

Final Report-100

*TherImmune  
Research  
Corporation*

**Assessment of Pubertal Development  
and Thyroid Function in  
Juvenile Male Rats**

**THERIMMUNE**  
Research Corporation



Sponsor:

Environmental Protection Agency  
RTP: MD-71 NHEERL  
Research Triangle Park, NC 27711

**FINAL REPORT**

Study Title:

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

Test Articles:

Flutamide, Methyl Testosterone, Propylthiouracil, Ketoconazole, Pimozide, Dibutylphthalate

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Study Completion Date:

June 29, 2000

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TherImmune Study Number:

1143-100

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**COMPLIANCE STATEMENT**

**Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats**

This study was conducted in compliance with the EPA FIFRA Good Laboratory Practice Standards as set forth in Title 40 of the U.S. Code of Federal Regulations Part 160, issued October 16, 1989, and any applicable amendments. All deviations from the protocol, and SOPs are listed in the raw data. There were no deviations from the aforementioned regulations or protocol which affected the quality or integrity of the study or the interpretation of the results in the report.

Study Director:

Meredith S. Rocca 6.19.00

Meredith S. Rocca, Ph.D./Date

**QUALITY ASSURANCE STATEMENT**

**Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats**

Quality Assurance inspections of the study and review of the final report of the above referenced project were conducted according to the standard operating procedures of the Quality Assurance Unit and according to the requirements of the EPA FIFRA Good Laboratory Practice Regulations as set forth in Title 40 CFR Part 160. Findings from the inspections and final report review were reported to management and to the study director on the following dates:

<u>Inspections/Review</u>	<u>Findings Reported</u>	<u>Inspector/Reviewer</u>
<b>Protocol</b>		
11/18,19,29,30/99	11/30/99	C. Matos-Rosa
12/01,02/99	12/02/99	J. Carignan
<b>Phase Inspection</b>		
01/14/00	01/14/00	C. Matos-Rosa
<b>Final Report and Data Audit</b>		
04/29 & 05/01-05/00	05/05/00	H. Shaffi
<b>Post-Audit</b>		
06/22,23,26/00	06/26/00	H. Shaffi

Quality Assurance Unit:

H. Shaffi 6/23/00  
 H. Shaffi /Date



**STUDY IDENTIFICATION**

**Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats**

TherImmune Study Number: 1143-100

Test Articles: Flutamide, Methyl Testosterone,  
Propylthiouracil, Ketoconazole, Pimozide, and  
Dibutylphthalate

Sponsor: Environmental Protection Agency

Sponsor's Representative: Kenneth H. Elstein, Project Officer  
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Study Timetable

Study Initiation:	December 14, 1999
Experimental Start Date:	January 8, 2000
Experimental Termination:	February 8, 2000

**STUDY PERSONNEL**

**Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats**

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Director of Quality Assurance: James Carignan, B.S.

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Laboratory Head Technician: Kelly Musselman, B.S.

SUMMARY

The purpose of this study was to quantify the effects of endocrine disrupting chemicals on pubertal development and thyroid function in the intact juvenile male rat. An additional goal was to validate this study design and examine the variation between Sprague Dawley (SD) and Long Evans (LE) rats. Males were treated from postnatal day (PND) 23 through 53 or 54, by oral gavage, with 2.5 mL/kg/day corn oil, 50 mg/kg/day flutamide, 80 mg/kg/day methyl testosterone, 240 mg/kg/day propylthiouracil (PTU), 100 mg/kg/day ketoconazole, 30 mg/kg/day pimozone, or 1000 mg/kg/day dibutylphthalate (DBP). During treatment males were observed for signs of toxicity, weighed, and examined for preputial separation daily. Serum was collected for T4 and TSH analysis at termination. A complete necropsy was performed and the following organs were weighed: testes, epididymides, ventral prostate, seminal vesicle, levator ani plus bulbocavernosus muscles, liver, pituitary, kidneys, and adrenals. The thyroid, epididymides and testes were preserved and examined histologically. The data were analyzed by multivariate analysis of covariance (MANCOVA), using body weight at weaning as a covariate. Results are summarized in Figure 1.

Figure 1: Changes in Selected Endpoints Compared to Controls

Test Article	Body Weight	Age at PPS	Histopathology	TSH	T4
Flutamide	↓LE	↓	✓		
Methyl Testosterone	↓	↓	✓		
Propylthiouracil	↓	↑	✓	↑	↓
Ketoconazole	↓	↑			
Pimozone	↓	↓	✓LE		
Dibutylphthalate	↓	↑LE	✓LE	↓LE	↓LE

KEY: ↓ = significantly decreased compared to control mean      LE = Long Evans only  
 ↑ = significantly increased compared to control mean      SD = Sprague Dawley only  
 ✓ = affected histopathology      PPS = preputial separation

This study design accurately identified endocrine disrupting compounds which were androgenic, anti-androgenic, inhibitors of steroid and thyroid hormone synthesis, or a dopamine antagonist and quantified their effect on the juvenile male rat. The inter-strain variation in response to treatment was minimal, except for DBP, which had a more pronounced effect in LE males. As evidenced by changes observed in body weights, preputial separation, organ weights, gross and histopathology and TSH and T4 levels, dosing male juvenile rats of the Sprague Dawley or Long-Evans strain from postnatal day 22 through 53 or 54 is a good model for identifying endocrine disrupting compounds.

**INTRODUCTION**

This study was designed to quantify the effects of endocrine disrupting chemicals on pubertal development and thyroid function in the intact juvenile male rat. The larger goal was to provide preliminary validation of the protocol for future EPA studies, and to assess intra-laboratory and inter-strain variation. Dosing began on January 8, 2000. The last terminal necropsies were performed on February 8, 2000.

**TEST AND CONTROL ARTICLES**

The control article, corn oil, and test articles, flutamide, methyl testosterone, propylthiouracil, ketoconazole, pimoziide, and dibutylphthalate, were received and stored as described below.

Test Article	Lot No.	Date Received	Received From	Purity	Storage Conditions
Corn Oil	107H1649	1/5/00	Sigma-Aldrich, Inc. St. Louis, Missouri	100%	Room Temperature
Flutamide	39H1278	1/5/00	Sigma-Aldrich, Inc. St. Louis, Missouri	100%	Room Temperature
Methyl Testosterone	41H0140	12/14/99	Sigma-Aldrich, Inc. St. Louis, Missouri	99.6%	Room Temperature
Propylthiouracil	099H2509	1/5/00	Sigma-Aldrich, Inc. St. Louis, Missouri	99%	Room Temperature
Ketoconazole	079H4087	1/5/00	Sigma-Aldrich, Inc. St. Louis, Missouri	98%	Refrigerate 2-8°C
	079H4087	1/6/00	Sigma-Aldrich, Inc. St. Louis, Missouri	99%	Refrigerate 2-8°C
	0078353	1/7/00	ICN Biomedicals Aurora, Ohio	99%	Room temperature, protected from light
Pimoziide	019H0578	1/5/00	Sigma-Aldrich, Inc. St. Louis, Missouri	100%	Refrigerate 2-8°C
Dibutylphthalate	03912ES	12/8/99	Aldrich Chemical	99+ %	Room Temperature

Reserve samples were taken as follows: 100 mg each of flutamide, methyl testosterone, propylthiouracil and ketoconazole; and 1 g each of pimoziide and dibutylphthalate. Ketoconazole

was acquired from two different sources due to a shortage of supply from Sigma-Aldrich, Inc. These samples will be stored according to the manufacturer's recommendations to minimize degradation for at least six months after the final report is issued. Information on the methods of synthesis and stability, as well as data on the composition or other characteristics which define the test articles, are on file with the manufacturer.

A 1 mL reserve sample of the first and last dosing solutions administered to the animals was taken and will be stored frozen for at least six months after the final report is issued.

### TEST ANIMALS AND HUSBANDRY

Rats were chosen since they have historically been used in safety evaluation studies of this type and are recommended by appropriate regulatory agencies. Twenty-two timed-pregnant female Hsd: Sprague Dawley® SD® Rats and twenty five timed-pregnant female Long-Evans Hooded Rats, were received on December 7, 1999 (gestation day 12) from Harlan Sprague Dawley, Inc., Indianapolis, Indiana. They were assigned temporary animal numbers, acclimated to laboratory conditions for 8 days, and released for study use by a staff veterinarian.

Upon receipt, animals were housed individually in polycarbonate cages measuring 19 x 10½ x 8 inches (length x width x height) suspended on stainless-steel racks with an Edstrom automatic watering system providing filtered tap water. Racks were equipped with filter paper liners. Polycarbonate caging contained Sani Chip® heat treated hardwood laboratory bedding. Tap water and TEKLAD™ Certified Rodent Diet 7012C were provided *ad libitum*. The water is routinely analyzed for contaminants and specific microbes. The feed is analyzed by the manufacturer for concentrations of specified heavy metals, aflatoxin, chlorinated hydrocarbons, organophosphates, and specific nutrients. The results of the feed and water analyses are on file at TherImmune Research Corporation. No contaminants were known to be present in the diet or water at levels which might interfere with achieving the objectives of the study.

During the study period, the temperature and relative humidity in the animal rooms were

monitored continuously using the Rees™ Scientific Monitoring System and recorded twice daily using a Bacharach® sling psychrometer. The environmental controls in the animal room were set to maintain temperatures between 20 and 24°C and relative humidity between 40 and 50%. Ten or greater air changes/hour and a 14-hour light/10-hour dark cycle were maintained. Exceptions were noted in the raw data and had no adverse effect on the integrity of the study.

## METHODS

### Observations and Records - Prior to Selection of Study Animals

All of the pregnant females and pups, were observed for mortality, moribundity and clinical observations twice daily, at least six hours apart. Observations included skin and fur, eyes and mucous membrane, respiratory system, circulatory system, autonomic and central nervous system, somatomotor pattern, and behavior pattern. Pregnant females were observed at least twice daily for signs of parturition. The pregnant females were allowed to deliver and rear their pups until weaning on PND 21.

Pups were weighed on PND 1 and weekly thereafter to identify runt and/or unthrifty litters. On PND 4, litters were culled to 10 pups, with approximately the same number of male and female pups. The remaining pups were weaned on PND 21 and randomized into dosage groups (males on this study and females to TherImmune Study No. 1143-101).

### Group Assignment and Dose Levels

On PND 21, male pups were initially accepted into the randomization pool based upon physical examinations. They were assigned to study using computer-generated random numbers. The weight variation of selected males did not exceed 3 and 6 grams above or below the mean body weight for Sprague Dawley rats and Long-Evans rats respectively, and the mean weight for each group was not statistically different. During the randomization process, each study animal was assigned a unique number, assigned to groups as shown below and housed three per cage.

All animals not used on study were removed from the study room, with the exception of the female pups chosen for study 1143-101. This protocol was conducted as a "blind study" - with the technicians performing the study activities having no knowledge of which test article was administered to which study group.

Group	Treatment	Dosage (per kg/day)	Number of Males/Strain
1	Corn Oil	2.5 mL	6
2	Flutamide	50 mg	6
3	Methyl Testosterone	80 mg	6
4	Propylthiouracil (PTU)	240 mg	6
5	Ketoconazole	100 mg	6
6	Pimozide	30 mg	6
7	Dibutylphthalate	1000 mg	6

Test and Control Article Formulation and Administration

Dosing formulations were prepared weekly. The test materials were considered to be 100% pure for formulating purposes.

The appropriate amounts of each test article were diluted with the required amount of corn oil and then transferred to amber glass jars. The formulations were stirred continuously for 24 to 48 hours prior to first use. All formulations were stirred continuously during dosing.

Animals were given the appropriate dosing formulation via oral gavage daily on PND 22 through 53 or 54, between 0700 and 0900 h, at a dose volume of 2.5 mL/kg, adjusted daily. Test material was administered using an 18-gauge needle and a 1 cc glass tuberculin syringe. The dosing technician performed the procedure without knowledge of the test article. The test material was administered orally because this is the expected route of human exposure.



Observations and Records - Study Animals

All study animals were observed for mortality and moribundity twice daily, at least six hours apart each day. Observations included skin and fur, eyes and mucous membrane, respiratory system, circulatory system, autonomic and central nervous system, somatomotor pattern, and behavior pattern. Potential signs of toxicity including tremors, convulsions, salivation, diarrhea, lethargy, coma, limb impairment and resolution, changes in fecal and urinary output, or other atypical behavior or appearance were recorded. Detailed clinical observations were recorded weekly.

The males were weighed daily. Beginning on PND 23, the males were examined daily for preputial separation, with the appearance of partial separation, complete separation or a persistent thread of tissue between the glans and prepuce being recorded on the days observed.

Termination

On SD 53 or 54, between 1300 and 1700, all animals were sacrificed by decapitation and exsanguination. The decapitation was performed in a room separate from the animal room and within 15 seconds of removing the animal from its cage.

Serum Collection and Analysis

Following decapitation, trunk blood was collected from each animal and serum obtained. Approximately 500  $\mu$ L serum/animal was aliquoted into 1.7 mL siliconized microcentrifuge tubes, stored at approximately  $-80^{\circ}\text{C}$ , and later shipped on dry ice by express carrier to Dr. Ralph Cooper, US EPA, Durham, North Carolina. Approximately 550  $\mu$ L serum/animal was aliquoted into 1.7 mL siliconized microcentrifuge tubes, stored at approximately  $-80^{\circ}\text{C}$ , and delivered on dry ice to AniLytics, Inc., Gaithersburg, Maryland, for T4 and TSH analysis.

Necropsy

Necropsies were conducted on each animal by trained personnel and included examination of the external surface of the body, all orifices, and the cranial, thoracic, and abdominal cavities and their contents.

Organ Weights

The following organs were weighed wet from all animals:

testes	epididymides
liver	kidney
adrenals	pituitary
ventral prostate	seminal vesicle
levator ani plus bulbocavernosus muscles	

Tissue Preservation

The thyroid, epididymides, and testes were placed in Bouin's fixative for approximately 24 hours, then rinsed and stored in 70% ethanol.

Histopathology

The preserved thyroid, epididymides and testes from all animals were embedded in paraffin, stained with hematoxylin and eosin, and examined microscopically by the pathologist at Pathology Associates International.

Statistical Analyses

Methods used for statistical analysis are presented in Appendix 10. Briefly, data was tested for homogeneity of variance and analyzed by MANCOVA using weight at weaning as a covariate.

For preputial separation analysis, there were some animals which never reached the stated

endpoint (complete preputial separation). In order to perform statistical analysis of these endpoints, these animals were assumed to have reached the endpoint on the day after they were necropsied and at their terminal body weight. Therefore the means for these endpoints in groups including these animals are artificially low. This is noted on the appropriate tables as censored data.

The only group for which the null hypothesis could not be rejected by MANCOVA for all endpoints, except organ to body weight ratios, was ketoconazole-treated LE males. For this group  $p=0.0568$ . As this  $p$  value was very close to the cut off value of 0.05, post-hoc tests were performed, however, it should be noted that this may lead to an overstatement of the significance of the differences between data for this group and the control group.

“Increased” or “decreased” are used throughout the text of this report to describe the statistical significance at  $p \leq 0.05$ , unless otherwise indicated.

#### Record Retention

All records, study protocol, report, protocol and report revisions, written communications, and specimens generated by TherImmune and/or PAI are retained at TherImmune Research Corporation Archive. Documentation of any transfer of study records and reports will be maintained by TherImmune for a period of one year.

## RESULTS

### Mortality

Individual day of death for each animal is presented in Appendix 9. All animals survived until scheduled euthanasia.

### Clinical Observations

Weekly clinical observations are summarized in Table 1 and presented individually in Appendix 1. No treatment-related clinical signs were observed during this study.

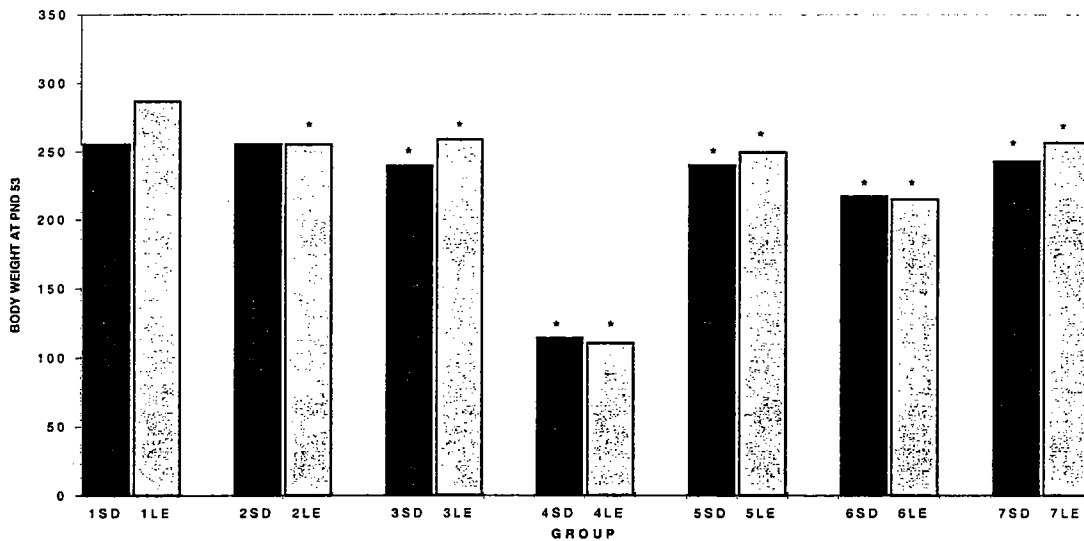
### Daily Body Weights

Body weights are shown in Figure 2, summarized in Table 2 and presented individually in Appendix 2. Mean body weight changes from PND 22 to necropsy are summarized in Table 3.

The mean body weight of males increased daily, with a few exceptions, in all groups except pimozide and PTU-treated males. Between PND 23 and 24, pimozide-treated males mean body weight decreased 13.5% for SD and 11.1% for LE rats. These animals then gained weight steadily, but PND 53 mean body weights were only 85.2 and 75.0% of controls.

The PND 53 mean body weights for all treatment groups, except flutamide-treated SD, were lower than control males. The greatest effect was with PTU treatment. PTU-treated males reached their maximum body weights on PND 45 and had PND 53 mean body weights which were only 44.8 and 38.6% of control mean body weights for SD and LE males respectively.

Figure 2: PND 53 Mean Body Weights



KEY: PND = Postnatal Day

\* = significantly different than control

GROUP: 1 = 2.5 ml/kg/day Corn Oil

5 = 100 mg/kg/day Ketoconazole

2 = 50 mg/kg/day Flutamide

6 = 30 mg/kg/day Pimozide

3 = 80 mg/kg/day Methyl Testosterone

7 = 1000 mg/kg/day Dibutylphthalate

4 = 240 mg/kg/day Propylthiouracil

### Age and Weight at Complete Preputial Separation

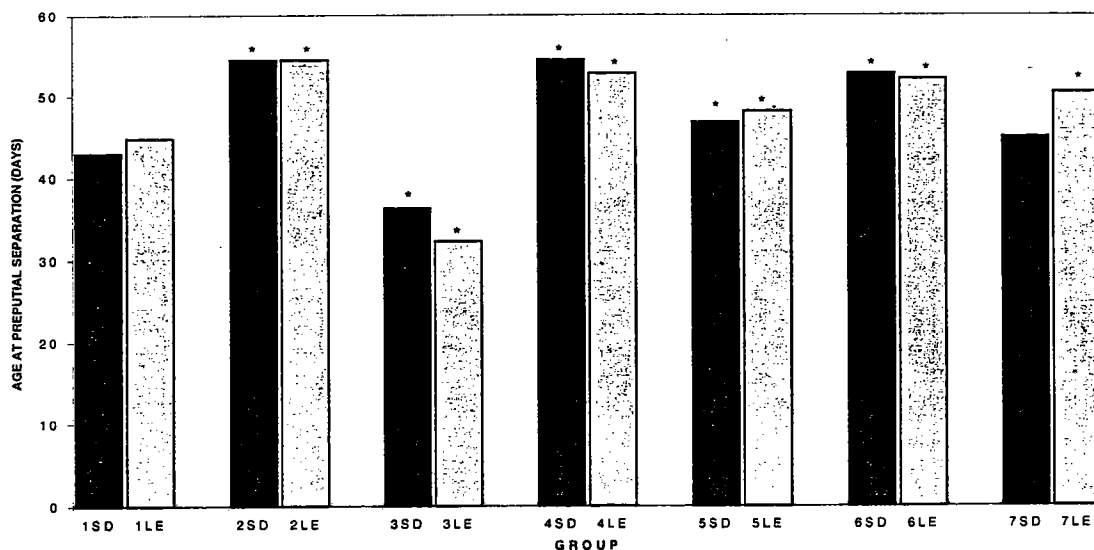
Preputial separation data are shown in Figures 3 and 4, summarized in Table 4, and presented individually in Appendices 3 and 4.

