.26×10^{-4}
0	30	F	4.43×10^{-2}	5.13×10^{-2}	7.14×10^{-5}	2.58×10^{-4}

TABLE 12. ORGAN WEIGHT: BRAIN WEIGHT RATIO

ETU (ppm)	Days on Study	Sex	Ovary (paired; g)	Testicle (paired; g)	Pituitary (mg)	Thyroid (paired; g)	Adrenal (paired; mg)
625	90	M		2.43	5.61×10^{-3}	2.68×10^{-2}	2.26×10^{-2}
625	90	F	4.70×10^{-2}		7.99×10^{-3}	2.77×10^{-2}	2.60×10^{-2}
125	90	M		2.52	5.27×10^{-3}	1.82×10^{-2}	2.35×10^{-2}
125	90	F	5.15×10^{-2}		7.08×10^{-3}	1.31×10^{-2}	2.88×10^{-2}
25	90	M		2.59	5.04×10^{-3}	1.43×10^{-2}	2.49×10^{-2}
25	90	F	5.10×10^{-2}		7.72×10^{-3}	1.06×10^{-2}	3.13×10^{-2}
5	90	M		2.58	5.36×10^{-3}	1.25×10^{-2}	2.38×10^{-2}
5	90	F	5.67×10^{-2}		7.52×10^{-3}	1.00×10^{-2}	3.37×10^{-2}
1	90	M		2.50	4.79×10^{-3}	1.35×10^{-2}	2.44×10^{-2}
1	90	F	5.51×10^{-2}		7.71×10^{-3}	1.11×10^{-2}	3.51×10^{-2}
0	90	M		2.73	5.50×10^{-3}	1.47×10^{-2}	2.47×10^{-2}
0	90	F	5.28×10^{-2}		8.09×10^{-3}	1.36×10^{-2}	3.61×10^{-2}
625	60	M		1.81	5.81×10^{-3}	3.28×10^{-2}	2.36×10^{-2}
625	60	F	4.92×10^{-2}		5.54×10^{-3}	2.31×10^{-2}	2.49×10^{-2}
125	60	M		2.30	6.85×10^{-3}	1.85×10^{-2}	2.79×10^{-2}
125	60	F	7.08×10^{-2}		6.54×10^{-3}	1.48×10^{-2}	3.41×10^{-2}
25	60	M		2.62	5.09×10^{-3}	1.69×10^{-2}	2.38×10^{-2}
25	60	F	5.15×10^{-2}		4.68×10^{-3}	1.22×10^{-2}	3.16×10^{-2}
5	60	M		2.58	4.41×10^{-3}	1.05×10^{-2}	2.44×10^{-2}
5	60	F	5.48×10^{-2}		5.95×10^{-3}	0.96×10^{-2}	3.37×10^{-2}
1	60	M		2.51	4.63×10^{-3}	1.36×10^{-2}	2.52×10^{-2}
1	60	F	5.66×10^{-2}		6.75×10^{-3}	1.19×10^{-2}	3.11×10^{-2}
0	60	M		2.38	4.89×10^{-3}	1.41×10^{-2}	2.53×10^{-2}
0	60	F	6.25×10^{-2}		8.80×10^{-3}	1.22×10^{-2}	3.44×10^{-2}
625	30	M		2.25	7.21×10^{-3}	1.72×10^{-2}	2.23×10^{-2}
625	30	F	5.23×10^{-2}		4.34×10^{-3}	1.71×10^{-2}	2.21×10^{-2}
125	30	M		2.17	5.53×10^{-3}	1.37×10^{-2}	2.42×10^{-2}
125	30	F	6.52×10^{-2}		5.96×10^{-3}	1.34×10^{-2}	3.27×10^{-2}
25	30	M		2.25	4.63×10^{-3}	1.38×10^{-2}	2.57×10^{-2}
25	30	F	6.58×10^{-2}		4.68×10^{-3}	1.22×10^{-2}	3.42×10^{-2}
5	30	M		2.20	4.52×10^{-3}	1.02×10^{-2}	2.52×10^{-2}
5	30	F	6.36×10^{-2}		4.66×10^{-3}	0.94×10^{-2}	3.15×10^{-2}
1	30	M		2.06	4.01×10^{-3}	1.01×10^{-2}	2.36×10^{-2}
1	30	F	6.82×10^{-2}		4.31×10^{-3}	0.83×10^{-2}	3.43×10^{-2}
0	30	M		2.21	5.01×10^{-3}	1.26×10^{-2}	2.38×10^{-2}
0	30	F	6.69×10^{-2}		6.36×10^{-3}	0.88×10^{-2}	3.19×10^{-2}