Mean age and weight at complete preputial separation was greater for LE males (PND 44.83, 218.85 g) than for SD males (PND 43.00, 184.92 g). Flutamide treatment completely inhibited preputial separation in both strains. No PTU-treated SD and only two (33%) of LE males achieved complete preputial separation. Ketoconazole-treated males had a significant increase in the mean age of complete preputial separation (SD 46.83; LE 48.17). One ketoconazole-treated LE male never achieved complete preputial separation, so this mean is artificially low as the day after necropsy was used as the day of preputial separation for statistical

purposes for this male. Pimozide treatment also increased the mean age of complete preputial separation and two SD (33%) and one LE (17%) males never achieved complete preputial separation. Similarly, the mean age of complete preputial separation was increased by DBP treatment, but the effect was significant only in LE males (50.5). Two DBP-treated LE males (33%) never achieved complete preputial separation.

Methyl testosterone was the only treatment which decreased the age of complete preputial separation. Mean age at complete preputial separation was PND 36.33 and 32.33 for methyl testosterone-treated SD and LE males respectively. Body weight varied widely with treatment and does not appear to be related to the age of preputial separation.

Figure 3: Mean Age of Preputial Separation



KEY: PND = Postnatal Day

\* = significantly different than control

GROUP: 1 = 2.5 ml/kg/day Corn Oil

5 = 100 mg/kg/day Ketoconazole

2 = 50 mg/kg/day Flutamide

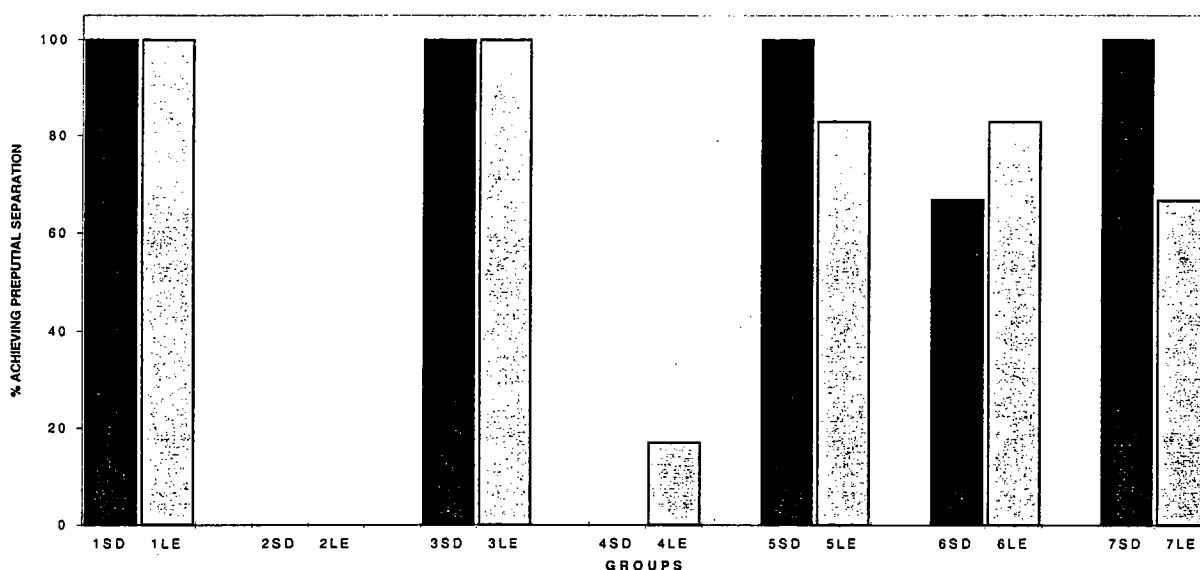
6 = 30 mg/kg/day Pimozide

3 = 80 mg/kg/day Methyl Testosterone

7 = 1000 mg/kg/day Dibutylphthalate

4 = 240 mg/kg/day Propylthiouracil

Figure 4: Percent Achieving Preputial Separation



KEY: PND = Postnatal Day

GROUP: 1 = 2.5 ml/kg/day Corn Oil

2 = 50 mg/kg/day Flutamide

3 = 80 mg/kg/day Methyl Testosterone

4 = 240 mg/kg/day Propylthiouracil

5 = 100 mg/kg/day Ketoconazole

6 = 30 mg/kg/day Pimozide

7 = 1000 mg/kg/day Dibutylphthalate

### Gross Pathology

Gross pathology findings are summarized in Table 5 and are presented individually in Appendix 5.

There were treatment related gross pathology findings in the testis, seminal vesicle, ventral prostate, adrenal and thyroid. The testes were small in 42 and 33% of methyl testosterone and DBP-treated males, respectively. The seminal vesicles were small in 92% of flutamide, 67% of PTU, and 17% of DBP (2 LE) treated males. Small ventral prostates were observed in flutamide (33%), and PTU (50%) treated males. PTU treatment also caused enlarged thyroids in 83% of males. Enlarged adrenals were seen in 50% of ketoconazole-treated rats. These findings, though subjective are generally in agreement with organ weights and histopathology.

Organ Weights

Organ weights and organ-to-body weight ratios are summarized in Tables 6 and 7, respectively, and presented individually in Appendix 6. Organ weights which were outside of physiological range were excluded from group means and analysis by the study director. Exclusions are noted on Appendix 6.

The effects of treatment were generally similar for both SD and LE males when both absolute organ weights and organ to body weight ratios were considered. Figure 5 details which organs were affected as absolute and/or as a percent of body weight in each strain. Adrenal weights were decreased by PTU and increased ketoconazole treatment. Kidney weights were increased by methyl testosterone and decreased by PTU and pimoziide. Liver weights tended increased in flutamide and DBP-treated rats, but decreased in PTU and pimoziide-treated males. Flutamide increased pituitary weights in SD males, however there was large variability in weights. As the pituitaries are very small in these juvenile animals, the variability in weights may be an artifact of the removal and weighing procedures.

There were also treatment related effects in reproductive organs. Seminal vesicle weight was generally decreased by all treatments, except methyl testosterone which increased weights. Seminal vesicles were weighed with the fluid retained which may have resulted in some variability in weights. Ventral prostate weights were decreased by flutamide, PTU and DBP treatment (LE only) and increased by methyl testosterone. Testes weight was decreased by methyl testosterone, PTU, pimoziide, and DBP treatment (LE only), and increased by flutamide. Epididymides weighed significantly less in flutamide, methyl testosterone (SD only), PTU, ketoconazole, pimoziide and DBP (LE only) treated rats compared to controls. The weight of levator ani and bulbocavernosus muscles was decreased in flutamide, PTU, ketoconazole (LE only), pimoziide, and DBP (LE only) treated rats. Overall DBP treatment appeared to have a more pronounced effect on organ weights in LE males.



Figure 5: Organ Weights

Tissue	Flutamide		Methyl Testosterone		PTU		Ketoconazole		Pimozide		DBP	
	Wt.	%	Wt.	%	Wt.	%	Wt.	%	Wt.	%	Wt.	%
Adrenals					↓	↑SD	↑	↑		↑LE		
Kidneys	↓LE		↑SD	↑	↓	↓SD			↓	↓SD		↑LE
Liver	↑SD	↑	↓LE		↓	↓		↑	↓	↑LE	↑SD	↑LE
Pituitary	↑SD	↑SD			↓LE	↑						
Seminal vesicles	↓	↓SD	↑	↑	↓	↓SD	↓SD	↓SD	↓	↓SD	↓	↓SD
Ventral prostate	↓	↓LE	↑	↑	↓						↓LE	
Testes	↑SD	↑	↓	↓	↓	↑			↓		↓LE	↓LE
Epididymides	↓	↓	↓SD	↓SD	↓	↑	↓		↓		↓LE	
Levator ani and bulbocavernosus	↓	↓			↓	↓	↓LE		↓	↓SD	↓LE	↓LE

KEY: ↓ = significantly decreased compared to control mean    Wt. = absolute organ weight  
 ↑ = significantly increased compared to control mean    % = organ weight as a percentage of body weight  
 LE = Long Evans only    SD = Sprague Dawley only

Histopathology

Summary and individual pathology findings are shown in Figure 6 and presented and discussed in the Pathology Report located in Appendix 7.

The three tissues examined in this study were thyroids, testes, and epididymides. All test articles, except ketoconazole, affected histopathology. Reproductive organs were affected in both strains by flutamide, methyl testosterone, PTU, pimozide (LE only) and DBP (LE only). PTU was the only treatment which affected thyroid histopathology.

Figure 6: Histopathology Findings

Tissue	Flutamide	Methyl Testosterone	PTU	Ketoconazole	Pimozide	DBP
Thyroid			✓			
Testes	✓	✓	✓			✓LE
Epididymides	✓	✓	✓		✓LE	✓LE

KEY: ✓ = affected histopathology

LE = Long Evans only

Serum T4 and TSH

Serum T4 and TSH levels are summarized in Table 8 and presented individually in Appendix 8.

Serum T4 levels on the day of necropsy were 4.95 and 6.45  $\mu\text{g}/\text{dL}$  for SD and LE males respectively. TSH levels were 3.40 and 3.89  $\text{ng}/\text{mL}$  for SD and LE males respectively. PTU treatment had significant effects on T4 and TSH levels. T4 levels were less than 5% of the mean control, while TSH levels were greater than seven times higher in PTU-treated males. DBP treatment resulted in a small, but significant decrease in both T4 and TSH levels in LE males.

## DISCUSSION

The purpose of this study was to quantify the effects of endocrine disrupting chemicals on pubertal development and thyroid function in the intact juvenile male rat and to evaluate the ability of this protocol to detect endocrine disruptors. The compounds used disrupt normal endocrine function in a variety of ways and have differing effects on growth and sexual maturation.

The effect of endogenous testosterone is mimicked by methyl testosterone which act as an androgen receptor agonist. Males treated with methyl testosterone had significantly lower body weights, age at preputial separation, testes and epididymides (SD only) weights, but increased kidney, ventral prostate and seminal vesicle weights when compared to control means. Histopathology findings included hypospermatogenesis, hypospermia, and interstitial cell atrophy in the testes.

Flutamide also acts at the androgen receptor, but functions as an antagonist. Flutamide-treated males had lower body weights (LE only), never exhibited preputial separation, and had decreased weights of androgen sensitive tissues - epididymides, levator ani and bulbocavernosus muscles, seminal vesicles, and ventral prostate - when compared to control means. Liver and testis weights were increased in flutamide-treated males. Microscopic evaluation found hyperplasia/hypertrophy of the testes, dilation of the seminiferous tubules and atrophy of the epididymides.

DBP, which may act as an anti-androgen at high doses, resulted in lower body weights. SD males had decreased seminal vesicle weights. All the other effects of treatment were only significant in LE males and include increased age of complete preputial separation, decreases in ventral prostate, testes, epididymides, levator ani and bulbocavernosus weights and TSH and T4 levels, and seminiferous tubule degeneration, hypospermatogenesis, and hypospermia.

Ketoconazole disrupts endocrine function by inhibiting cytochrome P<sub>450</sub> enzymes which are necessary for steroidogenesis. Males treated with ketoconazole had lower body weights and an increase in the age at preputial separation. Adrenal weights were increased in both strains, but,

seminal vesicle weights were decreased (SD only). There were no adverse histopathological findings in the organs examined in ketoconazole-treated males.

Pimozide is a D<sub>2</sub> receptor antagonist, which suppresses the action of dopamine, resulting in an increase in prolactin secretion. Pimozide treatment resulted in severe weight loss (> 11%) the first day of treatment. Subsequently, the males gained weight, but body weights were always significantly lower than controls. Due to the effect on body weight, many organ weights were decreased compared to control means. The age of preputial separation was increased by pimozide-treatment. LE males only displayed hypospermia and sporadic hypospermatogenesis.

PTU acts by inhibiting iodination of thyroid hormones. This inhibition disrupts growth and, indirectly, sexual maturation. PTU-treated males had severely depressed body weights and increased age to preputial separation. Only two LE and no SD males achieved preputial separation. The effect of PTU treatment on thyroid function were dramatic. PTU was very effective at inhibiting T4 levels and without the negative feedback TSH levels soared. Thyroids appeared grossly enlarged and hyperplasia/hypertrophy was observed at microscopic evaluation. Due to the severe effect on body weight, many organ weights were decreased compared to control means. PTU also produced histological changes in testes and epididymides.

Another goal of this study was to assess whether Sprague Dawley and Long Evans rats respond differently to endocrine disruptors. Both strains responded similarly to all treatments, in most of the parameters examined, except DBP. DBP treatment had an effect on organ weights and histopathology in LE males which was not seen in SD males.

**CONCLUSION**

This study design accurately identified endocrine disrupting compounds which were androgenic, anti-androgenic, inhibitors of steroid and thyroid hormone synthesis, or a dopamine antagonist and quantified their effect on the juvenile male rat. The inter-strain variation in response to treatment was minimal, except for DBP, which had a more pronounced effect in LE males. As evidenced by changes observed in body weights, preputial separation, organ weights, gross and histopathology and TSH and T4 levels, dosing male juvenile rats of the Sprague Dawley or Long-Evans strain from postnatal day 22 through 53 or 54 is a good model for identifying endocrine disrupting compounds.

Study Director:

Project Leader:

Meredith S. Rocca 6-29-00

Meredith S. Rocca, Ph.D. / Date

Stefanie Pepperl 6-29-00

Stefanie Pepperl, B.S. / Date

TABLE 1  
 SUMMARY OF WEEKLY CLINICAL OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

PERIOD	GROUP:	1	2	3	4	5	6	7
PND 22	No. Observed	12	12	12	12	12	12	12
	Normal	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
PND 29	No. Observed	12	12	12	12	12	12	12
	Normal	12 100%	12 100%	12 100%	12 100%	12 100%	11 92%	12 100%
	Hunched	0	0	0	0	0	1 8%	0
	Thin	0	0	0	0	0	1 8%	0
PND 36	No. Observed	12	12	12	12	12	12	12
	Normal	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
PND 43	No. Observed	12	12	12	12	12	12	12
	Normal	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
PND 50	No. Observed	12	12	12	12	12	12	12
	Normal	12 100%	12 100%	11 92%	12 100%	12 100%	12 100%	12 100%
	Discharge	0	0	1 8%	0	0	0	0

KEY: GROUP: 1 = 2.5 ml/kg/day Corn Oil  
 2 = 50 mg/kg/day Flutamide  
 3 = 80 mg/kg/day Methyl Testosterone  
 4 = 240 mg/kg/day Propylthiouracil  
 PND = Postnatal Day  
 5 = 100 mg/kg/day Ketoconazole  
 6 = 30 mg/kg/day Pimozide  
 7 = 1000 mg/kg/day Dibutylphthalate

TABLE 2  
SUMMARY OF BODY WEIGHTS  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats (Sprague-Dawley)

GROUP: PERIOD	1	2	3	4	5	6	7
PND22	49.60± 0.67 (6)	50.87± 0.76 (6)	49.73± 0.68 (6)	51.23± 0.64 (6)	49.87± 0.20 (6)	51.25± 0.68 (6)	49.78± 0.47 (6)
PND23	53.50± 0.88 (6)	**56.00± 0.83 (6)	54.98± 0.86 (6)	*55.63± 0.78 (6)	53.85± 0.31 (6)	53.53± 0.67 (6)	54.70± 0.34 (6)
PND24	59.55± 0.65 (6)	**62.17± 0.90 (6)	59.97± 0.78 (6)	61.05± 0.85 (6)	59.88± 0.40 (6)	**46.33± 0.61 (6)	60.90± 0.43 (6)
PND25	64.40± 0.84 (6)	66.78± 1.06 (6)	66.83± 0.70 (6)	65.02± 0.99 (6)	64.20± 0.84 (6)	**49.73± 1.16 (6)	64.92± 0.75 (6)
PND26	69.33± 0.86 (6)	*71.77± 0.93 (6)	**72.55± 0.86 (6)	**72.55± 0.86 (6)	69.60± 0.74 (6)	**56.45± 1.05 (6)	70.27± 0.64 (6)
PND27	75.20± 0.65 (6)	**78.25± 1.13 (6)	**78.50± 0.81 (6)	**75.10± 1.14 (6)	73.37± 0.71 (6)	**64.62± 0.93 (6)	75.18± 0.45 (6)
PND28	80.77± 0.83 (6)	*83.72± 1.34 (6)	**85.88± 1.03 (6)	79.93± 0.68 (6)	79.43± 0.93 (6)	**67.22± 1.09 (6)	81.63± 0.85 (6)
PND29	86.83± 0.82 (6)	88.85± 1.04 (6)	**92.67± 1.19 (6)	84.43± 1.38 (6)	84.95± 1.13 (6)	**70.42± 1.67 (6)	86.83± 0.92 (6)
PND30	92.13± 0.87 (6)	*96.15± 1.15 (6)	**99.50± 1.53 (6)	92.15± 1.36 (6)	90.70± 1.16 (6)	**79.73± 1.54 (6)	91.95± 1.07 (6)
PND31	99.08± 0.75 (6)	102.35± 1.25 (6)	**104.83± 1.37 (6)	98.03± 0.93 (6)	96.75± 1.29 (6)	**83.98± 1.37 (6)	98.83± 1.47 (6)
PND32	106.77± 1.04 (6)	110.23± 1.60 (6)	**113.43± 1.54 (6)	*102.08± 1.53 (6)	103.40± 1.48 (6)	**93.25± 1.15 (6)	106.68± 2.06 (6)
PND33	113.80± 1.03 (6)	115.10± 1.46 (6)	116.97± 1.63 (6)	**102.60± 0.53 (6)	**108.33± 1.65 (6)	**95.15± 1.38 (6)	111.98± 1.72 (6)
PND34	122.75± 1.11 (6)	124.13± 1.45 (6)	125.80± 1.49 (6)	**106.92± 1.23 (6)	**116.70± 1.56 (6)	**103.12± 0.90 (6)	119.78± 1.90 (6)
PND35	129.50± 1.00 (6)	131.23± 1.59 (6)	133.37± 1.60 (6)	**111.12± 1.74 (6)	**123.23± 1.43 (6)	**108.75± 1.29 (6)	126.42± 2.51 (6)
PND36	133.05± 1.28 (6)	136.20± 1.33 (6)	*138.37± 2.37 (6)	**108.63± 1.52 (6)	*127.52± 1.77 (6)	**110.65± 1.11 (6)	128.60± 2.54 (6)
PND37	140.78± 1.47 (6)	144.92± 1.42 (6)	145.27± 2.81 (6)	**114.78± 2.37 (6)	137.83± 2.37 (6)	**112.43± 2.34 (6)	138.98± 2.38 (6)
PND38	148.53± 0.99 (6)	152.52± 1.18 (6)	152.85± 2.07 (6)	**117.13± 2.24 (6)	144.32± 2.88 (6)	**123.97± 2.24 (6)	143.57± 2.78 (6)
PND39	156.53± 1.19 (6)	159.50± 1.08 (6)	159.35± 2.33 (6)	**116.02± 1.71 (6)	150.97± 2.57 (6)	**133.03± 1.70 (6)	152.07± 2.91 (6)
PND40	164.18± 1.51 (6)	166.58± 1.69 (6)	163.77± 2.21 (6)	**115.12± 1.46 (6)	**155.82± 2.91 (6)	**138.33± 2.68 (6)	*157.27± 2.95 (6)
PND41	170.33± 1.85 (6)	172.13± 1.42 (6)	168.67± 2.95 (6)	**116.58± 1.57 (6)	**161.88± 2.79 (6)	**142.28± 1.83 (6)	*163.28± 2.95 (6)
PND42	179.38± 1.74 (6)	181.90± 1.07 (6)	176.57± 2.51 (6)	**118.37± 2.18 (6)	*170.88± 3.53 (6)	**149.57± 2.98 (6)	172.85± 3.15 (6)
PND43	184.70± 1.84 (6)	185.77± 1.79 (6)	183.32± 2.90 (6)	**115.83± 1.60 (6)	**175.42± 3.38 (6)	**153.83± 2.79 (6)	*176.78± 3.13 (6)
PND44	194.05± 2.18 (6)	194.38± 2.10 (6)	188.23± 3.93 (6)	**120.50± 1.66 (6)	**182.68± 2.70 (6)	**162.98± 2.86 (6)	**181.90± 3.03 (6)
PND45	202.42± 1.31 (6)	201.92± 2.02 (6)	**190.48± 4.74 (6)	**120.65± 1.67 (6)	**191.12± 3.10 (6)	**171.40± 2.50 (6)	**189.47± 3.33 (6)
PND46	208.28± 1.57 (6)	206.37± 2.12 (6)	*199.87± 3.95 (6)	**118.40± 1.75 (6)	**194.35± 3.61 (6)	**176.32± 3.17 (6)	**195.20± 3.31 (6)
PND47	211.72± 1.58 (6)	209.90± 2.75 (6)	*200.97± 5.02 (6)	**113.75± 1.84 (6)	**200.25± 3.54 (6)	**178.22± 2.87 (6)	**200.05± 3.22 (6)
PND48	216.55± 1.96 (6)	218.00± 3.02 (6)	*205.35± 5.06 (6)	**114.12± 1.77 (6)	**203.82± 4.05 (6)	**182.90± 4.15 (6)	**203.65± 3.18 (6)
PND49	224.38± 2.00 (6)	224.48± 3.00 (6)	215.90± 3.89 (6)	**115.58± 1.15 (6)	**211.85± 3.79 (6)	**191.15± 4.09 (6)	214.68± 4.83 (6)
PND50	232.77± 2.15 (6)	233.93± 3.13 (6)	**220.75± 4.41 (6)	**116.15± 1.64 (6)	**219.23± 3.94 (6)	**195.45± 3.60 (6)	**220.73± 3.86 (6)
PND51	236.82± 2.20 (6)	239.93± 3.31 (6)	**224.55± 4.09 (6)	**115.63± 1.50 (6)	**224.00± 4.03 (6)	**203.47± 4.15 (6)	*226.85± 3.99 (6)
PND52	244.87± 2.13 (6)	246.12± 2.79 (6)	*232.78± 4.55 (6)	**115.07± 1.49 (6)	*232.87± 4.30 (6)	**209.46± 4.65 (6)	*236.68± 4.96 (6)
PND53	255.53± 1.59 (6)	255.68± 2.94 (6)	**239.95± 5.02 (6)	**114.52± 1.75 (6)	**240.27± 4.04 (6)	**217.63± 4.49 (6)	*243.33± 4.74 (6)
PND54	263.60± 4.65 (3)	259.63± 5.67 (3)	253.40± 5.86 (3)	**111.63± 2.40 (3)	246.80± 1.30 (3)	**222.33± 9.77 (3)	246.93± 6.57 (3)

Table Continued

KEY: GROUP: 1 = 2.5 ml/kg/day Corn Oil  
 2 = 50 mg/kg/day Flutamide  
 3 = 80 mg/kg/day Methyl Testosterone  
 4 = 240 mg/kg/day Propylthiouracil  
 PND = Postnatal Day  
 5 = 100 mg/kg/day Ketoconazole  
 6 = 30 mg/kg/day Pimozide  
 7 = 1000 mg/kg/day Dibutylphthalate

TABLE 2 (CONTINUED)  
SUMMARY OF BODY WEIGHTS  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats (Long-Evans)

GROUP: PERIOD	1	2	3	4	5	6	7
PND22	47.82± 1.00 (6)	48.25± 1.02 (6)	48.78± 2.38 (6)	49.85± 1.17 (6)	48.67± 1.53 (6)	47.32± 2.20 (6)	48.72± 1.63 (6)
PND23	52.33± 1.64 (6)	53.27± 0.98 (6)	54.63± 2.68 (6)	54.90± 1.27 (6)	52.73± 1.54 (6)	50.55± 2.45 (6)	52.78± 1.68 (6)
PND24	59.00± 1.75 (6)	59.23± 1.56 (6)	59.52± 2.99 (6)	59.62± 1.52 (6)	58.75± 2.15 (6)	**44.95± 2.06 (6)	59.05± 2.11 (6)
PND25	65.47± 2.01 (6)	65.60± 1.52 (6)	65.77± 2.95 (6)	66.73± 1.46 (6)	63.82± 2.19 (6)	**45.43± 2.61 (6)	65.18± 1.59 (6)
PND26	70.62± 1.84 (6)	70.87± 1.71 (6)	71.12± 2.85 (6)	69.80± 1.76 (6)	69.02± 1.78 (6)	**48.77± 3.39 (6)	69.30± 1.48 (6)
PND27	77.45± 2.03 (6)	77.32± 1.73 (6)	78.80± 3.34 (6)	78.18± 1.32 (6)	75.25± 2.25 (6)	**49.62± 4.40 (6)	77.70± 1.97 (6)
PND28	84.62± 1.89 (6)	84.07± 1.79 (6)	85.95± 3.49 (6)	81.33± 1.58 (6)	81.03± 2.43 (6)	**50.38± 5.21 (6)	83.83± 1.67 (6)
PND29	90.13± 1.46 (6)	88.23± 2.40 (6)	92.85± 4.04 (6)	85.87± 1.95 (6)	86.08± 2.49 (6)	**58.72± 5.33 (6)	87.98± 1.81 (6)
PND30	97.22± 1.83 (6)	96.38± 2.48 (6)	100.95± 4.59 (6)	89.87± 2.22 (6)	92.13± 2.65 (6)	**64.03± 5.31 (6)	96.23± 1.34 (6)
PND31	106.02± 1.78 (6)	103.73± 3.04 (6)	109.47± 4.59 (6)	97.38± 2.21 (6)	100.55± 2.59 (6)	**70.55± 6.35 (6)	104.32± 1.33 (6)
PND32	113.37± 1.56 (6)	110.60± 2.96 (6)	115.02± 4.62 (6)	**98.85± 1.52 (6)	108.35± 3.59 (6)	**78.05± 6.87 (6)	111.40± 1.57 (6)
PND33	121.42± 1.48 (6)	116.72± 3.21 (6)	120.95± 4.93 (6)	**98.27± 2.13 (6)	112.77± 2.95 (6)	**82.08± 7.44 (6)	117.28± 2.10 (6)
PND34	131.00± 1.17 (6)	125.60± 4.18 (6)	131.55± 5.13 (6)	**102.77± 2.00 (6)	121.25± 3.41 (6)	**87.95± 7.60 (6)	127.00± 1.66 (6)
PND35	137.77± 1.31 (6)	130.97± 3.51 (6)	138.33± 5.32 (6)	**105.00± 2.84 (6)	126.57± 3.04 (6)	**91.88± 7.85 (6)	135.52± 2.08 (6)
PND36	145.15± 1.43 (6)	135.57± 3.51 (6)	144.62± 5.79 (6)	**102.32± 2.13 (6)	*131.87± 3.22 (6)	**96.27± 7.79 (6)	142.13± 1.94 (6)
PND37	153.02± 1.29 (6)	143.95± 5.28 (6)	152.05± 5.90 (6)	**105.70± 2.39 (6)	140.65± 3.45 (6)	**100.83± 8.25 (6)	146.35± 1.99 (6)
PND38	162.08± 1.75 (6)	150.92± 5.20 (6)	159.63± 6.27 (6)	**108.13± 2.71 (6)	*148.08± 3.41 (6)	**110.57± 8.44 (6)	154.95± 2.62 (6)
PND39	170.77± 2.17 (6)	158.82± 6.70 (6)	168.23± 6.55 (6)	**110.13± 2.27 (6)	155.55± 3.37 (6)	**118.68± 8.93 (6)	164.35± 2.81 (6)
PND40	179.40± 2.50 (6)	166.82± 6.23 (6)	173.45± 7.03 (6)	**108.80± 2.73 (6)	**160.03± 3.38 (6)	**124.45± 8.83 (6)	169.70± 3.37 (6)
PND41	185.25± 2.51 (6)	171.32± 6.39 (6)	177.78± 6.91 (6)	**108.58± 2.73 (6)	**167.77± 4.05 (6)	**130.25± 8.62 (6)	177.05± 3.84 (6)
PND42	196.13± 2.29 (6)	180.28± 6.79 (6)	186.58± 7.51 (6)	**111.10± 2.53 (6)	**175.23± 3.76 (6)	**139.52± 8.94 (6)	184.37± 3.38 (6)
PND43	203.45± 3.71 (6)	*186.42± 6.42 (6)	193.02± 7.62 (6)	**109.38± 2.96 (6)	**179.30± 3.95 (6)	**145.28± 8.64 (6)	189.43± 4.43 (6)
PND44	213.43± 4.09 (6)	196.10± 7.40 (6)	201.13± 7.73 (6)	**111.07± 2.86 (6)	**187.58± 4.25 (6)	**155.08± 9.13 (6)	198.32± 5.07 (6)
PND45	222.82± 4.10 (6)	*202.00± 7.20 (6)	210.08± 8.50 (6)	**112.78± 2.55 (6)	**195.93± 5.18 (6)	**159.48± 8.06 (6)	*202.90± 4.62 (6)
PND46	231.25± 3.74 (6)	**209.05± 7.15 (6)	215.85± 8.63 (6)	**110.87± 2.98 (6)	**201.70± 4.65 (6)	**165.73± 7.64 (6)	*210.38± 5.38 (6)
PND47	237.22± 3.75 (6)	**215.52± 7.92 (6)	222.63± 9.17 (6)	**109.32± 2.86 (6)	**207.48± 4.60 (6)	**172.47± 8.11 (6)	*216.40± 4.34 (6)
PND48	245.58± 4.27 (6)	**219.63± 8.02 (6)	227.92± 9.09 (6)	**108.52± 2.53 (6)	**211.02± 3.11 (6)	**177.65± 7.88 (6)	**221.37± 4.72 (6)
PND49	255.02± 4.52 (6)	**229.57± 8.14 (6)	*235.20± 9.19 (6)	**108.07± 2.57 (6)	**217.88± 3.28 (6)	**183.52± 7.73 (6)	**231.70± 5.40 (6)
PND50	264.67± 4.51 (6)	**234.65± 8.02 (6)	**240.73± 9.75 (6)	**110.47± 2.80 (6)	**225.53± 3.67 (6)	**191.40± 7.59 (6)	**233.18± 5.21 (6)
PND51	270.62± 4.80 (6)	**240.95± 7.96 (6)	**247.37± 10.61 (6)	**110.50± 2.65 (6)	**232.07± 4.29 (6)	**197.83± 8.00 (6)	**243.52± 4.90 (6)
PND52	280.70± 5.03 (6)	**250.03± 3.64 (6)	**254.43± 10.43 (6)	**110.98± 2.47 (6)	**239.75± 4.77 (6)	**207.18± 8.20 (6)	**249.75± 5.20 (6)
PND53	287.13± 5.57 (6)	**255.43± 8.66 (6)	**259.23± 10.40 (6)	**110.83± 2.51 (6)	**249.67± 4.51 (6)	**215.22± 8.20 (6)	**256.62± 5.75 (6)
PND54	300.00± 1.85 (3)	**261.70± 8.51 (6)	**252.63± 15.18 (3)	**110.13± 4.21 (3)	**262.30± 11.41 (3)	**215.37± 15.87 (3)	**258.10± 10.90 (3)

KEY: GROUP: 1 = 2.5 ml/kg/day Corn Oil  
2 = 50 mg/kg/day Flutamide  
3 = 80 mg/kg/day Methyl Testosterone  
4 = 240 mg/kg/day Propylthiouracil  
5 = 100 mg/kg/day Ketoconazole  
6 = 30 mg/kg/day Pimozide  
7 = 1000 mg/kg/day Dibutylphthalate  
PND = Postnatal Day



TABLE 3  
 SUMMARY OF BODY WEIGHT CHANGE FROM PND 22 TO NECROPSY  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
	209.5± 6.10 (6)	204.2± 7.78 (6)	193.8±13.25 (6)	62.9± 3.94 (6)	194.2± 9.80 (6)	169.6±12.92 (6)	196.2±12.12 (6)
	244.5±16.47 (6)	210.9±19.07 (6)	213.1±20.35 (6)	60.3± 5.62 (6)	204.7±13.29 (6)	171.1±18.92 (6)	211.9±13.21 (6)

Sprague Dawley

Long-Evans

KEY: GROUP: 1 = 2.5 ml/kg/day Corn Oil  
 2 = 50 mg/kg/day Flutamide  
 3 = 80 mg/kg/day Methyl Testosterone  
 4 = 240 mg/kg/day Propylthiouracil  
 PND = Postnatal Day

5 = 100 mg/kg/day Ketoconazole  
 6 = 30 mg/kg/day Pimozide  
 7 = 1000 mg/kg/day Dibutylphthalate

TABLE 4  
SUMMARY OF PREPUBERTAL SEPARATION DATA  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: PERIOD	1	2	3	4	5	6	7
AGE DAYS	43.00± 0.45 (6)	**54.50± 0.22 <sup>a</sup> (6)	**36.33± 1.61 (6)	<u>Sprague Dawley</u> **54.50± 0.22 <sup>a</sup> (6)	**46.83± 0.95 (6)	**52.83± 0.60 <sup>a</sup> (6)	45.00± 0.45 (6)
WEIGHT (GRAMS)	184.92± 3.73 (6)	**255.10± 3.25 <sup>a</sup> (6)	**139.72± 7.03 (6)	**114.10± 1.72 <sup>a</sup> (6)	*198.45± 4.72 (6)	**212.87± 3.00 <sup>a</sup> (6)	188.47± 3.10 (6)
AGE DAYS	44.83± 0.91 (6)	**54.50± 0.22 <sup>a</sup> (6)	**32.33± 0.33 (6)	<u>Long-Evans</u> **52.83± 1.45 <sup>a</sup> (6)	*48.17± 1.35 <sup>a</sup> (6)	**52.17± 0.75 <sup>a</sup> (6)	50.50± 1.73 <sup>a</sup> (6)
WEIGHT (GRAMS)	218.85± 7.03 (6)	**259.10± 8.44 <sup>a</sup> (6)	**117.32± 5.45 (6)	**110.57± 2.73 <sup>a</sup> (6)	214.57± 7.63 <sup>a</sup> (6)	207.35± 8.29 <sup>a</sup> (6)	238.30± 9.77 <sup>a</sup> (6)

KEY: GROUP: 1 = 2.5 ml/kg/day Corn Oil  
2 = 50 mg/kg/day Flutamide  
3 = 80 mg/kg/day Methyl Testosterone  
4 = 240 mg/kg/day Propylthiouracil  
5 = 100 mg/kg/day Ketoconazole  
6 = 30 mg/kg/day Pimozide  
7 = 1000 mg/kg/day Dibutylphthalate

a = This mean includes censored data

TABLE 5  
INCIDENCE OF GROSS PATHOLOGY FINDINGS  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
Liver							
No. of Observations	12	12	12	12	12	12	12
ACCESSORY LOBE	0	0	1 8%	0	1 8%	0	0
NO GROSS FINDINGS	12 100%	12 100%	11 92%	12 100%	11 92%	12 100%	12 100%
Kidneys (paired)							
No. of Observations	12	12	12	12	12	12	12
CYST	0	0	1 8%	0	0	1 8%	1 8%
NO GROSS FINDINGS	12 100%	12 100%	11 92%	12 100%	12 100%	11 92%	11 92%
Testes (Paired)							
No. of Observations	12	12	12	12	12	12	12
DARK	0	1 8%	0	0	0	0	0
SMALL	0	0	5 42%	0	0	0	2 17%
NO GROSS FINDINGS	12 100%	11 92%	7 58%	12 100%	12 100%	12 100%	10 83%
Epididymides (Paired)							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Seminal Vesicle							
No. of Observations	12	12	12	12	12	12	12
SMALL	0	11 92%	0	8 67%	1 8%	0	2 17%
NO GROSS FINDINGS	12 100%	1 8%	12 100%	4 33%	11 92%	12 100%	10 83%
Levator Ani/Bulbocavernosus							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Ventral Prostate							
No. of Observations	12	12	12	12	12	12	12
SMALL	0	4 33%	0	6 50%	0	0	0
NO GROSS FINDINGS	12 100%	8 67%	12 100%	6 50%	12 100%	12 100%	12 100%

Table Continued

TABLE 5 (CONTINUED)  
 INCIDENCE OF GROSS PATHOLOGY FINDINGS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
<b>Adrenals</b>							
No. of Observations	12	12	12	12	12	12	12
ENLARGED	0	0	0	0	6 50%	0	0
PALE	0	0	0	0	2 17%	0	0
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	6 50%	12 100%	12 100%
<b>Pituitary</b>							
No. of Observations	12	12	12	12	12	12	12
SOFT CYST	0	0	0	1 8%	0	0	0
NO GROSS FINDINGS	12 100%	12 100%	12 100%	11 92%	12 100%	12 100%	12 100%
<b>Thyroid</b>							
No. of Observations	12	12	12	12	12	12	12
ENLARGED	0	0	1 8%	10 83%	0	0	0
NO GROSS FINDINGS	12 100%	12 100%	11 92%	2 17%	12 100%	12 100%	12 100%
<b>Brain</b>							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
<b>Spinal Cord</b>							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
<b>Preputial Gland</b>							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
<b>Esophagus</b>							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%

Table Continued

TABLE 5 (CONTINUED)  
 INCIDENCE OF GROSS PATHOLOGY FINDINGS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
Eye	No. of Observations	12	12	12	12	12	12
	NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Harderian Gland	No. of Observations	12	12	12	12	12	12
	NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Duodenum	No. of Observations	12	12	12	12	12	12
	NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Jejunum	No. of Observations	12	12	12	12	12	12
	NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Ileum	No. of Observations	12	12	12	12	12	12
	NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Cecum	No. of Observations	12	12	12	12	12	12
	NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Colon	No. of Observations	12	12	12	12	12	12
	NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Rectum	No. of Observations	12	12	12	12	12	12
	NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%

Table Continued

TABLE 5 (CONTINUED)  
 INCIDENCE OF GROSS PATHOLOGY FINDINGS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
Lacrimal Gland							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Larynx							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Heart							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Mandibular Lymph Node							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Mammary Gland							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Mesentery							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Nose							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Muscle							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%

Table Continued

TABLE 5 (CONTINUED)  
 INCIDENCE OF GROSS PATHOLOGY FINDINGS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
Salivary Glands							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Pancreas							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Peripheral Nerve							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Pharynx							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Pituitary Gland							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%
Other							
No. of Observations	12	12	12	12	12	12	12
NO GROSS FINDINGS	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%	12 100%

TABLE 6  
SUMMARY OF BODY AND ORGAN WEIGHTS AT NECROPSY  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
Sprague Dawley							
BODY (g)	259.1 ± 2.99 (6)	255.1 ± 3.25 (6)	*243.5 ± 5.90 (6)	**114.1 ± 1.72 (6)	244.1 ± 4.05 (6)	**220.9 ± 4.86 (6)	246.0 ± 4.58 (6)
ADRENALS (g)	0.042 ± 0.004 (6)	0.048 ± 0.002 (6)	0.045 ± 0.005 (6)	**0.027 ± 0.002 (6)	**0.073 ± 0.004 (6)	0.044 ± 0.002 (6)	0.046 ± 0.003 (6)
EPIDIDYMIDES (g)	0.495 ± 0.020 (6)	**0.279 ± 0.019 (6)	**0.398 ± 0.018 (6)	**0.243 ± 0.017 (6)	*0.431 ± 0.021 (6)	**0.402 ± 0.015 (6)	0.458 ± 0.010 (6)
KIDNEYS (g)	2.093 ± 0.026 (6)	1.953 ± 0.054 (6)	*2.335 ± 0.094 (6)	**0.849 ± 0.027 (6)	1.959 ± 0.059 (6)	**1.644 ± 0.047 (6)	2.002 ± 0.026 (6)
LEVATOR ANI AND BULBOCAVERNOSUS MUSCLES (g)	0.667 ± 0.078 (6)	**0.257 ± 0.013 (6)	0.718 ± 0.061 (6)	**0.103 ± 0.008 (6)	0.528 ± 0.070 (6)	**0.376 ± 0.024 (6)	0.567 ± 0.045 (6)
LIVER (g)	11.205 ± 0.202 (6)	**12.710 ± 0.339 (6)	11.054 ± 0.401 (6)	**4.458 ± 0.113 (6)	11.357 ± 0.105 (6)	**9.665 ± 0.405 (6)	*12.430 ± 0.642 (6)
PITUITARY (g)	0.008 ± 0.001 (6)	*0.010 ± 0.001 (6)	0.007 ± 0.001 (6)	0.006 ± 0.000 (6)	0.007 ± 0.000 (6)	0.007 ± 0.001 (6)	0.008 ± 0.001 (6)
SEMINAL VESICLES (g)	0.548 ± 0.067 (6)	**0.086 ± 0.016 (6)	*0.717 ± 0.065 (6)	**0.065 ± 0.019 (6)	**0.272 ± 0.039 (6)	**0.220 ± 0.023 (6)	*0.393 ± 0.045 (6)
TESTES (g)	3.092 ± 0.034 (6)	*3.705 ± 0.218 (6)	**0.848 ± 0.048 (6)	**1.855 ± 0.161 (6)	2.901 ± 0.062 (6)	*2.548 ± 0.082 (6)	2.694 ± 0.161 (6)
VENTRAL PROSTATE (g)	0.223 ± 0.010 (6)	*0.107 ± 0.034 (6)	*0.353 ± 0.036 (6)	**0.082 ± 0.046 (6)	0.137 ± 0.023 (6)	0.121 ± 0.010 (6)	0.233 ± 0.052 (6)
Long-Evans							
BODY (g)	292.3 ± 6.40 (6)	*259.1 ± 8.44 (6)	*261.8 ± 9.98 (6)	**110.2 ± 2.58 (6)	**253.4 ± 6.70 (6)	**218.4 ± 7.80 (6)	*260.7 ± 5.24 (6)
ADRENALS (g)	0.047 ± 0.003 (6)	0.050 ± 0.004 (6)	0.041 ± 0.002 (6)	*0.027 ± 0.001 (6)	*0.072 ± 0.003 (6)	0.057 ± 0.017 (6)	0.048 ± 0.006 (6)
EPIDIDYMIDES (g)	0.506 ± 0.034 (6)	**0.308 ± 0.031 (6)	0.500 ± 0.021 (6)	**0.253 ± 0.024 (6)	*0.394 ± 0.020 (6)	**0.310 ± 0.023 (6)	*0.399 ± 0.050 (6)
KIDNEYS (g)	2.326 ± 0.051 (6)	*2.086 ± 0.086 (6)	2.378 ± 0.103 (6)	**0.879 ± 0.027 (6)	2.149 ± 0.077 (6)	**1.747 ± 0.076 (6)	2.266 ± 0.094 (6)
LEVATOR ANI AND BULBOCAVERNOSUS MUSCLES (g)	0.660 ± 0.052 (6)	**0.397 ± 0.032 (6)	0.641 ± 0.034 (6)	**0.153 ± 0.022 (6)	**0.488 ± 0.029 (6)	**0.422 ± 0.058 (6)	**0.383 ± 0.026 (6)
LIVER (g)	12.335 ± 0.479 (6)	12.408 ± 0.325 (6)	*11.229 ± 0.400 (6)	**4.224 ± 0.107 (6)	11.920 ± 0.415 (6)	**9.876 ± 0.474 (6)	11.647 ± 0.161 (6)
PITUITARY (g)	0.008 ± 0.001 (6)	0.008 ± 0.001 (6)	0.007 ± 0.000 (6)	*0.006 ± 0.000 (6)	0.007 ± 0.001 (6)	0.007 ± 0.001 (6)	0.007 ± 0.001 (6)
SEMINAL VESICLES (g)	0.414 ± 0.048 (6)	**0.092 ± 0.009 (6)	*0.679 ± 0.067 (6)	**0.177 ± 0.110 (6)	0.252 ± 0.048 (6)	*0.194 ± 0.032 (6)	*0.202 ± 0.046 (6)
TESTES (g)	2.732 ± 0.035 (6)	3.301 ± 0.214 (6)	**0.563 ± 0.046 (6)	**1.923 ± 0.161 (6)	2.576 ± 0.073 (6)	**1.869 ± 0.085 (6)	**0.872 ± 0.102 (6)
VENTRAL PROSTATE (g)	0.184 ± 0.024 (6)	**0.057 ± 0.012 (6)	**0.307 ± 0.022 (6)	**0.062 ± 0.016 (6)	0.139 ± 0.010 (6)	0.159 ± 0.014 (6)	*0.130 ± 0.018 (6)