TABLE 12. (Continued)

(ppm)	Days on Study	Sex	Heart (g)	Spleen (g)	Rt. Kidney (g)	Liver (g)
625	90	M	4.25×10^{-1}	1.57×10^{-1}	4.67×10^{-1}	4.20
625	90	F	3.51×10^{-1}	1.44×10^{-1}	3.89×10^{-1}	3.92
125	90	F	6.70×10^{-1}	4.04×10^{-1}	8.22×10^{-1}	9.30
125	90	F	4.88×10^{-1}	2.97×10^{-1}	5.12×10^{-1}	5.40
25	90	M	6.87×10^{-1}	4.10×10^{-1}	7.32×10^{-1}	8.56
25	90	F	5.07×10^{-1}	2.76×10^{-1}	5.27×10^{-1}	5.71
5	90	M	6.85×10^{-1}	4.29×10^{-1}	7.25×10^{-1}	8.10
5	90	F	4.78×10^{-1}	2.83×10^{-1}	5.32×10^{-1}	5.68
1	90	M	6.78×10^{-1}	3.89×10^{-1}	7.57×10^{-1}	8.80
1	90	F	4.66×10^{-1}	2.88×10^{-1}	5.21×10^{-1}	5.86
0	90	M	6.88×10^{-1}	4.32×10^{-1}	7.81×10^{-1}	8.35
0	90	F	5.08×10^{-1}	3.02×10^{-1}	5.51×10^{-1}	5.57
625	60	M	4.38×10^{-1}	1.76×10^{-1}	4.92×10^{-1}	4.56
625	60	F	3.45×10^{-1}	1.26×10^{-1}	4.07×10^{-1}	4.60
125	60	M	6.87×10^{-1}	3.77×10^{-1}	7.33×10^{-1}	8.71
125	60	F	5.11×10^{-1}	2.89×10^{-1}	5.09×10^{-1}	5.47
25	60	M	6.76×10^{-1}	3.91×10^{-1}	8.05×10^{-1}	10.20
25	60	F	4.69×10^{-1}	2.83×10^{-1}	5.31×10^{-1}	5.48
5	60	M	7.32×10^{-1}	4.30×10^{-1}	8.44×10^{-1}	9.14
5	60	F	4.88×10^{-1}	2.87×10^{-1}	5.08×10^{-1}	5.60
1	60	M	6.47×10^{-1}	3.61×10^{-1}	7.81×10^{-1}	8.40
1	60	F	4.54×10^{-1}	3.01×10^{-1}	5.37×10^{-1}	5.17
0	60	M	6.54×10^{-1}	3.59×10^{-1}	7.93×10^{-1}	8.35
0	60	F	4.73×10^{-1}	2.94×10^{-1}	5.50×10^{-1}	5.43
625	30	M	3.57×10^{-1}	1.96×10^{-1}	4.67×10^{-1}	4.90
625	30	F	3.06×10^{-1}	1.64×10^{-1}	3.81×10^{-1}	4.71
125	30	M	5.59×10^{-1}	3.94×10^{-1}	6.72×10^{-1}	8.37
125	30	F	4.65×10^{-1}	2.87×10^{-1}	5.03×10^{-1}	5.31
25	30	M	6.14×10^{-1}	4.21×10^{-1}	6.87×10^{-1}	7.91
25	30	F	4.59×10^{-1}	3.01×10^{-1}	5.11×10^{-1}	5.44
5	30	M	5.02×10^{-1}	4.02×10^{-1}	6.75×10^{-1}	8.17
5	30	F	4.39×10^{-1}	2.97×10^{-1}	4.70×10^{-1}	5.02
1	30	M	6.01×10^{-1}	3.76×10^{-1}	6.53×10^{-1}	7.38
1	30	F	4.13×10^{-1}	2.82×10^{-1}	4.51×10^{-1}	4.83
0	30	M	6.41×10^{-1}	4.00×10^{-1}	7.25×10^{-1}	7.97
0	30	F	4.76×10^{-1}	2.95×10^{-1}	4.67×10^{-1}	5.49

TABLE 12. (Continued)

Amitrole (ppm)	Days on Study	Sex	Heart (g)	Spleen (g)	Rt. Kidney (g)	Liver (g)
50	90	M	6.44×10^{-1}	3.98×10^{-1}	7.45×10^{-1}	8.59
50	90	F	4.68×10^{-1}	3.20×10^{-1}	5.35×10^{-1}	5.53
50	60	M	6.23×10^{-1}	3.67×10^{-1}	7.74×10^{-1}	8.52
50	60	F	4.92×10^{-1}	3.06×10^{-1}	5.35×10^{-1}	5.62
50	30	M	4.70×10^{-1}	2.89×10^{-1}	5.79×10^{-1}	7.26
50	30	F	4.17×10^{-1}	3.12×10^{-1}	4.66×10^{-1}	6.22
PTU (ppm)						
125	90	M	3.82×10^{-1}	1.33×10^{-1}	4.14×10^{-1}	4.54
125	90	F	3.03×10^{-1}	1.10×10^{-1}	3.40×10^{-1}	3.68
125	60	M	3.81×10^{-1}	1.83×10^{-1}	4.88×10^{-1}	4.97
125	60	F	3.44×10^{-1}	1.58×10^{-1}	3.82×10^{-1}	4.15
125	30	M	3.34×10^{-1}	1.73×10^{-1}	4.34×10^{-1}	4.45
125	30	F	3.06×10^{-1}	1.43×10^{-1}	3.55×10^{-1}	4.04
Control (ppm)						
0	90	M	6.68×10^{-1}	4.32×10^{-1}	7.81×10^{-1}	8.35
0	90	F	5.05×10^{-1}	3.02×10^{-1}	5.51×10^{-1}	5.57
0	60	M	6.54×10^{-1}	3.59×10^{-1}	7.93×10^{-1}	8.35
0	60	F	4.73×10^{-1}	2.94×10^{-1}	5.50×10^{-1}	5.43
0	30	M	6.41×10^{-1}	4.00×10^{-1}	7.25×10^{-1}	7.97
0	30	F	4.76×10^{-1}	2.95×10^{-1}	4.76×10^{-1}	5.49

TABLE 12. (Continued)

Amitrole (ppm)	Days on Study	Sex	Ovary (paired; g)	Testicle (paired; g)	Pituitary (mg)	Thyroid (paired; g)	Adrenal (paired; mg)
50	90	M	--	2.58	6.20×10^{-3}	3.23×10^{-2}	2.40×10^{-2}
50	90	F	5.28×10^{-2}	--	9.13×10^{-3}	2.20×10^{-2}	3.22×10^{-2}
50	60	M	--	2.47	5.12×10^{-3}	1.79×10^{-2}	2.20×10^{-2}
50	60	F	5.50×10^{-2}	--	7.79×10^{-3}	1.30×10^{-2}	3.59×10^{-2}
50	30	M	--	2.17	4.13×10^{-3}	3.80×10^{-2}	1.88×10^{-2}
50	30	F	7.79×10^{-2}	--	4.42×10^{-3}	3.13×10^{-2}	3.67×10^{-2}
PTU (ppm)							
125	90	M	--	2.42	4.39×10^{-3}	6.14×10^{-2}	1.55×10^{-2}
125	90	F	4.17×10^{-2}	--	5.58×10^{-3}	4.86×10^{-2}	1.50×10^{-2}
125	60	M	--	2.52	4.11×10^{-3}	5.30×10^{-2}	1.49×10^{-2}
125	60	F	5.06×10^{-2}	--	4.94×10^{-3}	5.01×10^{-2}	1.90×10^{-2}
125	30	M	--	2.14	4.05×10^{-3}	3.09×10^{-2}	1.30×10^{-2}
125	30	F	5.32×10^{-2}	--	4.21×10^{-3}	3.64×10^{-2}	1.62×10^{-2}
Control (ppm)							
0	90	M	--	2.73	5.50×10^{-3}	1.47×10^{-2}	2.47×10^{-2}
0	90	F	5.51×10^{-2}	--	8.09×10^{-3}	1.36×10^{-2}	3.61×10^{-2}
0	60	M	--	2.38	4.89×10^{-3}	1.41×10^{-2}	2.53×10^{-2}
0	60	F	6.21×10^{-2}	--	8.80×10^{-3}	1.22×10^{-2}	3.41×10^{-2}
0	30	M	--	2.21	5.01×10^{-3}	1.26×10^{-2}	2.38×10^{-2}
0	30	F	6.69×10^{-2}	--	6.36×10^{-3}	0.89×10^{-2}	3.19×10^{-2}