KEY: GROUP: 1 = 2.5 ml/kg/day Corn Oil  
 2 = 50 mg/kg/day Flutamide  
 3 = 80 mg/kg/day Methyl Testosterone  
 4 = 240 mg/kg/day Propylthiouracil  
 5 = 100 mg/kg/day Ketoconazole  
 6 = 30 mg/kg/day Pimozide  
 7 = 1000 mg/kg/day Dibutylphthalate



TABLE 7  
SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS AT NECROPSY (% BODY WEIGHT)  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
<u>Sprague Dawley</u>							
ADRENALS	0.017 ± 0.002 (6)	0.019 ± 0.001 (6)	0.019 ± 0.002 (6)	**0.024 ± 0.002 (6)	**0.030 ± 0.002 (6)	0.020 ± 0.001 (6)	0.019 ± 0.001 (6)
EPIDIDYMIDES	0.191 ± 0.006 (6)	**0.110 ± 0.008 (6)	*0.164 ± 0.007 (6)	*0.213 ± 0.014 (6)	0.176 ± 0.007 (6)	0.183 ± 0.011 (6)	0.186 ± 0.004 (6)
KIDNEYS	0.808 ± 0.008 (6)	0.766 ± 0.019 (6)	**0.958 ± 0.019 (6)	*0.745 ± 0.029 (6)	0.802 ± 0.018 (6)	*0.745 ± 0.015 (6)	0.815 ± 0.016 (6)
LEVATOR ANI AND BULBOCAVERNOSUS MUSCLES	0.258 ± 0.031 (6)	**0.101 ± 0.005 (6)	0.295 ± 0.024 (6)	**0.091 ± 0.007 (6)	0.216 ± 0.027 (6)	**0.170 ± 0.009 (6)	0.230 ± 0.017 (6)
LIVER	4.325 ± 0.044 (6)	**4.980 ± 0.095 (6)	4.535 ± 0.080 (6)	*3.907 ± 0.077 (6)	*4.659 ± 0.077 (6)	4.368 ± 0.100 (6)	**5.040 ± 0.177 (6)
PITUITARY	0.003 ± 0.000 (6)	*0.004 ± 0.000 (6)	0.003 ± 0.000 (6)	**0.005 ± 0.000 (6)	0.003 ± 0.000 (6)	0.003 ± 0.001 (6)	0.003 ± 0.000 (6)
SEMINAL VESICLES	0.211 ± 0.024 (6)	**0.034 ± 0.006 (6)	**0.293 ± 0.022 (6)	**0.057 ± 0.017 (6)	**0.111 ± 0.015 (6)	**0.100 ± 0.010 (6)	*0.160 ± 0.019 (6)
TESTES	1.194 ± 0.013 (6)	**1.450 ± 0.073 (6)	**0.349 ± 0.019 (6)	**1.628 ± 0.143 (6)	1.188 ± 0.012 (6)	1.155 ± 0.035 (6)	1.094 ± 0.057 (6)
VENTRAL PROSTATE	0.086 ± 0.004 (6)	0.042 ± 0.014 (6)	*0.146 ± 0.016 (6)	0.070 ± 0.038 (6)	0.056 ± 0.009 (6)	0.055 ± 0.005 (6)	0.095 ± 0.021 (6)
<u>Long-Evans</u>							
ADRENALS	0.016 ± 0.001 (6)	0.019 ± 0.001 (6)	0.016 ± 0.001 (6)	0.024 ± 0.001 (6)	*0.028 ± 0.001 (6)	*0.026 ± 0.008 (6)	0.018 ± 0.002 (6)
EPIDIDYMIDES	0.173 ± 0.009 (6)	**0.118 ± 0.009 (6)	0.192 ± 0.009 (6)	**0.229 ± 0.020 (6)	0.155 ± 0.007 (6)	0.142 ± 0.008 (6)	0.152 ± 0.017 (6)
KIDNEYS	0.797 ± 0.018 (6)	0.805 ± 0.020 (6)	**0.909 ± 0.022 (6)	0.798 ± 0.014 (6)	0.848 ± 0.023 (6)	0.802 ± 0.029 (6)	*0.868 ± 0.026 (6)
LEVATOR ANI AND BULBOCAVERNOSUS MUSCLES	0.227 ± 0.020 (6)	**0.152 ± 0.009 (6)	0.247 ± 0.018 (6)	**0.140 ± 0.021 (6)	0.193 ± 0.012 (6)	0.192 ± 0.023 (6)	**0.147 ± 0.010 (6)
LIVER	4.217 ± 0.116 (6)	**4.796 ± 0.070 (6)	4.292 ± 0.052 (6)	**3.835 ± 0.043 (6)	**4.701 ± 0.079 (6)	*4.522 ± 0.136 (6)	*4.474 ± 0.071 (6)
PITUITARY	0.003 ± 0.000 (6)	0.003 ± 0.000 (6)	0.003 ± 0.000 (6)	**0.006 ± 0.000 (6)	0.003 ± 0.000 (6)	0.003 ± 0.000 (6)	0.003 ± 0.000 (6)
SEMINAL VESICLES	0.142 ± 0.015 (6)	0.035 ± 0.003 (6)	*0.261 ± 0.029 (6)	0.154 ± 0.092 (6)	0.100 ± 0.019 (6)	0.088 ± 0.013 (6)	0.077 ± 0.016 (6)
TESTES	0.936 ± 0.014 (6)	**1.271 ± 0.055 (6)	**0.215 ± 0.014 (6)	**1.740 ± 0.124 (6)	1.019 ± 0.036 (6)	0.855 ± 0.021 (6)	**0.335 ± 0.038 (6)
VENTRAL PROSTATE	0.063 ± 0.007 (6)	**0.022 ± 0.004 (6)	**0.118 ± 0.009 (6)	0.055 ± 0.013 (6)	0.055 ± 0.004 (6)	0.073 ± 0.007 (6)	0.050 ± 0.007 (6)

KEY: GROUP: 1 = 2.5 ml/kg/day Corn Oil  
 2 = 50 mg/kg/day Flutamide  
 3 = 80 mg/kg/day Methyl Testosterone  
 4 = 240 mg/kg/day Propylthiouracil  
 5 = 100 mg/kg/day Ketoconazole  
 6 = 30 mg/kg/day Pimozide  
 7 = 1000 mg/kg/day Dibutylphthalate

TABLE 8  
 SUMMARY OF SERUM T4 AND TSH LEVELS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
T4, TOTAL (µg/dL)	4.95± 0.7 (6)	4.71± 0.62 (6)	4.69± 0.29 (6)	<u>Sprague Dawley</u> **0.00± 0.00 (6)			5.61± 0.26 (6)
TSH (ng/mL)	3.40± 0.0 (6)	2.64± 0.36 (6)	3.20± 0.76 (6)	**28.75± 2.70 (6)			3.41± 0.45 (6)
				<u>Long-Evans</u>			
T4, TOTAL (µg/dL)	6.45± 0.3 (6)	6.35± 0.56 (6)	6.33± 0.62 (6)	**0.02± 0.02 (6)			5.97± 0.43 (6)
TSH (ng/mL)	3.89± 0.0 (6)	5.20± 2.17 (6)	3.67± 0.65 (6)	**29.01± 1.98 (6)			2.54± 0.39 (6)

KEY: GROUP: 1 = 2.5 ml/kg/day Corn Oil  
 2 = 50 mg/kg/day Flutamide  
 3 = 80 mg/kg/day Methyl Testosterone  
 4 = 240 mg/kg/day Propylthiouracil  
 5 = 100 mg/kg/day Ketoconazole  
 6 = 30 mg/kg/day Pimozide  
 7 = 1000 mg/kg/day Dibutylphthalate

APPENDIX 1  
 INDIVIDUAL CLINICAL OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 1 - 2.5 mL/kg/day Corn Oil

SPRAGUE DAWLEY

PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15062	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15063	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15064	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15065	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15066	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15067	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
 INDIVIDUAL CLINICAL OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 1 - 2.5 mL/kg/day Corn Oil  
 PND 21-54

LONG-EVANS

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15068	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15069	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15070	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15071	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15072	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15073	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
 INDIVIDUAL CLINICAL OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 2 - 50 mg/kg/day Flutamide

SPRAGUE DAWLEY

PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
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R15074	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15075	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15076	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15077	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15078	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15079	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
 INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 2 - 50 mg/kg/day Flutamide

LONG-EVANS

PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15080	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15081	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15082	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15083	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15084	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15085	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 3 - 80 mg/kg/day Methyl Testosterone

SPRAGUE DAWLEY

PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
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R15086	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15087	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15088	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15089	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15090	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Discharge, Red		Head	PND 50
	Terminal Kill			PND 54
R15091	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
 INDIVIDUAL CLINICAL OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 3 - 80 mg/kg/day Methyl Testosterone  
 PND 21-54

LONG-EVANS

ANIMAL #    OBSERVATIONS            SEVERITY            LOCATION    TIME OCCURRED

R15092	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15093	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15094	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15095	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15096	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15097	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued



APPENDIX 1 (CONTINUED)  
 INDIVIDUAL CLINICAL OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 4 - 240 mg/kg/day Propylthiouracil

SPRAGUE DAWLEY

PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
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R15098	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15099	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15100	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15101	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15102	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15103	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 4 - 240 mg/kg/day Propylthiouracil

LONG-EVANS

PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15104	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15105	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15106	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15107	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15108	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15109	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 5 - 100 mg/kg/day Ketoconazole  
PND 21-54

SPRAGUE DAWLEY

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15110	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15111	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15112	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15113	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15114	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15115	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 5 - 100 mg/kg/day Ketoconazole

LONG-EVANS

PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
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R15116	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15117	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15118	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15119	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15120	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15121	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
 INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 6 - 30 mg/kg/day Pimozide  
 PND 21-54

SPRAGUE DAWLEY

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15122	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15123	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15124	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15125	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15126	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15127	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 6 - 30 mg/kg/day Pimozide

LONG-EVANS

PND 21-54

ANIMAL # OBSERVATIONS SEVERITY LOCATION TIME OCCURRED

R15128	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15129	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15130	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15131	Normal			PND 22
	Hunched			PND 29
	Thin			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15132	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15133	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
 INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 7 - 1000 mg/kg/day Dibutylphthalate  
 PND 21-54

SPRAGUE DAWLEY

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15134	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15135	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15136	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15137	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15138	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15139	Normal			PND 22
	Normal			PND 29
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)  
 INDIVIDUAL CLINICAL OBSERVATIONS

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 7 - 1000 mg/kg/day Dibutylphthalate

LONG-EVANS

PND 21-PND 43

ANIMAL # OBSERVATIONS SEVERITY LOCATION TIME OCCURRED

R15140 Normal PND 22  
 Normal PND 29  
 Normal PND 36  
 Normal PND 43  
 Normal PND 50  
 Terminal Kill PND 53

R15141 Normal PND 22  
 Normal PND 29  
 Normal PND 36  
 Normal PND 43  
 Normal PND 50  
 Terminal Kill PND 53

R15142 Normal PND 22  
 Normal PND 29  
 Normal PND 36  
 Normal PND 43  
 Normal PND 50  
 Terminal Kill PND 53

R15143 Normal PND 22  
 Normal PND 29  
 Normal PND 36  
 Normal PND 43  
 Normal PND 50  
 Terminal Kill PND 54

R15144 Normal PND 22  
 Normal PND 29  
 Normal PND 36  
 Normal PND 43  
 Normal PND 50  
 Terminal Kill PND 54

R15145 Normal PND 22  
 Normal PND 29  
 Normal PND 36  
 Normal PND 43  
 Normal PND 50  
 Terminal Kill PND 54



APPENDIX 2  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL #	GROUP: 1 - 2.5 ml/kg/day Corn Oil											
	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15062	47.2	50.8	58.6	63.4	68.2	73.8	79.5	85.9	90.8	99.1	104.9	112.5
R15063	49.6	52.4	58.2	63.1	67.8	73.7	78.3	85.6	91.3	98.0	104.8	111.8
R15064	50.8	55.6	60.7	66.8	69.9	75.3	81.3	87.9	92.1	99.3	105.4	112.6
R15065	48.2	51.6	57.6	61.5	66.7	74.2	79.4	84.5	89.5	96.9	106.4	112.1
R15066	50.2	55.5	61.4	66.2	72.1	77.4	83.5	90.2	95.5	102.4	111.5	118.1
R15067	51.6	55.1	60.8	65.4	71.3	76.8	82.6	86.9	93.6	98.8	107.6	115.7
R15068	48.1	53.3	60.2	66.4	70.5	77.6	84.4	90.6	98.6	107.1	114.6	120.3
R15069	44.6	49.8	56.5	63.4	68.6	76.1	84.0	89.7	97.4	105.7	113.2	121.7
R15070	51.3	56.8	64.4	72.9	77.3	85.1	92.2	95.6	103.4	112.8	120.0	128.0
R15071	46.7	51.9	58.7	64.2	70.4	76.3	82.5	88.7	96.5	105.4	110.3	119.0
R15072	49.8	56.1	62.0	67.8	73.1	79.7	86.4	91.5	97.9	106.0	113.0	121.9
R15073	46.4	46.1	52.2	58.1	63.8	69.9	78.2	84.7	89.5	99.1	109.1	117.6
MEAN	48.7	52.9	59.3	64.9	70.0	76.3	82.7	88.5	94.7	102.6	110.1	117.6
S.D.	2.19	3.13	3.10	3.65	3.42	3.71	3.95	3.26	4.28	4.83	4.64	4.97
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15062 - R15067 are Sprague Dawley  
 Animals R15068 - R15073 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 1 - 2.5 mL/kg/day Corn Oil - CONTINUED	Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats											
	ANIMAL #	PND 34	PND 35	PND 36	PND 37	PND 38	PND 39	PND 40	PND 41	PND 42	PND 43	PND 44
R15062	121.2	127.5	128.7	137.9	145.1	153.0	159.5	164.5	174.4	180.5	189.0	199.8
R15063	121.6	129.5	135.3	141.7	148.0	157.0	165.1	170.3	180.4	184.2	194.8	203.9
R15064	122.9	130.3	132.7	140.4	147.9	156.4	164.1	168.8	178.3	185.1	190.6	200.9
R15065	119.8	125.9	130.6	136.4	147.6	153.8	160.3	167.3	175.0	180.0	189.2	198.3
R15066	127.7	132.5	137.4	146.8	151.9	161.0	167.7	174.5	184.3	186.0	199.6	205.3
R15067	123.3	131.3	133.6	141.5	150.7	158.0	168.4	176.6	183.9	192.4	201.1	206.3
R15068	131.3	137.7	141.6	149.2	156.0	164.8	171.9	176.7	188.6	190.1	198.5	206.5
R15069	131.8	141.3	150.9	157.2	166.9	180.3	189.3	195.1	204.8	217.4	228.5	236.1
R15070	135.4	141.6	146.4	155.8	160.8	169.2	178.4	182.6	193.9	200.2	211.0	223.3
R15071	130.4	136.6	144.8	154.0	166.5	170.8	182.5	188.4	200.1	208.4	219.0	229.6
R15072	130.6	136.1	145.7	151.3	163.2	167.5	174.6	184.0	194.4	201.4	209.5	219.0
R15073	126.5	133.3	141.5	150.6	159.1	172.0	179.7	184.7	195.0	203.2	214.1	222.4
MEAN	126.9	133.6	139.1	146.9	155.3	163.7	171.8	177.8	187.8	194.1	203.7	212.6
S.D.	5.07	5.10	7.07	7.16	7.81	8.48	9.30	9.34	9.95	11.94	12.69	12.81
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15062 - R15067 are Sprague Dawley  
 Animals R15068 - R15073 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL #	GROUP: 1 - 2.5 mL/kg/day Corn Oil - CONTINUED											
	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54			
R15062	203.6	207.4	212.9	218.7	228.1	229.8	239.3	251.4				a
R15063	208.6	212.6	215.8	224.8	232.3	235.4	243.5	255.4				a
R15064	207.4	212.3	214.1	223.2	232.6	236.3	244.4	256.7				a
R15065	205.0	207.3	213.5	220.0	227.4	234.1	240.7	251.5				255.6
R15066	211.1	213.2	217.2	227.7	234.2	239.6	247.6	256.3				263.5
R15067	214.0	217.5	225.8	231.9	242.0	245.7	253.7	261.9				271.7
R15068	216.3	223.7	228.2	236.7	247.7	249.4	257.6	261.3				a
R15069	243.9	249.9	258.6	267.5	278.5	283.3	293.4	300.6				a
R15070	230.9	235.1	244.1	255.0	272.8	273.1	281.3	292.1				a
R15071	236.0	243.0	253.0	265.5	268.8	275.8	288.4	294.3				303.5
R15072	227.9	231.5	242.0	252.0	258.4	266.2	281.1	285.6				297.2
R15073	232.5	240.1	247.6	253.4	261.8	275.9	282.4	288.9				299.3
MEAN	219.8	224.5	231.1	239.7	248.7	253.7	262.8	271.3				281.8
S.D.	13.74	14.92	17.03	17.96	18.59	19.69	20.77	19.07				20.68
N	12	12	12	12	12	12	12	12				6

Appendix Continued

Key: Animals R15062 - R15067 are Sprague Dawley  
 Animals R15068 - R15073 are Long-Evans  
 PND = Postnatal Day  
 a = Terminal Kill

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 2 - 50 mg/kg/day Flutamide	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
ANIMAL #												
R15074	53.0	58.0	64.5	70.6	75.3	80.7	88.1	92.1	98.9	107.3	115.0	119.7
R15075	50.2	54.3	61.7	65.6	69.9	76.9	82.5	88.3	95.1	101.9	109.1	113.4
R15076	50.6	54.5	59.9	64.1	69.7	75.7	80.9	87.0	91.9	98.8	103.5	109.4
R15077	53.0	58.6	63.8	67.7	72.4	81.7	84.8	90.3	98.2	103.8	112.0	116.8
R15078	48.2	53.9	59.3	64.2	70.0	75.0	79.6	85.1	94.3	99.6	109.6	114.2
R15079	50.2	56.7	63.8	68.5	73.3	79.5	86.4	90.3	98.5	102.7	112.2	117.1
R15080	48.0	53.1	59.5	64.8	70.8	76.6	81.5	85.7	91.5	96.0	102.9	109.4
R15081	46.0	51.6	56.6	62.7	68.4	73.8	80.6	83.8	92.3	100.8	107.7	113.7
R15082	53.1	57.9	66.6	72.7	79.1	85.6	92.6	99.4	107.0	116.9	121.4	129.2
R15083	48.0	53.5	59.1	66.4	69.7	75.8	82.5	84.0	92.2	100.2	104.9	110.3
R15084	46.9	52.0	56.5	63.0	67.5	74.8	82.7	86.8	95.4	100.9	109.4	114.4
R15085	47.5	51.5	57.1	64.0	69.7	77.3	84.5	89.7	99.9	107.6	117.3	123.3
MEAN	49.6	54.6	60.7	66.2	71.3	77.8	83.9	88.5	96.3	103.0	110.4	115.9
S.D.	2.50	2.56	3.35	3.12	3.25	3.45	3.70	4.33	4.51	5.48	5.56	5.88
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15074 - R15079 are Sprague Dawley  
 Animals R15080 - R15085 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL #	GROUP: 2 - 50 mg/kg/day Flutamide - CONTINUED											
	PND 34	PND 35	PND 36	PND 37	PND 38	PND 39	PND 40	PND 41	PND 42	PND 43	PND 44	PND 45
R15074	129.7	135.9	139.2	149.2	156.3	163.1	170.1	175.3	184.9	190.2	198.1	206.1
R15075	124.3	131.7	137.1	145.3	151.7	158.8	164.6	174.4	182.0	185.7	190.5	198.3
R15076	119.7	124.7	130.2	140.0	147.9	155.0	160.6	167.9	180.5	179.3	189.4	198.4
R15077	126.5	134.3	137.7	148.3	154.1	160.5	172.3	175.1	184.1	189.5	197.9	206.0
R15078	122.1	130.3	134.9	144.3	153.7	160.2	165.8	172.3	182.3	188.1	200.9	206.9
R15079	122.5	130.5	138.1	142.4	151.4	159.4	166.1	167.8	177.6	181.8	189.5	195.8
R15080	114.5	124.0	127.0	132.9	138.3	142.3	147.5	156.0	160.7	167.3	176.7	183.8
R15081	118.6	125.8	128.7	133.1	141.6	148.2	159.1	160.9	172.7	178.8	187.2	195.6
R15082	138.9	144.5	146.8	163.9	169.4	182.5	187.2	193.0	202.7	208.1	219.8	230.1
R15083	119.0	124.9	130.8	135.2	143.5	148.2	158.0	160.4	168.9	176.8	181.8	189.0
R15084	125.5	127.7	134.6	143.6	148.9	156.1	166.9	169.3	178.9	185.3	194.5	197.3
R15085	137.1	138.9	145.5	155.0	163.8	175.6	182.2	188.3	197.8	202.2	216.6	216.2
MEAN	124.9	131.1	135.9	144.4	151.7	159.2	166.7	171.7	181.1	186.1	195.2	202.0
S.D.	7.35	6.36	6.21	9.05	8.85	11.22	10.65	10.82	11.38	11.01	12.74	12.35
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15074 - R15079 are Sprague Dawley  
 Animals R15080 - R15085 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 2 - 50 mg/kg/day Flutamide - CONTINUED	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
ANIMAL #									
R15074	207.8	215.5	221.3	229.1	237.7	244.7	242.9	251.1	a
R15075	202.0	201.9	208.2	216.4	222.7	231.5	241.0	249.7	a
R15076	200.8	211.5	211.9	216.5	229.6	233.8	243.5	250.9	a
R15077	213.5	214.9	226.9	231.8	242.9	249.0	257.7	265.2	269.1
R15078	211.0	214.7	224.5	231.9	240.4	247.9	251.1	264.6	260.3
R15079	203.1	200.9	215.2	221.2	230.3	232.7	240.5	252.6	249.5
R15080	187.9	193.8	198.8	210.9	214.0	218.7	227.8	235.6	a
R15081	200.3	205.4	211.3	217.7	223.9	232.0	237.6	244.5	a
R15082	233.5	244.0	248.1	259.3	263.6	268.7	281.3	289.4	a
R15083	199.8	204.7	205.2	217.1	221.3	228.9	235.3	240.6	249.3
R15084	205.9	210.8	215.1	222.6	231.5	236.7	245.3	249.1	257.8
R15085	226.9	234.4	239.3	249.8	253.6	260.7	272.9	273.4	278.0
MEAN	207.7	212.7	218.8	227.0	234.3	240.4	248.1	255.6	260.7
S.D.	12.40	14.15	14.18	14.57	14.22	14.24	15.58	15.10	11.26
N	12	12	12	12	12	12	12	12	6

Appendix Continued

Key: Animals R15074 - R15079 are Sprague Dawley  
 Animals R15080 - R15085 are Long-Evans  
 PND = Postnatal Day  
 a = Terminal Kill

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 3 - 80 mg/kg/day Methyl Testosterone	PND 22		PND 23		PND 24		PND 25		PND 26		PND 27		PND 28		PND 29		PND 30		PND 31		PND 32		PND 33	
	ANIMAL #	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight	Weight
R15086	47.1	52.8	58.8	65.2	69.0	75.2	81.6	87.6	93.5	99.7	107.3	112.4												
R15087	51.0	56.9	62.7	68.3	74.5	80.6	88.4	95.2	103.0	108.2	117.0	120.8												
R15088	48.4	53.4	59.0	66.7	74.1	79.1	86.3	94.9	102.0	105.1	113.8	121.7												
R15089	50.5	56.7	61.6	68.6	73.6	79.5	88.1	93.5	101.0	107.5	115.3	116.3												
R15090	51.4	56.8	60.1	67.8	73.0	79.5	86.4	93.9	101.2	106.6	116.5	118.1												
R15091	50.0	52.7	57.6	64.4	71.1	77.1	84.5	90.9	96.3	101.9	110.7	112.5												
R15092	54.1	60.0	64.9	71.2	76.4	84.7	91.2	100.8	107.5	118.1	123.3	130.9												
R15093	49.5	55.9	62.0	69.3	74.1	82.0	89.2	94.7	105.4	112.8	119.6	125.9												
R15094	53.2	60.1	65.7	70.5	76.3	85.9	93.5	101.7	111.7	118.5	123.8	129.6												
R15095	39.5	44.1	48.0	53.7	59.7	65.4	71.4	76.1	82.4	89.4	94.1	98.5												
R15096	44.0	49.2	52.8	60.0	65.2	72.1	79.8	86.3	94.0	103.5	110.4	116.7												
R15097	52.4	58.5	63.7	69.9	75.0	82.7	90.6	97.5	104.7	114.5	118.9	124.1												
MEAN	49.3	54.8	59.7	66.3	71.8	78.7	85.9	92.8	100.2	107.2	114.2	119.0												
S.D.	4.12	4.65	5.11	5.03	4.98	5.68	6.02	6.96	7.75	8.27	8.08	8.83												
N	12	12	12	12	12	12	12	12	12	12	12	12												

Appendix Continued

Key: Animals R15086 - R15091 are Sprague Dawley  
 Animals R15092 - R15097 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL #	Methyl Testosterone - CONTINUED											
	PND 34	PND 35	PND 36	PND 37	PND 38	PND 39	PND 40	PND 41	PND 42	PND 43	PND 44	PND 45
R15086	119.0	126.9	129.2	132.9	144.6	148.8	155.0	157.5	166.6	170.9	170.4	167.6
R15087	126.8	134.5	136.7	144.9	151.6	159.1	165.3	164.9	175.6	183.4	187.4	193.1
R15088	127.2	133.2	136.9	144.7	151.5	160.3	164.6	168.6	174.8	183.2	191.6	192.3
R15089	129.5	138.6	145.9	152.0	158.6	164.8	170.2	178.9	183.4	189.8	197.1	197.4
R15090	127.5	135.3	143.2	151.4	157.8	163.9	167.3	172.7	182.8	190.7	195.5	199.9
R15091	124.8	131.7	138.3	145.7	153.0	159.2	160.2	169.4	176.2	181.9	187.4	192.6
R15092	141.6	147.4	156.7	162.1	169.2	180.8	183.7	185.7	195.5	205.2	210.2	220.2
R15093	136.2	145.4	150.0	156.6	161.9	170.9	175.5	179.9	186.6	192.7	198.9	204.0
R15094	142.3	150.2	157.2	166.5	174.6	182.2	191.3	197.6	208.4	213.7	225.0	236.3
R15095	108.6	114.9	118.9	125.4	130.4	137.8	141.0	146.6	153.0	158.9	167.5	173.7
R15096	127.1	133.2	143.3	150.7	160.2	169.4	174.8	178.8	189.6	194.0	202.9	212.9
R15097	133.5	138.9	141.6	151.0	161.5	168.3	174.4	178.1	186.4	193.6	202.3	213.4
MEAN	128.7	135.9	141.5	148.7	156.2	163.8	168.6	173.2	181.6	188.2	194.7	200.3
S.D.	9.32	9.53	10.84	11.35	11.47	12.38	13.18	13.29	14.09	14.39	15.82	19.06
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15086 - R15091 are Sprague Dawley  
 Animals R15092 - R15097 are Long-Evans  
 PND = Postnatal Day



APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 3 - 80 mg/kg/day Methyl Testosterone - CONTINUED	Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats											
	ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54		
R15086	182.2	182.9	182.2	201.8	202.7	207.3	216.0	221.4			a	
R15087	200.1	199.9	205.4	213.5	219.0	224.0	228.2	236.1			a	
R15088	201.6	205.4	210.3	220.5	225.2	228.5	234.6	243.4			a	
R15089	209.0	214.7	214.5	227.1	232.0	233.6	244.5	252.1			254.6	
R15090	208.0	211.9	216.3	223.4	229.9	233.8	245.3	253.7			262.9	
R15091	198.3	191.0	203.4	209.1	215.7	220.1	228.1	233.0			242.7	
R15092	225.6	238.7	242.6	249.0	253.0	262.2	270.7	268.3			a	
R15093	211.3	216.7	219.5	227.2	233.0	237.7	242.9	249.1			a	
R15094	242.1	246.8	253.7	264.3	269.8	280.8	287.4	295.7			a	
R15095	178.3	182.3	189.1	197.4	198.8	203.4	212.4	217.9			222.3	
R15096	219.9	226.0	231.6	236.2	245.7	249.6	257.1	263.9			266.8	
R15097	217.9	225.3	231.0	237.1	244.1	250.5	256.1	260.5			268.8	
MEAN	207.9	211.8	216.6	225.6	230.7	236.0	243.6	249.6			253.0	
S.D.	17.76	20.64	20.84	19.32	20.52	22.24	21.93	21.57			17.83	
N	12	12	12	12	12	12	12	12			6	

Appendix Continued

Key: Animals R15086 - R15091 are Sprague Dawley  
 Animals R15092 - R15097 are Long-Evans  
 PND = Postnatal Day  
 a = Terminal Kill

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL #	GROUP: 4 - 240 mg/kg/day Propylthiouracil											
	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15098	51.8	56.2	60.7	68.4	71.2	79.3	81.9	90.8	97.0	101.7	106.5	103.0
R15099	52.3	55.6	61.3	63.0	70.0	75.5	79.4	84.0	91.9	97.6	104.9	104.2
R15100	53.5	59.1	64.9	66.9	71.8	77.1	80.0	85.3	95.3	99.7	104.7	102.6
R15101	49.3	53.7	58.9	61.9	66.8	71.6	77.3	81.9	88.6	95.7	97.8	100.5
R15102	50.3	54.6	59.6	64.3	68.8	73.6	81.5	81.9	90.4	97.4	100.3	103.5
R15103	50.2	54.6	60.9	65.6	69.0	73.5	79.5	82.7	89.7	96.1	98.3	101.8
R15104	49.7	54.8	56.9	63.4	70.3	77.4	82.8	84.7	82.7	89.2	93.1	91.2
R15105	51.7	57.5	60.1	66.6	67.6	80.2	84.2	82.2	88.4	100.3	99.0	103.1
R15106	51.2	54.8	60.8	68.4	69.6	77.0	82.8	87.6	93.2	99.8	99.7	102.0
R15107	51.6	57.9	64.6	71.3	76.0	83.7	84.9	93.3	95.3	103.0	104.4	103.4
R15108	44.2	49.2	53.9	61.8	63.2	74.9	75.0	79.7	84.6	92.1	97.0	95.0
R15109	50.7	55.2	61.4	68.9	72.1	75.9	78.3	87.7	95.0	99.9	99.9	94.9
MEAN	50.5	55.3	60.3	65.9	69.7	76.6	80.6	85.2	91.0	97.7	100.5	100.4
S.D.	2.32	2.49	2.98	3.05	3.15	3.30	2.93	4.02	4.46	3.98	3.94	4.27
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15098 - R15103 are Sprague Dawley  
 Animals R15104 - R15109 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 4 - 240 mg/kg/day Propylthiouracil - CONTINUED	Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats														
	ANIMAL #	PND 34	PND 35	PND 36	PND 37	PND 38	PND 39	PND 40	PND 41	PND 42	PND 43	PND 44	PND 45		
R15098	111.1	119.4	112.6	121.5	123.2	122.5	120.9	122.8	125.5	121.5	127.0	126.4			
R15099	107.8	107.6	108.5	118.5	119.5	116.1	115.3	116.6	118.7	114.7	120.8	122.5			
R15100	109.2	111.3	112.7	117.5	121.4	117.7	116.8	117.6	119.0	116.6	119.9	120.8			
R15101	103.1	108.7	104.2	106.3	109.1	112.3	111.5	116.4	115.6	115.7	118.3	120.0			
R15102	105.9	109.4	109.3	115.6	117.5	116.8	114.9	115.2	121.6	117.1	122.2	120.4			
R15103	104.4	110.3	104.5	109.3	112.1	110.7	111.3	110.9	109.8	109.4	114.8	113.8			
R15104	97.3	93.2	96.3	96.6	99.9	103.2	102.6	104.2	105.3	104.4	104.5	106.6			
R15105	107.7	111.9	108.4	118.0	116.3	118.1	118.6	117.9	119.6	120.5	121.3	123.1			
R15106	102.8	104.0	103.5	104.5	107.1	107.8	106.0	105.2	106.2	107.3	109.1	110.2			
R15107	108.6	112.1	108.2	108.2	113.1	115.3	115.4	116.1	118.2	116.3	117.6	117.5			
R15108	97.1	103.1	98.1	103.9	107.6	106.8	103.3	106.1	108.3	105.0	109.8	110.5			
R15109	103.1	105.7	99.4	103.0	104.8	109.6	106.9	102.0	109.0	102.8	104.1	108.8			
MEAN	104.8	108.1	105.5	110.2	112.6	113.1	112.0	112.6	114.7	112.6	115.8	116.7			
S.D.	4.45	6.36	5.43	7.80	7.17	5.61	6.06	6.67	6.70	6.50	7.35	6.50			
N	12	12	12	12	12	12	12	12	12	12	12	12			

Appendix Continued

Key: Animals R15098 - R15103 are Sprague Dawley  
 Animals R15104 - R15109 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 4 - 240 mg/kg/day Propylthiouracil - CONTINUED	Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats											
	ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54	PND 55	
R15098	123.6	119.9	121.2	120.8	120.9	122.2	120.9	120.9	120.0	120.0	a	
R15099	122.3	115.7	113.1	115.2	116.4	114.5	115.8	115.8	114.9	114.9	a	
R15100	119.3	116.3	116.7	115.7	118.2	114.5	114.6	114.6	114.8	114.8	a	
R15101	117.3	113.1	113.9	113.3	117.1	116.0	116.3	116.3	117.6	117.6	115.8	
R15102	116.0	110.0	110.0	115.6	115.4	115.6	112.7	112.7	112.1	112.1	111.6	
R15103	111.9	107.5	109.8	112.9	108.9	111.0	110.1	110.1	107.7	107.7	107.5	
R15104	106.0	104.0	101.9	101.6	106.5	106.0	105.9	105.9	105.4	105.4	a	
R15105	121.3	119.9	117.9	118.7	120.5	119.3	119.8	119.8	118.0	118.0	a	
R15106	108.7	107.5	105.7	106.4	106.5	106.5	106.8	106.8	107.2	107.2	a	
R15107	118.8	116.0	114.4	112.3	117.8	117.9	117.4	117.4	119.2	119.2	118.5	
R15108	106.3	105.9	105.9	104.4	107.2	109.1	109.3	109.3	109.0	109.0	106.7	
R15109	104.1	102.6	105.3	105.0	104.3	104.2	106.7	106.7	106.2	106.2	105.2	
MEAN	114.6	111.5	111.3	111.8	113.3	113.1	113.0	113.0	112.7	112.7	110.9	
S.D.	6.94	6.07	5.87	6.09	6.12	5.69	5.22	5.22	5.41	5.41	5.37	
N	12	12	12	12	12	12	12	12	12	12	6	

Appendix Continued

Key: Animals R15098 - R15103 are Sprague Dawley  
 Animals R15104 - R15109 are Long-Evans  
 PND = Postnatal Day  
 a = Terminal Kill

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 5 - 100 mg/kg/day Ketoconazole	Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats											
	ANIMAL #	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32
R15110	49.7	54.4	59.1	61.2	65.8	71.9	78.1	82.9	88.7	92.7	100.0	104.9
R15111	50.2	53.0	59.3	63.5	66.9	72.5	76.8	82.5	87.9	95.1	101.8	106.8
R15112	50.6	54.1	61.6	67.5	70.4	76.3	83.2	89.1	95.5	101.9	110.2	116.1
R15113	49.3	52.8	59.2	64.0	68.8	72.5	79.2	83.5	89.3	96.2	101.9	105.8
R15114	49.4	54.4	60.5	64.9	69.4	74.7	80.8	87.7	92.6	98.6	104.4	108.6
R15115	50.0	54.4	59.6	64.1	68.8	72.3	78.5	84.0	90.2	96.0	102.1	107.8
R15116	47.0	50.4	54.0	59.9	66.8	71.0	76.2	81.3	88.0	98.4	103.5	109.1
R15117	46.2	51.7	56.7	62.5	66.8	73.2	77.8	83.9	91.6	98.5	102.8	109.5
R15118	47.4	51.4	56.3	63.6	69.2	75.5	82.0	84.8	92.6	99.4	107.0	112.5
R15119	53.5	58.5	67.2	72.2	75.6	83.4	89.3	95.1	101.0	109.5	122.8	124.0
R15120	44.7	48.4	55.0	57.9	63.4	68.7	74.4	79.6	82.6	91.5	99.3	103.6
R15121	53.2	56.0	63.3	66.8	72.3	79.7	86.5	91.8	97.0	106.0	114.7	117.9
MEAN	49.3	53.3	59.3	64.0	68.7	74.3	80.2	85.5	91.4	98.7	105.9	110.6
S.D.	2.62	2.65	3.66	3.73	3.18	4.01	4.37	4.54	4.84	5.18	6.91	6.04
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15110 - R15115 are Sprague Dawley  
 Animals R15116 - R15121 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 5 - 100 mg/kg/day Ketoconazole - CONTINUED	PND 34	PND 35	PND 36	PND 37	PND 38	PND 39	PND 40	PND 41	PND 42	PND 43	PND 44	PND 45
ANIMAL #												
R15110	110.9	117.5	120.1	130.0	135.4	140.8	145.8	151.0	157.5	163.2	171.8	178.4
R15111	116.4	122.3	127.0	139.1	143.0	150.6	156.1	165.3	172.8	177.6	184.6	195.5
R15112	122.7	127.0	132.3	146.7	156.3	160.5	165.2	170.8	183.0	186.4	190.9	200.2
R15113	115.3	121.9	125.7	133.8	140.1	150.2	150.8	158.1	166.8	169.5	180.9	188.6
R15114	117.6	126.5	130.4	140.9	146.9	152.8	162.1	164.9	175.9	181.1	187.3	194.9
R15115	117.3	124.2	129.6	136.5	144.2	150.9	154.9	161.2	169.3	174.7	180.6	189.1
R15116	120.9	125.0	131.8	141.3	149.1	158.2	163.7	170.9	176.9	183.1	189.0	199.2
R15117	120.4	127.4	133.0	142.4	148.4	157.5	155.9	169.2	176.3	180.3	188.3	194.6
R15118	117.0	124.6	126.7	136.1	144.5	149.7	152.3	159.6	166.3	167.6	178.3	183.4
R15119	134.7	137.7	144.2	152.6	160.4	166.6	173.4	183.3	189.4	193.9	205.1	217.6
R15120	109.6	114.9	120.8	127.3	134.9	142.7	152.0	154.7	163.9	169.4	175.6	183.2
R15121	124.9	129.8	134.7	144.2	151.2	158.6	162.9	168.9	178.6	181.5	189.2	197.6
MEAN	119.0	124.9	129.7	139.2	146.2	153.3	157.9	164.8	173.1	177.4	185.1	193.5
S.D.	6.63	5.82	6.48	7.08	7.63	7.40	7.68	8.68	8.82	8.82	8.70	10.28
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15110 - R15115 are Sprague Dawley  
 Animals R15116 - R15121 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 5 - 100 mg/kg/day Ketoconazole - CONTINUED	Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats											
	ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54	PND 55	
R15110	179.7	185.9	186.4	194.2	202.2	206.1	214.6	224.6	246.8	a		
R15111	198.4	201.9	208.9	213.1	220.6	225.3	234.4	246.8	252.6	a		
R15112	205.1	210.5	215.1	220.0	230.4	235.2	246.6	252.6	238.9	a		
R15113	192.5	199.3	203.3	211.9	219.4	223.0	233.9	238.9	244.2	249.0		
R15114	199.7	207.2	208.8	219.0	225.9	230.3	237.5	244.2	234.5	244.5		
R15115	190.7	196.7	200.4	212.9	216.9	224.1	230.2	248.6	248.0	a		
R15116	204.8	209.5	216.4	221.3	228.2	234.0	243.4	248.0	236.8	a		
R15117	206.1	209.5	206.7	217.0	221.9	230.6	237.4	248.0	266.9	281.8		
R15118	190.8	196.3	204.4	210.6	218.9	220.6	227.3	236.8	240.4	242.3		
R15119	220.1	226.0	222.6	228.6	240.6	249.3	260.0	266.9	257.3	262.8		
R15120	189.2	194.9	203.2	207.0	215.3	221.9	229.9	240.4	245.0	254.6		
R15121	199.2	208.7	212.8	222.8	228.3	236.0	240.5	257.3	11.15	15.17		
MEAN	198.0	203.9	207.4	214.9	222.4	228.0	236.3	245.0	12	6		
S.D.	10.46	10.31	9.24	8.86	9.48	10.60	11.19	11.15	12	6		
N	12	12	12	12	12	12	12	12	12	6		