TABLE 13. ABNORMAL CHANGES OBSERVED FOR LIVER, SKIN AND THYROID*

Tissue Change	Days on Study	Sex	PTU 125	Amitrole 50	ETU 625	ETU 125	ETU 25	ETU 5	ETU 1	Control** 0
Enlarged Thyroids; Red	30	M	10	10	10	8	0	0	0	0
	30	F	10	10	5	2	0	0	0	0
Thyroids Normal Size but Red	30	M	0	0	0	0	3	0	0	0
	30	F	0	0	0	0	2	0	0	0
Centrilobular Congestion; liver	30	M	0	0	0	0	0	0	0	0
	30	F	0	0	0	0	0	0	0	0
Alopecia	30	M	0	0	8	0	0	0	0	0
	30	F	0	0	4	0	0	0	0	0
Small Adrenals	30	M	0	8	0	0	0	0	0	0
	30	F	0	2	0	0	0	0	0	0
Enlarged Thyroids; Red	60	M	10	5	5***	6	1	2	0	0
	60	F	10	2	9	1	0	2	0	0
Centrilobular Congestion; liver	60	M	0	2	0	2	3	2	0	1
	60	F	0	0	0	0	0	0	0	0
Alopecia	60	M	0	0	5	0	0	0	0	0
	60	F	0	0	9	0	0	0	0	0
Enlarged Thyroids; Red	90	M	10	10	8****	10	0	0	0	0
	90	F	10	5	6	6	0	0	0	0
Alopecia	90	M	0	0	6	0	0	0	0	0
	90	F	0	0	4	0	0	0	0	0
Centrilobular Congestion; liver	90	M	0	3	0	9	1	3	6	1
	90	F	0	2	0	0	1	0	2	0
Small Adrenals	90	M	8	0	0	0	0	0	0	0
	90	F	9	0	0	0	0	0	0	0
Adenocarcinoma of Salivary Gland	90	M	0	0	0	0	0	0	0	0
	90	F	1	0	0	0	0	0	0	0

*Presented as the number of animals with the indicated tissue change, out of the 10 animals evaluated.

**Twelve male and eleven female control rats were evaluated from 30 day group. Twelve male and twelve female rats were evaluated from the 60 and 90 day control groups.

***Five male rats and one female rat from the 625 ppm 60 day group died prior to the end of the study. Therefore, the values for this one group are based on the evaluation of five male and one female rat.

****Two female rats died prior to the end of the 90 days. Therefore, the values for females on this one group are based on eight rats.

TABLE 14. GRADING OF DEGREE OF HYPERPLASIA FROM MICROSCOPIC APPEARANCE OF THE THYROID GLAND

Grade of Hyperplasia	Description of Change in Morphology
0	Completely normal appearing gland.
>1	Very slightly altered lining cells and scalloping of colloid.
1	Distinct hyperplasia or hypertrophy of lining cells and a moderate reduction of colloid.
>2	Hyperplastic change of lining cells and folding of follicular wall with a moderate reduction of colloid.
2	Moderate hyperplasia of lining cells, increase in apparent number of micro-follicular follicles reducing apparent colloid to less than fifty percent of normal.
>3	More extensive microfollicular pattern but still retaining approximately twenty-five percent colloid.
3	Marked hyperplasia of lining cells with virtually all microfollicular follicles and nearly complete absence of colloid.