Appendix Continued

Key: Animals R15110 - R15115 are Sprague Dawley  
 Animals R15116 - R15121 are Long-Evans  
 PND = Postnatal Day  
 a = Terminal Kill

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 6 - 30 mg/kg/day Pimozide	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
ANIMAL #												
R15122	52.8	55.0	47.8	53.9	61.1	67.4	69.9	73.5	81.7	85.9	93.5	97.6
R15123	53.4	55.9	48.2	52.3	57.4	67.1	68.2	75.1	84.8	86.4	94.9	96.0
R15124	51.3	53.5	46.7	48.1	54.6	64.5	67.0	69.3	81.2	85.5	95.5	97.8
R15125	50.0	52.2	45.4	46.7	53.9	62.2	66.4	69.8	77.9	81.8	93.2	95.2
R15126	51.0	52.9	45.6	49.8	55.7	64.3	69.3	71.4	79.0	86.2	94.6	95.7
R15127	49.0	51.7	44.3	47.6	56.0	62.2	62.5	63.4	73.8	78.1	87.8	88.6
R15128	52.8	56.2	51.0	51.5	54.7	53.2	51.6	65.3	71.5	78.0	86.1	92.6
R15129	54.2	58.2	50.2	53.3	56.3	56.8	54.6	69.2	74.8	81.5	92.4	94.7
R15130	41.1	45.0	39.9	42.7	47.0	43.4	42.1	54.6	60.0	64.2	75.4	82.5
R15131	42.1	43.0	39.0	35.6	33.2	30.4	29.4	34.0	39.5	41.5	45.6	45.9
R15132	46.0	49.4	43.8	44.9	50.3	57.1	61.6	64.1	70.3	77.7	83.2	87.6
R15133	47.7	51.5	45.8	44.6	51.1	56.8	63.0	65.1	68.1	80.4	85.6	89.2
MEAN	49.3	52.0	45.6	47.6	52.6	57.1	58.8	64.6	71.9	77.3	85.7	88.6
S.D.	4.32	4.48	3.62	5.22	7.11	10.79	12.43	11.06	12.27	12.81	13.97	14.24
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15122 - R15127 are Sprague Dawley  
 Animals R15128 - R15133 are Long-Evans  
 PND = Postnatal Day



APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 6 - 30 mg/kg/day Pimozide - CONTINUED	INDIVIDUAL BODY WEIGHTS (GRAMS)														
	ANIMAL #	PND 34	PND 35	PND 36	PND 37	PND 38	PND 39	PND 40	PND 41	PND 42	PND 43	PND 44	PND 45		
R15122	106.2	109.0	108.7	106.7	121.5	127.3	132.7	140.4	143.8	149.8	161.0	173.4			
R15123	104.8	111.7	113.3	108.6	122.3	131.7	139.8	143.4	148.1	147.4	161.4	169.4			
R15124	101.2	111.2	113.0	110.1	128.1	139.2	147.6	150.0	160.0	161.6	168.6	178.5			
R15125	103.2	108.2	111.1	122.9	132.9	136.4	144.2	143.2	156.4	162.5	170.3	175.7			
R15126	103.1	109.5	111.6	112.7	121.0	132.0	133.3	136.9	141.0	147.5	150.9	160.9			
R15127	100.2	102.9	106.2	113.6	118.0	131.6	132.4	139.8	148.1	154.2	165.7	170.5			
R15128	97.9	101.5	99.4	102.7	113.7	120.3	125.9	131.7	142.0	148.1	159.1	159.5			
R15129	100.3	106.6	111.1	115.5	124.5	134.6	139.9	147.2	153.1	160.8	168.8	173.8			
R15130	87.7	92.6	98.0	103.1	114.8	123.8	130.8	136.6	148.0	148.5	164.9	167.6			
R15131	51.0	53.8	58.5	62.0	69.7	75.5	81.4	89.3	95.5	103.4	110.0	120.3			
R15132	94.2	99.4	105.0	118.2	125.5	133.1	136.4	145.2	151.2	158.4	166.3	168.7			
R15133	96.6	97.4	105.6	103.5	115.2	124.8	132.3	131.5	147.3	152.5	161.4	167.0			
MEAN	95.5	100.3	103.5	106.6	117.3	125.9	131.4	136.3	144.5	149.6	159.0	165.4			
S.D.	14.91	15.81	15.02	15.40	16.03	16.78	16.87	15.86	16.42	15.64	16.32	15.26			
N	12	12	12	12	12	12	12	12	12	12	12	12			

Appendix Continued

Key: Animals R15122 - R15127 are Sprague Dawley  
 Animals R15128 - R15133 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 6 - 30 mg/kg/day Pimozide - CONTINUED	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
ANIMAL #									
R15122	174.8	174.3	176.5	188.7	191.9	198.7	207.2	214.2	a
R15123	172.4	176.4	179.9	186.4	194.5	201.5	207.9	215.6	a
R15124	180.5	180.6	194.7	195.6	203.2	214.0	223.3	228.5	a
R15125	187.2	188.4	191.5	205.7	205.4	213.5	215.2	227.6	232.4
R15126	164.4	167.9	167.6	176.0	180.8	187.0	189.5	198.7	202.8
R15127	178.6	181.7	187.2	194.5	196.9	206.1	213.8	221.2	231.8
R15128	165.3	168.6	175.8	180.0	183.6	188.9	200.7	208.8	a
R15129	179.6	187.7	189.9	197.6	202.5	210.2	219.0	224.6	a
R15130	174.3	181.4	190.8	194.3	201.6	206.5	221.1	230.8	a
R15131	128.7	134.1	139.8	146.8	156.6	161.5	169.0	177.3	184.6
R15132	173.1	183.8	185.9	191.9	202.7	210.2	215.5	221.6	224.0
R15133	173.4	179.2	183.7	190.5	201.4	209.7	217.8	228.2	237.5
MEAN	171.0	175.3	180.3	187.3	193.4	200.7	208.3	216.4	218.9
S.D.	14.73	14.52	14.96	14.98	14.03	15.18	15.61	15.50	20.77
N	12	12	12	12	12	12	12	12	6

Appendix Continued

Key: Animals R15122 - R15127 are Sprague Dawley  
 Animals R15128 - R15133 are Long-Evans  
 PND = Postnatal Day  
 a = Terminal Kill

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL #	Dibutylphthalate															
	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33				
R15134	49.2	54.0	60.5	64.4	72.5	76.7	83.4	89.3	92.6	103.4	113.1	117.5				
R15135	50.4	53.8	62.3	63.3	70.3	74.6	79.2	84.9	89.3	95.5	98.8	108.2				
R15136	51.6	55.5	61.7	65.4	71.7	74.7	83.0	86.7	90.9	98.7	106.2	112.1				
R15137	50.0	55.5	61.3	68.4	69.5	75.9	82.2	86.5	92.8	97.5	105.3	109.7				
R15138	48.3	55.4	59.4	64.1	69.3	75.6	83.2	89.6	96.4	102.9	111.2	116.6				
R15139	49.2	54.0	60.2	63.9	68.3	73.6	78.8	84.0	89.7	95.0	105.5	107.8				
R15140	51.5	54.9	61.2	67.0	72.7	82.6	89.0	92.7	98.2	104.9	112.1	117.8				
R15141	52.8	56.5	63.5	68.9	72.2	80.2	87.1	92.6	98.8	107.7	118.0	122.9				
R15142	45.8	50.5	56.1	62.9	67.0	75.6	82.5	86.3	95.5	105.1	111.0	117.3				
R15143	51.3	56.1	65.0	69.0	71.6	81.7	83.6	89.7	99.3	107.2	112.0	122.8				
R15144	42.4	45.7	51.2	59.0	63.4	69.7	77.2	81.7	90.6	99.3	106.8	110.4				
R15145	48.5	53.0	57.3	64.3	68.9	76.4	83.6	84.9	95.0	101.7	108.5	112.5				
MEAN	49.3	53.7	60.0	65.1	69.8	76.4	82.7	87.4	94.1	101.6	109.0	114.6				
S.D.	2.85	3.00	3.68	2.91	2.71	3.59	3.30	3.41	3.60	4.35	4.94	5.27				
N	12	12	12	12	12	12	12	12	12	12	12	12				

Appendix Continued

Key: Animals R15134 - R15139 are Sprague Dawley  
 Animals R15140 - R15145 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL #	GROUP: 7 - 1000 mg/kg/day Dibutylphthalate - CONTINUED														
	PND 34	PND 35	PND 36	PND 37	PND 38	PND 39	PND 40	PND 41	PND 42	PND 43	PND 44	PND 45			
R15134	125.3	133.2	136.5	145.9	151.5	162.8	167.8	172.0	181.9	188.1	190.8	199.4			
R15135	117.6	122.9	128.4	136.4	143.8	150.2	157.5	167.0	173.8	178.5	181.3	190.4			
R15136	116.9	125.7	128.7	137.1	144.1	152.5	155.8	162.1	173.1	175.5	179.7	187.6			
R15137	118.2	124.6	126.1	139.2	140.9	149.1	153.9	158.5	170.7	174.7	183.1	187.8			
R15138	125.9	134.0	133.4	145.0	149.0	156.2	162.0	168.0	178.2	179.4	187.3	195.8			
R15139	114.8	118.1	118.5	130.3	132.1	141.6	146.6	152.1	159.4	164.5	169.2	175.8			
R15140	126.5	131.5	145.2	146.6	150.3	162.7	166.4	175.0	183.2	187.8	200.3	204.0			
R15141	132.7	141.3	147.0	150.1	162.2	170.7	178.4	185.3	189.6	197.3	208.7	213.1			
R15142	129.7	140.1	145.1	150.9	160.9	171.8	179.0	186.4	191.4	197.3	207.8	210.2			
R15143	127.4	137.6	142.8	147.0	154.8	165.7	168.3	179.6	187.6	191.9	199.9	204.2			
R15144	124.9	134.4	137.7	146.3	156.3	162.4	169.3	175.5	185.9	193.8	198.7	204.8			
R15145	120.8	128.2	135.0	137.2	145.2	152.8	156.8	160.5	168.5	168.5	174.5	181.1			
MEAN	123.4	131.0	135.4	142.7	149.3	158.2	163.5	170.2	178.6	183.1	190.1	196.2			
S.D.	5.62	7.18	8.82	6.41	8.67	9.27	9.84	10.76	9.71	11.14	12.99	11.73			
N	12	12	12	12	12	12	12	12	12	12	12	12			

Appendix Continued

Key: Animals R15134 - R15139 are Sprague Dawley  
 Animals R15140 - R15145 are Long-Evans  
 PND = Postnatal Day

APPENDIX 2 (CONTINUED)  
 INDIVIDUAL BODY WEIGHTS (GRAMS)  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats  
 GROUP: 7 - 1000 mg/kg/day Dibutylphthalate - CONTINUED

ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
R15134	206.5	211.2	213.3	232.3	235.3	241.7	256.0	260.2	a
R15135	194.7	196.5	204.4	210.6	221.4	227.9	235.5	240.9	a
R15136	190.3	197.5	202.3	206.2	211.9	221.7	228.3	234.2	a
R15137	194.4	201.1	199.8	208.8	218.9	219.8	230.0	237.1	242.8
R15138	201.7	205.6	210.5	226.6	226.9	234.3	246.2	255.2	259.8
R15139	183.6	188.4	191.6	203.6	210.0	215.7	224.1	232.4	238.2
R15140	208.8	216.1	219.1	228.6	229.6	239.8	248.1	256.6	a
R15141	225.3	225.7	229.8	242.8	242.7	253.5	257.8	268.4	a
R15142	217.8	224.3	228.4	239.8	241.2	249.1	256.8	264.6	a
R15143	213.2	219.3	228.3	239.9	241.9	255.7	262.1	263.5	272.4
R15144	210.9	216.8	223.4	232.1	234.4	239.8	247.1	257.2	265.2
R15145	186.3	196.2	199.2	207.0	209.3	223.2	226.6	229.4	236.7
MEAN	202.8	208.2	212.5	223.2	227.0	235.2	243.2	250.0	252.5
S.D.	13.11	12.35	13.19	14.90	12.53	13.59	13.70	14.12	15.22
N	12	12	12	12	12	12	12	12	6

Key: Animals R15134 - R15139 are Sprague Dawley  
 Animals R15140 - R15145 are Long-Evans  
 PND = Postnatal Day  
 a = Terminal Kill

## APPENDIX 3

## INDIVIDUAL AGE AND WEIGHT AT COMPLETE PREPUTIAL SEPARATION

## ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (SPRAGUE DAWLEY)

ANIMAL ID	WEIGHT AT PREPUTIAL SEPARATION (GRAMS)	AGE AT PREPUTIAL SEPARATION (DAYS)
<u>GROUP: 1 - 2.5 ML/KG/DAY CORN OIL</u>		
R15062	189.0	44
R15063	184.2	43
R15064	190.6	44
R15065	167.3	41
R15066	186.0	43
R15067	192.4	43
<u>GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE</u>		
R15074	NS	NS
R15075	NS	NS
R15076	NS	NS
R15077	NS	NS
R15078	NS	NS
R15079	NS	NS
<u>GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE</u>		
R15086	170.4	44
R15087	134.5	35
R15088	121.7	33
R15089	145.9	36
R15090	127.5	34
R15091	138.3	36
<u>GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL</u>		
R15098	NS	NS
R15099	NS	NS
R15100	NS	NS
R15101	NS	NS
R15102	NS	NS
R15103	NS	NS
<u>GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE</u>		
R15110	194.2	49
R15111	220.6	50
R15112	190.9	44
R15113	188.6	45
R15114	199.7	46
R15115	196.7	47
<u>GROUP: 6 - 30 MG/KG/DAY PIMOZIDE</u>		
R15122	214.2	53
R15123	NS	NS
R15124	223.3	52
R15125	215.2	52
R15126	NS	NS
R15127	206.1	51
<u>GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE</u>		
R15134	190.8	44
R15135	181.3	44
R15136	190.3	46
R15137	183.1	44
R15138	201.7	46
R15139	183.6	46

Appendix Continued

NS = NO COMPLETE PREPUTIAL SEPARATION WAS SEEN

## APPENDIX 3 (CONTINUED)

## INDIVIDUAL AGE AND WEIGHT AT COMPLETE PREPUTIAL SEPARATION

## ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG-EVANS)

ANIMAL ID	WEIGHT AT PREPUTIAL SEPARATION (GRAMS)	AGE AT PREPUTIAL SEPARATION (DAYS)
<u>GROUP: 1 - 2.5 ML/KG/DAY CORN OIL</u>		
R15068	223.7	47
R15069	236.1	45
R15070	211.0	44
R15071	188.4	41
R15072	231.5	47
R15073	222.4	45
<u>GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE</u>		
R15080	NS	NS
R15081	NS	NS
R15082	NS	NS
R15083	NS	NS
R15084	NS	NS
R15085	NS	NS
<u>GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE</u>		
R15092	130.9	33
R15093	125.9	33
R15094	118.5	31
R15095	94.1	32
R15096	110.4	32
R15097	124.1	33
<u>GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL</u>		
R15104	106.0	46
R15105	119.8	52
R15106	NS	NS
R15107	NS	NS
R15108	NS	NS
R15109	NS	NS
<u>GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE</u>		
R15116	209.5	47
R15117	209.5	47
R15118	NS	NS
R15119	220.1	46
R15120	183.2	45
R15121	228.3	50
<u>GROUP: 6 - 30 MG/KG/DAY PIMOZIDE</u>		
R15128	183.6	50
R15129	224.6	53
R15130	NS	NS
R15131	184.6	54
R15132	202.7	50
R15133	217.8	52
<u>GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE</u>		
R15140	NS	NS
R15141	208.7	44
R15142	256.8	52
R15143	219.3	47
R15144	NS	NS
R15145	223.2	51

NS = NO COMPLETE PREPUTIAL SEPARATION WAS SEEN







APPENDIX 4 (CONTINUED)  
 INDIVIDUAL DAILY PREPUTIAL SEPARATION DATA  
 ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG-EVANS)

ANIMAL ID	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54				
	POSTNATAL DAY																																			
	<u>GROUP: 1 - 2.5 ML/KG/DAY CORN OIL</u>																																			
R15068	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
R15069	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
R15070	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
R15071	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
R15072	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
R15073	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
	<u>GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE</u>																																			
R15080	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
R15081	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
R15082	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
R15083	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
R15084	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
R15085	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	<u>GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE</u>																																			
R15092	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
R15093	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
R15094	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
R15095	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
R15096	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
R15097	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
	<u>GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL</u>																																			
R15104	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
R15105	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
R15106	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
R15107	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
R15108	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
R15109	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Appendix Continued

Y = Yes, prepuce separated  
 P = Prepuce partially separated  
 N = No, prepuce not separated  
 T = Persistent thread of tissue between glans and prepuce

APPENDIX 4 (CONTINUED)  
 INDIVIDUAL DAILY PREPUTIAL SEPARATION DATA  
 ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG-EVANS)

ANIMAL ID	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54						
	POSTNATAL DAY																																					
	<u>GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE</u>																																					
R15116	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y										
R15117	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y											
R15118	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	T	T	T	T	T	T	T	T	T				
R15119	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	Y	Y	Y											
R15120	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y												
R15121	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y	Y	Y	Y	Y				
	<u>GROUP: 6 - 30 MG/KG/DAY PIMOZIDE</u>																																					
R15128	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y	Y	Y	Y	Y				
R15129	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	T	T	T	T	T	Y				
R15130	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	T	T	T	T	T	T				
R15131	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	Y			
R15132	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y		
R15133	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	
	<u>GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE</u>																																					
R15140	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	T	T	T	T	T	T	T			
R15141	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	T	T	T	T	T	T	T			
R15142	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	T	T	T	T	T	Y	Y	Y		
R15143	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	Y	Y	Y	Y	Y	Y	Y	Y		
R15144	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	T	T	
R15145	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y

Y = Yes, prepuce separated  
 P = Prepuce partially separated  
 N = No, prepuce not separated  
 T = Persistent thread of tissue between glans and prepuce

APPENDIX 5  
 INDIVIDUAL NECROPSY OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 1 - 2.5 mL/kg/day Corn Oil	FATE	PND	LOCATION	OBSERVATION
R15062	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15063	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15064	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15065	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15066	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15067	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15068	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15069	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15070	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15071	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15072	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15073	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS

Appendix Continued

Key: Animals R15062 - R15067 are Sprague Dawley  
 Animals R15068 - R15073 are Long-Evans  
 PND = Postnatal Day

APPENDIX 5 (CONTINUED)  
 INDIVIDUAL NECROPSY OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL ID	FATE	PND	LOCATION	OBSERVATION
R15074	Terminal Kill	53	Testes (Paired)	DARK, left, gray
R15075	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
R15076	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
R15077	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
R15078	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
R15079	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
R15080	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
R15081	Terminal Kill	53	Ventral Prostate	SMALL
R15082	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
R15083	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
R15084	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
R15085	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL

Appendix Continued

Key: Animals R15074 - R15079 are Sprague Dawley  
 Animals R15080 - R15085 are Long-Evans  
 PND = Postnatal Day

APPENDIX 5 (CONTINUED)  
 INDIVIDUAL NECROPSY OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL ID	FATE	PND	LOCATION	OBSERVATION
R15086	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15087	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15088	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15089	Terminal Kill	54	Kidneys (paired)	CYST, LEFT, CORTEX, ONE, CLEAR, 1X1 mm
R15090	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15091	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
			Thyroid	ENLARGED, Moderate
R15092	Terminal Kill	53	Liver	ACCESSORY LOBE, median lobe at cleft, one, tan, 10x5x3
			Testes (Paired)	SMALL, Bilateral
R15093	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
R15094	Terminal Kill	53	Testes (Paired)	NO ORGANS WITH GROSS FINDINGS
R15095	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
R15096	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15097	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral

Appendix Continued

Key: Animals R15086 - R15091 are Sprague Dawley  
 Animals R15092 - R15097 are Long-Evans  
 PND = Postnatal Day

APPENDIX 5 (CONTINUED)  
 INDIVIDUAL NECROPSY OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 4 - 240 mg/kg/day Propylthiouracil	FATE	PND	LOCATION	OBSERVATION
R15098	Terminal Kill	53	Seminal Vesicle Thyroid	SMALL, Bilateral ENLARGED, Bilateral
R15099	Terminal Kill	53	Seminal Vesicle Ventral Prostate	SMALL, Bilateral SMALL
R15100	Terminal Kill	53	Seminal Vesicle Ventral Prostate	SMALL, Bilateral SMALL
R15101	Terminal Kill	54	Thyroid Seminal Vesicle	ENLARGED, Moderate SMALL, Bilateral
R15102	Terminal Kill	54	Thyroid Seminal Vesicle	ENLARGED, Severe SMALL, Bilateral
R15103	Terminal Kill	54	Ventral Prostate Seminal Vesicle Ventral Prostate	SMALL SMALL, Bilateral SMALL
R15104	Terminal Kill	53	Pituitary Thyroid	SOFT CYST, 1, CLEAR, 1x1 mm ENLARGED, Severe
R15105	Terminal Kill	53	Thyroid	ENLARGED, Severe
R15106	Terminal Kill	53	Thyroid	ENLARGED, Severe
R15107	Terminal Kill	54	Thyroid	ENLARGED, Severe
R15108	Terminal Kill	54	Seminal Vesicle Ventral Prostate	ENLARGED, Severe SMALL
R15109	Terminal Kill	54	Thyroid Seminal Vesicle Ventral Prostate	ENLARGED, Severe SMALL, Bilateral SMALL
			Thyroid	ENLARGED, Severe

Appendix Continued

Key: Animals R15098 - R15103 are Sprague Dawley  
 Animals R15104 - R15109 are Long-Evans  
 PND = Postnatal Day

APPENDIX 5 (CONTINUED)  
 INDIVIDUAL NECROPSY OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 5M - 100 mg/kg/day Ketoconazole	ANIMAL ID	FATE	PND	LOCATION	OBSERVATION
	R15110	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
	R15111	Terminal Kill	53	Adrenals	ENLARGED, Bilateral, 4x3x3mm
	R15112	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
	R15113	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
	R15114	Terminal Kill	54	Adrenals	ENLARGED, BILATERAL, 4x4x4mm; PALE, BILATERAL, GREY
	R15115	Terminal Kill	54	Adrenals	ENLARGED, Bilateral, 5x4x3 mm
	R15116	Terminal Kill	53	Liver	ACCESSORY LOBE, median lobe, one, tan, 13x5x4mm
				Adrenals	ENLARGED, Bilateral, 5x3x3mm
	R15117	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
	R15118	Terminal Kill	53	Adrenals	ENLARGED, Bilateral, 4x3x3mm
	R15119	Terminal Kill	54	Adrenals	ENLARGED, BILATERAL, 4x3x3 mm; PALE, BILATERAL, GREY
	R15120	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
	R15121	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS

Appendix Continued

Key: Animals R15110 - R15115 are Sprague Dawley  
 Animals R15116 - R15121 are Long-Evans  
 PND = Postnatal Day



APPENDIX 5 (CONTINUED)  
INDIVIDUAL NECROPSY OBSERVATIONS  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 6 - 30 mg/kg/day Pimozide	LOCATION	PND	OBSERVATION	ANIMAL ID	FATE
R15122	Terminal Kill	53			NO ORGANS WITH GROSS FINDINGS
R15123	Terminal Kill	53			NO ORGANS WITH GROSS FINDINGS
R15124	Terminal Kill	53			NO ORGANS WITH GROSS FINDINGS
R15125	Terminal Kill	54			NO ORGANS WITH GROSS FINDINGS
R15126	Terminal Kill	54			NO ORGANS WITH GROSS FINDINGS
R15127	Terminal Kill	54			NO ORGANS WITH GROSS FINDINGS
R15128	Terminal Kill	53	Kidneys (paired)		CYST, left, one, clear, 1x1mm
R15129	Terminal Kill	53			NO ORGANS WITH GROSS FINDINGS
R15130	Terminal Kill	53			NO ORGANS WITH GROSS FINDINGS
R15131	Terminal Kill	54			NO ORGANS WITH GROSS FINDINGS
R15132	Terminal Kill	54			NO ORGANS WITH GROSS FINDINGS
R15133	Terminal Kill	54			NO ORGANS WITH GROSS FINDINGS

Appendix Continued

Key: Animals R15122 - R15127 are Sprague Dawley  
Animals R15128 - R15133 are Long-Evans  
PND = Postnatal Day

APPENDIX 5 (CONTINUED)  
 INDIVIDUAL NECROPSY OBSERVATIONS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

ANIMAL ID	FATE	PND	LOCATION	OBSERVATION
R15134	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15135	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15136	Terminal Kill	53	Kidneys (paired)	CYST, right, one, clear, 1x1mm
R15137	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15138	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15139	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15140	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
R15141	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
R15142	Terminal Kill	54	Testes (Paired)	NO ORGANS WITH GROSS FINDINGS
R15143	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
R15144	Terminal Kill	54		SMALL, Bilateral
R15145	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS

Key: Animals R15134 - R15139 are Sprague Dawley  
 Animals R15140 - R15145 are Long-Evans  
 PND = Postnatal Day

APPENDIX 6  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 1 - 2.5 mL/kg/day Corn Oil	R15062		R15063		R15064		R15065		R15066		R15067	
	ANIMAL ID:										STRAIN: SPRAGUE DAWLEY	
BODY WEIGHT (g)	251.4	255.4	255.4	256.7	255.6	263.5	271.7					
Liver (g)	10.759	10.745	10.864	11.471	11.431	11.962						
% BODY WEIGHT	4.280	4.207	4.232	4.488	4.488	4.403						
Kidneys (Paired) (g)	2.060	2.098	2.036	2.112	2.046	2.207						
% BODY WEIGHT	0.819	0.821	0.793	0.826	0.776	0.812						
Testes (Paired) (g)	2.973	3.107	3.181	3.079	3.033	3.181						
% BODY WEIGHT	1.183	1.217	1.239	1.205	1.151	1.171						
Epididymides (Paired) (g)	0.455	0.440	0.486	0.506	0.501	0.580						
% BODY WEIGHT	0.181	0.172	0.189	0.198	0.190	0.213						
Seminal Vesicle (g)	0.465	0.621	0.441	0.327	0.775	0.656						
% BODY WEIGHT	0.185	0.243	0.172	0.128	0.294	0.241						
Levator Ani plus Bulbocavernosus Muscle (g)	0.578	0.760	0.999	0.630	0.440	0.59						
% BODY WEIGHT	0.230	0.298	0.389	0.246	0.167	0.219						
Ventral Prostate (g)	0.221	0.248	0.234	0.200	0.248	0.188						
% BODY WEIGHT	0.088	0.097	0.091	0.078	0.094	0.069						
Adrenals (g)	0.039	0.035	0.060	0.050	0.033	0.035						
% BODY WEIGHT	0.016	0.014	0.023	0.020	0.013	0.013						
Pituitary (g)	0.009	0.010	0.006	0.008	0.008	0.009						
% BODY WEIGHT	0.004	0.004	0.002	0.003	0.003	0.003						

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats  
 STRAIN: LONG-EVANS

GROUP: 1 - 2.5 mL/kg/day Corn Oil	R15068	R15069	R15070	R15071	R15072	R15073
ANIMAL ID:						
BODY WEIGHT (g)	261.3	300.6	292.1	303.5	297.2	299.3
Liver (g)	10.813	14.210	11.659	12.501	12.938	11.891
% BODY WEIGHT	4.138	4.727	3.991	4.119	4.353	3.973
Kidneys (Paired) (g)	2.223	2.550	2.308	2.341	2.198	2.336
% BODY WEIGHT	0.851	0.848	0.790	0.771	0.740	0.780
Testes (Paired) (g)	2.589	2.733	2.775	2.790	2.828	2.678
% BODY WEIGHT	0.991	0.909	0.950	0.919	0.952	0.895
Epididymides (Paired) (g)	0.393	0.510	0.422	0.603	0.558	0.552
% BODY WEIGHT	0.150	0.170	0.144	0.199	0.188	0.184
Seminal Vesicle (g)	0.354	0.215	0.415	0.545	0.477	0.478
% BODY WEIGHT	0.135	0.072	0.142	0.180	0.160	0.160
Levator Ani plus Bulbocavernosus Muscle (g)	0.768	0.577	0.653	0.853	0.507	0.603
% BODY WEIGHT	0.294	0.192	0.224	0.281	0.171	0.201
Ventral Prostate (g)	0.127	0.223	0.125	0.276	0.177	0.176
% BODY WEIGHT	0.049	0.074	0.043	0.091	0.060	0.059
Adrenals (g)	0.050	0.050	0.034	0.052	0.047	0.046
% BODY WEIGHT	0.019	0.017	0.012	0.017	0.016	0.015
Pituitary (g)	0.008	0.009	0.008	0.008	0.010	0.006
% BODY WEIGHT	0.003	0.003	0.003	0.003	0.003	0.002

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats  
 STRAIN: SPRAGUE-DAWLEY

GROUP: 2 - 50 mg/kg/day Flutamide	R15074	R15075	R15076	R15077	R15078	R15079
ANIMAL ID:						
BODY WEIGHT (g)	251.1	249.7	250.9	269.1	260.3	249.5
Liver (g)	12.327	12.640	12.470	13.363	13.916	11.546
% BODY WEIGHT	4.909	5.062	4.970	4.966	5.346	4.628
Kidneys (paired) (g)	1.773	1.875	2.129	2.084	1.952	1.904
% BODY WEIGHT	0.706	0.751	0.849	0.774	0.750	0.763
Testes (Paired) (g)	2.938	3.731	3.957	4.342	4.050	3.212
% BODY WEIGHT	1.170	1.494	1.577	1.614	1.556	1.287
Epididymides (Paired) (g)	0.214	0.261	0.303	0.263	0.281	0.352
% BODY WEIGHT	0.085	0.105	0.121	0.098	0.108	0.141
Seminal Vesicle (g)	0.046	0.037	0.088	0.146	0.094	0.107
% BODY WEIGHT	0.018	0.015	0.035	0.054	0.036	0.043
Levator Ani plus Bulbocavernosus Muscle (g)	0.273	0.256	0.262	0.237	0.302	0.212
% BODY WEIGHT	0.109	0.103	0.104	0.088	0.116	0.085
Ventral Prostate (g)	0.271	0.087	0.049	0.057	0.115	0.061
% BODY WEIGHT	0.108	0.035	0.020	0.021	0.044	0.024
Adrenals (g)	0.047	0.045	0.055	0.044	0.048	0.048
% BODY WEIGHT	0.019	0.018	0.022	0.016	0.018	0.019
Pituitary (g)	0.010	0.012	0.009	0.011	0.012	0.007
% BODY WEIGHT	0.004	0.005	0.004	0.004	0.005	0.003

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats  
 STRAIN: LONG-EVANS

GROUP: 2 - 50 mg/kg/day Flutamide	R15080	R15081	R15082	R15083	R15084	R15085
ANIMAL ID:						
BODY WEIGHT (g)	235.6	244.5	289.4	249.3	257.8	278.0
Liver (g)	11.376	11.805	13.610	12.211	12.907	12.539
% BODY WEIGHT	4.829	4.828	4.703	4.898	5.007	4.510
Kidneys (paired) (g)	2.055	1.847	2.473	1.968	2.071	2.100
% BODY WEIGHT	0.872	0.755	0.855	0.789	0.803	0.755
Testes (Paired) (g)	2.785	2.829	4.191	3.337	3.543	3.123
% BODY WEIGHT	1.182	1.157	1.448	1.339	1.374	1.123
Epididymides (Paired) (g)	0.277	0.276	0.458	0.259	0.302	0.273
% BODY WEIGHT	0.118	0.113	0.158	0.104	0.117	0.098
Seminal Vesicle (g)	0.088	0.090	0.131	0.072	0.096	0.074
% BODY WEIGHT	0.037	0.037	0.045	0.029	0.037	0.027
Levator Ani plus Bulbocavernosus Muscle (g)	0.348	0.400	0.528	0.290	0.405	0.409
% BODY WEIGHT	0.148	0.164	0.182	0.116	0.157	0.147
Ventral Prostate (g)	0.038	0.089	0.091	0.021	0.060	0.044
% BODY WEIGHT	0.016	0.036	0.031	0.008	0.023	0.016
Adrenals (g)	0.036	0.044	0.066	0.056	0.044	0.051
% BODY WEIGHT	0.015	0.018	0.023	0.022	0.017	0.018
Pituitary (g)	0.004	0.010	0.010	0.010	0.007	0.009
% BODY WEIGHT	0.002	0.004	0.003	0.004	0.003	0.003

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 3 - 80 mg/kg/day Methyl Testosterone	STRAIN: SPRAGUE DAWLEY					
ANIMAL ID:	R15086	R15087	R15088	R15089	R15090	R15091
BODY WEIGHT (g)	221.4	236.1	243.4	254.6	262.9	242.7
Liver (g)	10.191	10.369	10.408	12.059	12.509	10.790
% BODY WEIGHT	4.603	4.392	4.276	4.736	4.758	4.446
Kidneys (Paired) (g)	2.105	2.117	2.243	2.439	2.707	2.400
% BODY WEIGHT	0.951	0.897	0.922	0.958	1.030	0.989
Testes (Paired) (g)	0.756	0.902	0.898	1.037	0.753	0.744
% BODY WEIGHT	0.341	0.382	0.369	0.407	0.286	0.307
Epididymides (Paired) (g)	0.402	0.397	0.347	0.471	0.411	0.358
% BODY WEIGHT	0.182	0.168	0.143	0.185	0.156	0.148
Seminal Vesicle (g)	0.593	0.653	0.859	0.644	0.967	0.585
% BODY WEIGHT	0.268	0.277	0.353	0.253	0.368	0.241
Levator Ani plus Bulbocavernosus Muscle (g)	0.583	0.697	0.998	0.659	0.753	0.616
% BODY WEIGHT	0.263	0.295	0.410	0.259	0.286	0.254
Ventral Prostate (g)	0.471	0.276	0.323	0.446	0.346	0.258
% BODY WEIGHT	0.213	0.117	0.133	0.175	0.132	0.106
Adrenals (g)	0.048	0.050	0.028	0.041	0.039	0.065
% BODY WEIGHT	0.022	0.021	0.012	0.016	0.015	0.027
Pituitary (g)	0.010	0.005	0.007	0.006	0.008	0.006
% BODY WEIGHT	0.005	0.002	0.003	0.002	0.003	0.002

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 3 - 80 mg/kg/day Methyl Testosterone	STRAIN: LONG-EVANS					
	R15092	R15093	R15094	R15095	R15096	R15097
BODY WEIGHT (g)	268.3	249.1	295.7	222.3	266.8	268.8
Liver (g)	11.903	10.422	12.296	9.721	11.760	11.272
% BODY WEIGHT	4.436	4.184	4.158	4.373	4.408	4.193
Kidneys (Paired) (g)	2.341	2.423	2.544	1.896	2.587	2.477
% BODY WEIGHT	0.873	0.973	0.860	0.853	0.970	0.922
Testes (Paired) (g)	0.421	0.525	0.704	0.490	0.544	0.691
% BODY WEIGHT	0.157	0.211	0.238	0.220	0.204	0.257
Epididymides (Paired) (g)	0.436	0.528	0.496	0.441	0.532	0.566
% BODY WEIGHT	0.163	0.212	0.168	0.198	0.199	0.211
Seminal Vesicle (g)	0.873	0.394	0.610	0.773	0.740	0.682
% BODY WEIGHT	0.325	0.158	0.206	0.348	0.277	0.254
Levator Ani plus Bulbocavernosus Muscle (g)	0.679	0.526	0.673	0.706	0.715	0.544
% BODY WEIGHT	0.253	0.211	0.228	0.318	0.268	0.202
Ventral Prostate (g)	0.395	0.248	0.259	0.284	0.337	0.318
% BODY WEIGHT	0.147	0.100	0.088	0.128	0.126	0.118
Adrenals (g)	0.037	0.041	0.047	0.042	0.040	0.036
% BODY WEIGHT	0.014	0.016	0.016	0.019	0.015	0.013
Pituitary (g)	0.008	0.005	0.008	0.007	0.006	0.006
% BODY WEIGHT	0.003	0.002	0.003	0.003	0.002	0.002

Appendix Continued



APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 4 - 240 mg/kg/day Propylthiouracil	STRAIN: SPRAGUE DAWLEY					
	R15098	R15099	R15100	R15101	R15102	R15103
ANIMAL ID:						
BODY WEIGHT (g)	120.0	114.9	114.8	115.8	111.6	107.5
Liver (g)	4.891	4.168	4.270	4.693	4.404	4.321
% BODY WEIGHT	4.076	3.628	3.720	4.053	3.946	4.020
Kidneys (Paired) (g)	0.849	0.739	0.864	0.901	0.818	0.921
% BODY WEIGHT	0.708	0.643	0.753	0.778	0.733	0.857
Testes (Paired) (g)	1.713	2.185	1.184	2.294	1.892	1.862
% BODY WEIGHT	1.428	1.902	1.031	1.981	1.695	1.732
Epididymides (Paired) (g)	0.283	0.215	0.186	0.296	0.232	0.246
% BODY WEIGHT	0.236	0.187	0.162	0.256	0.208	0.229
Seminal Vesicle (g)	0.019	0.131	0.023	0.111	0.068	0.040
% BODY WEIGHT	0.016	0.114	0.020	0.096	0.061	0.037
Levator Ani plus Bulbocavernosus Muscle (g)	0.131	0.078	0.091	0.099	0.099	0.122
% BODY WEIGHT	0.109	0.068	0.079	0.085	0.089	0.113
Ventral Prostate (g)	0.302	0.013	0.027	0.099	0.017	0.033
% BODY WEIGHT	0.252	0.011	0.024	0.085	0.015	0.031
Adrenals (g)	0.024	0.024	0.026	0.038	0.025	0.027
% BODY WEIGHT	0.020	0.021	0.023	0.033	0.022	0.025
Pituitary (g)	0.007	0.006	0.005	0.005	0.007	0.005
% BODY WEIGHT	0.006	0.005	0.004	0.004	0.006	0.005

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 4 - 240 mg/kg/day Propylthiouracil	STRAIN: LONG-EVANS					
	R15104	R15105	R15106	R15107	R15108	R15109
ANIMAL ID:						
BODY WEIGHT (g)	105.4	118.0	107.2	118.5	106.7	105.2
Liver (g)	4.065	4.521	4.315	4.519	3.981	3.945
% BODY WEIGHT	3.857	3.831	4.025	3.814	3.731	3.750
Kidneys (Paired) (g)	0.827	0.981	0.905	0.916	0.805	0.839
% BODY WEIGHT	0.785	0.831	0.844	0.773	0.754	0.798
Testes (Paired) (g)	1.953	2.536	1.946	1.924	1.889	1.292
% BODY WEIGHT	1.853	2.149	1.815	1.624	1.770	1.228
Epididymides (Paired) (g)	0.280	0.356	0.255	0.204	0.214	0.207
% BODY WEIGHT	0.266	0.302	0.238	0.172	0.201	0.197
Seminal Vesicle (g)	0.089	0.724	0.098	0.072	0.044	0.036
% BODY WEIGHT	0.084	0.614	0.091	0.061	0.041	0.034
Levator Ani plus Bulbocavernosus Muscle (g)	0.251	0.160	0.149	0.124	0.140	0.095
% BODY WEIGHT	0.238	0.136	0.139	0.105	0.131	0.090
Ventral Prostate (g)	0.065	0.135	0.064	0.045	0.041	0.020
% BODY WEIGHT	0.062	0.114	0.060	0.038	0.038	0.019
Adrenals (g)	0.028	0.032	0.027	0.022	0.024	0.027
% BODY WEIGHT	0.027	0.027	0.025	0.019	0.022	0.026
Pituitary (g)	0.007	0.008	0.006	0.007	0.005	0.005
% BODY WEIGHT	0.007	0.007	0.006	0.006	0.005	0.005

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 5 - 100 mg/kg/day Ketoconazole ANIMAL ID:	STRAIN: SPRAGUE DAWLEY					
	R15110	R15111	R15112	R15113	R15114	R15115
BODY WEIGHT (g)	224.6	246.8	252.6	246.9	249.0	244.5
Liver (g)	11.165	11.694	11.276	11.644	11.305	11.056
% BODY WEIGHT	4.971	4.738	4.464	4.716	4.540	4.522
Kidneys (Paired) (g)	1.768	1.877	2.078	2.172	1.943	1.915
% BODY WEIGHT	0.787	0.761	0.823	0.880	0.780	0.783
Testes (Paired) (g)	2.625	2.888	2.925	3.013	3.066	2.890
% BODY WEIGHT	1.169	1.170	1.158	1.220	1.231	1.182
Epididymides (Paired) (g)	0.351	0.386	0.473	0.473	0.473	0.428
% BODY WEIGHT	0.156	0.156	0.187	0.192	0.190	0.175
Seminal Vesicle (g)	0.151	0.209	0.328	0.426	0.270	0.248
% BODY WEIGHT	0.067	0.085	0.130	0.173	0.108	0.101
Levator Ani plus Bulbocavernosus Muscle (g)	0.464	0.437	0.847	0.597	0.399	0.422
% BODY WEIGHT	0.207	0.177	0.335	0.242	0.160	0.173
Ventral Prostate (g)	0.091	0.131	0.215	0.182	0.138	0.062
% BODY WEIGHT	0.041	0.053	0.085	0.074	0.055	0.025
Adrenals (g)	0.080	0.067	0.089	0.061	0.072	0.069
% BODY WEIGHT	0.036	0.027	0.035	0.025	0.029	0.028
Pituitary (g)	0.007	0.008	0.006	0.007	0.007	0.009
% BODY WEIGHT	0.003	0.003	0.002	0.003	0.003	0.004