TABLE 15. THYROID HYPERPLASIA OBSERVED IN ETU TEST ANIMALS

Degree of Hyperplasia	Days on Study	PTU 125	Amitrole 50	ETU 625	ETU 125	ETU 25	ETU 5	ETU 1	ETU 0
0	30	0	0	0	0	0	1	0	4
>1	30	0	0	0	0	9	6	7	9
1	30	0	0	2	18	11	13	13	10
>2	30	0	0	4	1	0	0	0	0
2	30	8	0	12	1	0	0	0	0
>3	30	3	5	2	0	0	0	0	0
3	30	9	15	0	0	0	0	0	0
0	60	0	0	0	1	7	4	1	5
>1	60	0	4	0	3	2	7	9	10
1	60	0	5	2	7	0	9	10	9
>2	60	0	8	2	5	7	0	0	0
2	60	0	3	10	2	4	0	0	0
>3	60	17	0	0	0	0	0	0	0
3	60	3	0	0	2	0	0	0	0
0	90	0	0	0	1	3	6	6	12
>1	90	0	5	0	0	8	8	6	9
1	90	0	14	1	14	9	6	8	3
>2	90	0	0	1	3	0	0	0	0
2	90	1	1	12	1	0	0	0	0
>3	90	10	0	3	0	0	0	0	0
3	90	9	0	1	1	0	0	0	0

TABLE 16. CHANGES IN THYROID MORPHOLOGY IN RATS WHICH INGESTED 625 PPM ETU FOR NINETY DAYS*

Rat Number	Sex	Solid Adenomas	Cystic Adenomas	Adenomatous Changes	Cyst-like Follicles
560	M	1	0	0	0
561	M	1	2	2	0
562	M	1	1	0	0
563	M	0	0	1	0
564	M	1	0	2	0
565	M	0	0	0	1
566	M	0	0	0	0
567	M	2	0	0	0
568	M	0	0	0	1
569	M	0	0	0	0
570	F	Died			
571	F	Died			
572	F	2	0	1	0
573	F	0	0	0	1
574	F	0	0	0	0
575	F	0	0	1	0
576	F	0	0	0	0
577	F	0	0	0	1
578	F	1	0	0	0
579	F	0	0	0	0

*Thyroids examined by serial sectioning.

TECHNICAL REPORT DATA

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4. TITLE AND SUBTITLE DIETARY SUBACTURE TOXICITY OF ETHYLENE THIOUREA IN THE LABORATORY RAT		5. REPORT DATE May 1977
		6. PERFORMING ORGANIZATION CODE
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16. ABSTRACT

Ethylene thiourea (ETU) was fed to groups of rats at 0, 1, 5, 25, 125 or 625 ppm for up to 90 days. Other groups of rats received either propulthiouracil (PTU; 125 ppm) or amitrole (50 ppm) in their diets as positive controls. Only those rats which received ETU at 125 or 625 ppm and those ingesting PTU or amitrole demonstrated a measurable toxic response. This toxicity was reflected as an alteration in thyroid function and a significant change in thyroid morphology. Ingestion of 625 ppm ETU or 125 ppm PTU resulted in very substantial decreases in serum triiodothyronine (T-3) and thyroxine (T-4). Marked increases in serum thryroid stimulating hormone (TSH) levels were found in the 625 and 125 ppm ETU rats, the 125 PTU rats and the rats receiving amitrole, at each time point this hormone was measured. A decrease in iodide uptake by the thyroid was also found in the rats ingesting 625 ppm ETU. While a statistically significant increase in serum T-4 and degree of thyroid hyperplasia was observed for the rats ingesting 25 ppm ETU for 60 days, normal thyroid hormone levels and thyroid morphology was found in the rats on 25 ppm ETU for either 30 or 90 days. Based on biochemical and microscopic changes examined, the no-effect level for dietary ETU in this 90-day study is considered to be 25 ppm, equivalent to an average intake ranging from 19.5 mg/kg body weight at Week 1 to 12.5 mg/kg body weight at Week 12.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
thioureas toxicity toxic tolerances rats	ethylene thiourea ETU	06, T
18. DISTRIBUTION STATEMENT RELEASE TO PUBLIC	19. SECURITY CLASS (This Report) UNCLASSIFIED	21. NO. OF PAGES 47
	20. SECURITY CLASS (This page) UNCLASSIFIED	22. PRICE

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