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 5 - 100 mg/kg/day Ketoconazole	STRAIN: LONG-EVANS					
	R15116	R15117	R15118	R15119	R15120	R15121
ANIMAL ID:						
BODY WEIGHT (g)	248.6	248.0	236.8	281.8	242.3	262.8
Liver (g)	12.042	11.976	10.551	13.041	10.953	12.957
% BODY WEIGHT	4.844	4.829	4.456	4.628	4.520	4.930
Kidneys (Paired) (g)	1.968	2.244	2.163	2.395	1.889	2.234
% BODY WEIGHT	0.792	0.905	0.913	0.850	0.780	0.850
Testes (Paired) (g)	2.299	2.435	2.730	2.749	2.676	2.565
% BODY WEIGHT	0.925	0.982	1.153	0.976	1.104	0.976
Epididymides (Paired) (g)	0.321	0.383	0.356	0.436	0.430	0.436
% BODY WEIGHT	0.129	0.154	0.150	0.155	0.177	0.166
Seminal Vesicle (g)	0.134	0.232	0.134	0.280	0.448	0.286
% BODY WEIGHT	0.054	0.094	0.057	0.099	0.185	0.109
Levator Ani plus Bulbocavernosus Muscle (g)	0.568	0.525	0.489	0.457	0.367	0.521
% BODY WEIGHT	0.228	0.212	0.207	0.162	0.151	0.198
Ventral Prostate (g)	0.143	0.152	0.093	0.151	0.162	0.132
% BODY WEIGHT	0.058	0.061	0.039	0.054	0.067	0.050
Adrenals (g)	0.069	0.077	0.059	0.080	0.073	0.071
% BODY WEIGHT	0.028	0.031	0.025	0.028	0.030	0.027
Pituitary (g)	0.009	0.005	0.008	0.009	0.006	0.007
% BODY WEIGHT	0.004	0.002	0.003	0.003	0.002	0.003

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 6 - 30 mg/kg/day Pimozide ANIMAL ID:	STRAIN: SPRAGUE DAWLEY			
	R15122	R15123	R15124	R15125
BODY WEIGHT (g)	214.2	215.6	228.5	232.4
Liver (g)	9.013	9.244	9.590	11.097
% BODY WEIGHT	4.208	4.288	4.197	4.775
Kidneys (Paired) (g)	1.630	1.686	1.776	1.609
% BODY WEIGHT	0.761	0.782	0.777	0.692
Testes (Paired) (g)	2.267	2.562	2.755	2.783
% BODY WEIGHT	1.058	1.188	1.206	1.198
Epididymides (Paired) (g)	0.402	0.385	0.430	0.361
% BODY WEIGHT	0.188	0.179	0.188	0.155
Seminal Vesicle (g)	0.262	0.178	0.303	0.186
% BODY WEIGHT	0.122	0.083	0.133	0.080
Levator Ani plus Bulbocavernosus Muscle (g)	0.408	0.354	0.314	0.390
% BODY WEIGHT	0.190	0.164	0.137	0.168
Ventral Prostate (g)	0.156	0.112	0.087	0.142
% BODY WEIGHT	0.073	0.052	0.038	0.061
Adrenals (g)	0.051	0.039	0.051	0.038
% BODY WEIGHT	0.024	0.018	0.022	0.016
Pituitary (g)	0.001 <sup>a</sup>	0.006	0.008	0.009
% BODY WEIGHT	0.000 <sup>a</sup>	0.003	0.004	0.004

Appendix Continued

a Weight out of range - excluded from summary data

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 6 - 30 mg/kg/day Pimozide	STRAIN: LONG-EVANS					
	R15128	R15129	R15130	R15131	R15132	R15133
ANIMAL ID:						
BODY WEIGHT (g)	208.8	224.6	230.8	184.6	224.0	237.5
Liver (g)	9.390	9.114	9.879	8.393	11.197	11.284
% BODY WEIGHT	4.497	4.058	4.280	4.547	4.999	4.751
Kidneys (Paired) (g)	1.803	1.643	1.861	1.477	2.009	1.689
% BODY WEIGHT	0.864	0.732	0.806	0.800	0.897	0.711
Testes (Paired) (g)	1.712	2.022	1.917	1.539	2.104	1.920
% BODY WEIGHT	0.820	0.900	0.831	0.834	0.939	0.808
Epididymides (Paired) (g)	0.270	0.275	0.285	0.279	0.343	0.409
% BODY WEIGHT	0.129	0.122	0.123	0.151	0.153	0.172
Seminal Vesicle (g)	0.129	0.138	0.254	0.178	0.143	0.322
% BODY WEIGHT	0.062	0.061	0.110	0.096	0.064	0.136
Levator Ani plus Bulbocavernosus Muscle (g)	0.390	0.450	0.691	0.297	0.328	0.374
% BODY WEIGHT	0.187	0.200	0.299	0.161	0.146	0.157
Ventral Prostate (g)	0.093	0.154	0.175	0.184	0.164	0.181
% BODY WEIGHT	0.045	0.069	0.076	0.100	0.073	0.076
Adrenals (g)	0.140	0.032	0.038	0.024	0.064	0.044
% BODY WEIGHT	0.067	0.014	0.016	0.013	0.029	0.019
Pituitary (g)	0.009	0.010	0.007	0.004	0.004	0.009
% BODY WEIGHT	0.004	0.004	0.003	0.002	0.002	0.004

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 7 - 1000 mg/kg/day Dibutylphthalate	R15134	R15135	R15136	R15137	R15138	R15139
ANIMAL ID:	STRAIN: SPRAGUE-DAWLEY					
BODY WEIGHT (g)	260.2	240.9	234.2	242.8	259.8	238.2
Liver (g)	13.591	12.362	11.317	11.797	14.899	10.616
% BODY WEIGHT	5.223	5.132	4.832	4.859	5.735	4.457
Kidneys (Paired) (g)	2.069	2.033	2.049	1.988	1.982	1.892
% BODY WEIGHT	0.795	0.844	0.875	0.819	0.763	0.794
Testes (Paired) (g)	3.295	2.773	2.618	2.830	2.558	2.089
BODY WEIGHT	1.266	1.151	1.118	1.166	0.985	0.877
Epididymides (Paired) (g)	0.489	0.443	0.432	0.490	0.447	0.446
% BODY WEIGHT	0.188	0.184	0.184	0.202	0.172	0.187
Seminal Vesicle (g)	0.465	0.559	0.277	0.287	0.339	0.428
% BODY WEIGHT	0.179	0.232	0.118	0.118	0.130	0.180
Levator Ani plus Bulbocavernosus Muscle (g)	0.678	0.680	0.389	0.587	0.528	0.539
% BODY WEIGHT	0.261	0.282	0.166	0.242	0.203	0.226
Ventral Prostate (g)	0.374	0.413	0.121	0.196	0.139	0.157
% BODY WEIGHT	0.144	0.171	0.052	0.081	0.054	0.066
Adrenals (g)	0.046	0.036	0.051	0.055	0.042	0.048
% BODY WEIGHT	0.018	0.015	0.022	0.023	0.016	0.020
Pituitary (g)	0.011	0.009	0.008	0.005	0.009	0.006
% BODY WEIGHT	0.004	0.004	0.003	0.002	0.003	0.003

Appendix Continued

APPENDIX 6 (CONTINUED)  
 INDIVIDUAL ORGAN WEIGHTS (GRAMS) AND ORGAN-TO-BODY-WEIGHT RATIOS  
 Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP: 7 - 1000 mg/kg/day Dibutylphthalate ANIMAL ID:	R15141			R15142			R15143			R15144		
	R15140			R15142			R15143			R15144		
BODY WEIGHT (g)	256.6	268.4	264.6	268.4	264.6	272.4	268.4	264.6	272.4	265.2	266.7	236.7
Liver (g)	11.605	12.039	11.170	12.039	11.170	12.143	11.605	11.170	12.143	11.663	11.259	11.259
% BODY WEIGHT	4.523	4.485	4.221	4.485	4.221	4.458	4.398	4.221	4.458	4.398	4.757	4.757
Kidneys (Paired) (g)	2.419	2.559	2.210	2.559	2.210	2.313	2.419	2.210	2.313	2.210	1.882	1.882
% BODY WEIGHT	0.943	0.953	0.835	0.953	0.835	0.849	0.833	0.835	0.849	0.833	0.795	0.795
Testes (Paired) (g)	1.064	0.657	0.779	0.657	0.779	1.278	0.650	0.779	1.278	0.650	0.805	0.805
% BODY WEIGHT	0.415	0.245	0.294	0.245	0.294	0.469	0.245	0.294	0.469	0.245	0.340	0.340
Epididymides (Paired) (g)	0.295	0.431	0.363	0.431	0.363	0.629	0.351	0.363	0.629	0.351	0.325	0.325
% BODY WEIGHT	0.115	0.161	0.137	0.161	0.137	0.231	0.132	0.137	0.231	0.132	0.137	0.137
Seminal Vesicle (g)	0.156	0.381	0.136	0.381	0.136	0.302	0.108	0.136	0.302	0.108	0.127	0.127
% BODY WEIGHT	0.061	0.142	0.051	0.142	0.051	0.111	0.041	0.051	0.111	0.041	0.054	0.054
Levator Ani plus Bulbocavernosus Muscle (g)	0.390	0.383	0.453	0.383	0.453	0.437	0.271	0.453	0.437	0.271	0.361	0.361
% BODY WEIGHT	0.152	0.143	0.171	0.143	0.171	0.160	0.102	0.171	0.160	0.102	0.153	0.153
Ventral Prostate (g)	0.076	0.144	0.206	0.144	0.206	0.135	0.096	0.206	0.135	0.125	0.096	0.096
% BODY WEIGHT	0.030	0.054	0.078	0.054	0.078	0.050	0.047	0.078	0.050	0.047	0.041	0.041
Adrenals (g)	0.047	0.049	0.069	0.049	0.069	0.048	0.051	0.069	0.048	0.051	0.025	0.025
% BODY WEIGHT	0.018	0.018	0.026	0.018	0.026	0.018	0.019	0.026	0.018	0.019	0.011	0.011
Pituitary (g)	0.004	0.010	0.008	0.010	0.008	0.007	0.007	0.008	0.007	0.007	0.006	0.006
% BODY WEIGHT	0.002	0.004	0.003	0.004	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003



APPENDIX 7  
PATHOLOGY REPORT  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats



**Pathology Associates International**  
A Company of Science Applications International Corporation



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PATHOLOGY REPORT  
FOR  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE  
MALE RATS

THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

PREPARED FOR  
THERIMMUNE RESEARCH CORPORATION

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**PATHOLOGY REPORT****Assessment of Pubertal Development and Thyroid Function  
in Juvenile Male Rats**

TherImmune Research Corporation 1143-100

**INTRODUCTION**

The purpose of this protocol was to quantify the effects of environmental compounds on pubertal development and thyroid function in the intact juvenile male rat. This report prepared by Pathology Associates International (PAI) for TherImmune Research Corporation, 15 Firstfield Road, Gaithersburg, MD 20878, presents the results of the evaluation of pathology endpoints. The portion of this study performed by PAI was conducted in accordance with the Environmental Protection Agency (EPA) FIFRA Good Laboratory Practice Standards, 40 CFR Part 160.

**EXPERIMENTAL DESIGN AND METHODS**

The procedures described below were performed on two strains of juvenile rats concurrently to compare inter-strain variability. Forty-two male Sprague-Dawley rats and forty-two male Long-Evans rats were randomly distributed into seven groups as in Text Table 1.

**Text Table 1. Group Designation and Dosage Levels**

Group	Treatment	Dosage (per kg/day)	# of males per strain
1	Corn Oil	2.5 ml	6
2	Flutamide	50 mg	6
3	Methyl testosterone	80 mg	6
4	Propylthiouracil (PTU)	240 mg	6
5	Ketoconazole	100 mg	6
6	Pimozide	30 mg	6
7	Dibutylphthalate (DBP)	1000 mg	6

Juvenile rats, approximately 23 days old, were dosed by oral gavage at a volume of 2.5 ml/kg body weight. The animals were dosed daily, between 0700 and 0900 hours, for at least 31 days.

Animals were necropsied as close as possible to the time of death. Animals surviving to the scheduled terminal sacrifice time point (between 1300 and 1700 hours on post-natal day [PND] 53 or 54) were killed by decapitation and necropsied in accordance with the study protocol. The thyroid, epididymides and testes were placed in Bouin's fixative for approximately 24 hours, after which they were rinsed and stored in 70% ethanol. These selected tissues were embedded in paraffin, sectioned at approximately 5 microns, stained with hematoxylin and eosin (H&E) and examined microscopically by the undersigned board certified pathologist.

**RESULTS****Gross pathology**

A table listing gross lesions is provided below.

**Text Table 2. Number of Rats with Specific Gross Lesions**

Groups Organ/ Lesion	1		2		3		4		5		6		7	
	6SD	6LE	6SD	6LE	6SD	6LE	6SD	6LE	6SD	6LE	6SD	6LE	6SD	6LE
Thyroid/enlarged	0	0	0	0	1	0	4	6	0	0	0	0	0	0
Testes/small	0	0	0	0	1	4	0	0	0	0	0	0	0	2
Testes/dark	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Seminal Vesicle/ small	0	0	4	2	0	0	5	2	0	0	0	0	0	2
Ventral Prostate/ small	0	0	1	1	0	0	2	2	0	0	0	0	0	0
Epididymides/ small	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Adrenals/enlarged	0	0	0	0	0	0	0	0	3	3	0	0	0	0
Adrenals/pale	0	0	0	0	0	0	0	0	1	1	0	0	0	0
Kidneys/cyst	0	0	0	0	1	0	0	0	0	0	0	1	1	0
Pituitary/cyst	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Liver/accessory lobe, tan	0	0	0	0	0	1	0	0	0	1	0	0	0	0

6SD = Six Sprague-Dawley rats 6LE = Six Long-Evans rats

All gross lesions in the thyroid, testes, seminal vesicles, ventral prostate and the adrenal glands were considered to be test article related.

**Histopathology**

Microscopic findings for all groups are summarized on the Project Summary Table (Section II) in which the numbers of animals per group and lesions per group are indicated. Microscopic findings are presented by treatment group with all diagnoses for individual animals in the Tabulated Animal Data tables (Section III). Microscopic lesions are correlated to gross findings, when applicable, in the Correlation of Gross and Microscopic Findings (Section IV). Comments for individual animals, where appropriate, are in the Comment Report (Section V). The codes used as entries in these tables are explained in the Reports Code Table, Appendix 1, and abbreviations are explained in the Abbreviations List, Appendix 2.

Microscopic findings occurring in 3 or less of the 6 animals/strain/group were considered to be sporadic. Findings occurring in 4 or more of the 6 animals/strain/group were considered to be consistent.

Corn Oil Controls

Sprague-Dawley – There were no findings in any tissues in these animals.

Long-Evans - There were no findings in any tissues in these animals.

Flutamide (50 mg/kg/day)

Sprague-Dawley – There were no test article related findings in the thyroid glands. Test article related changes in the testes were hyperplasia/hypertrophy of the interstitial cells (consistent finding) and dilation of the seminiferous tubules (sporadic finding). Other changes in the testes were considered to be spontaneous changes unrelated to the test article. Atrophy of the epididymides (consistent finding) was considered to be a direct test article effect. Other changes in the epididymides were considered to be spontaneous changes unrelated to the test article.

Dilation of the seminiferous tubules occurred without any detectable decrease in spermatogenesis. The study pathologist considered that this dilation may have been related to the atrophy of the epididymides.

Long-Evans – There were no test article related findings in the thyroid glands. All thyroid findings were considered to be spontaneous changes unrelated to the test article. Test article related changes in the testes were hyperplasia/hypertrophy of the interstitial cells (consistent finding) and dilation of the seminiferous tubules (sporadic finding). Atrophy of the epididymides (consistent finding) was also test article related.

Dilation of the seminiferous tubules occurred without any detectable decrease in spermatogenesis. The study pathologist considered that this dilation may have been related to the atrophy of the epididymides.

Flutamide is reported to have anti-androgen activity. This reported action was considered to be consistent with the test article related lesions found in both strains of rats.

Methyl testosterone (80 mg/kg/day)

Sprague-Dawley – There were no test article related findings in the thyroid glands. All thyroid findings were considered to be spontaneous changes unrelated to the test article. Test article related changes in the testes were hypospermatogenesis (decreased sperm production; consistent finding) and interstitial cell atrophy (consistent finding). Test article related changes in the epididymides were hypospermia (decreased content of sperm secondary to the decreased production in the testes; consistent finding) and degenerative germ cells (due to the release of degenerated cells from the testes; consistent finding).

Long-Evans – There were no test article related findings in the thyroid glands. All thyroid findings were considered to be spontaneous changes unrelated to the test article. Test article related changes in the testes were hypospermatogenesis (consistent finding) and interstitial cell atrophy (consistent finding). Test article related changes in the epididymides were hypospermia (consistent finding) and degenerative germ cells (consistent finding).

The test article related findings in both strains were considered to be consistent with a hyperandrogenic effect of the methyl testosterone.

Propylthiouracil (240 mg/kg/day)

Sprague-Dawley – Test article related findings in the thyroid were hyperplasia/hypertrophy of the follicular cells and colloid depletion. Both changes were diffuse throughout the thyroid glands. Test article related findings in the testes were hypospermatogenesis (sporadic finding) and interstitial cell atrophy (sporadic finding). Test article related findings in the epididymides were hypospermia (sporadic finding) and degenerative germ cells (consistent finding). These epididymal changes were considered to be secondary to changes occurring in the testes (although an alteration of spermatogenesis was not apparent in all testes).

Long-Evans – Test article related findings in the thyroid were hyperplasia/hypertrophy of the follicular cells and colloid depletion. Both changes were diffuse throughout the thyroid glands. The only test article related finding in the testes was interstitial cell atrophy (sporadic finding). Test article related findings in the epididymides were atrophy (sporadic finding), hypospermia (consistent finding) and degenerative germ cells (consistent finding). The epididymal changes other than atrophy were considered to be secondary to changes occurring in the testes (although an alteration of spermatogenesis was not apparent in all testes).

The thyroid effects were considered to be direct effects of the test article. The changes in the testes and epididymides were considered to be possibly related to the suspected hypothyroid state induced by administration of the test article.

Ketoconazole (100 mg/kg/day)

Sprague-Dawley – There were no test article related findings in the thyroid glands, testes or epididymides. Any changes in these tissues were considered to be sporadic in nature and of no significance to the animal.

Long-Evans – There were no test article related findings in the thyroid glands, testes or epididymides. Any changes in these tissues were considered to be sporadic in nature and of no significance to the animal.

Ketoconazole is reported to be an inhibitor of testosterone. However, at the doses tested, no test article related morphologic effects were noted in the test animals of either strain.

Pimozide (30 mg/kg/day)

Sprague-Dawley – There were no test article related findings in the thyroid glands, testes or epididymides.

Long-Evans – There were no test article related findings in the thyroid glands. The only test article related change in the testes was hypospermatogenesis (sporadic finding). Test article related changes in the epididymides were atrophy (sporadic finding) and hypospermia (consistent finding). The low incidence of atrophy in the epididymides indicated that this change may be incidental and thus unrelated to the test article. The hypospermia was considered to be secondary to decreased sperm production in the testes (although a testis effect was not apparent in all animals).

Pimozide is reported to be a dopamine antagonist and possibly to cause incomplete initiation of spermatogenesis. The test article findings in the Long-Evans rats were consistent with the second of these actions. The cause of the difference between the two strains was suspected to have a genetic basis.

Dibutylphthalate (1000 mg/kg/day)

Sprague-Dawley – There were no test article related findings in the thyroid glands, testes or epididymides.

Long-Evans – There were no test article related findings in the thyroid glands. Findings in the thyroid glands were considered to be incidental and unrelated to the test article. Test article related changes in the testes were seminiferous tubule degeneration (consistent finding) and hypospermatogenesis (consistent finding). The tubular degeneration was characterized by variable but widespread changes in the tubules including a decrease of cell layers, a complete lack of spermatogenic cells and a general lack of spermatogenesis. Test article related changes in the epididymides were hypospermia (consistent finding) and degenerative germ cells (consistent finding). The epididymal changes were considered to be secondary to the changes in the testes.

Dibutylphthalate is reported to induce seminiferous tubule degeneration. The changes in the Long-Evans rats were consistent with this action. The difference between the two strains was considered to have a genetic basis.

**CONCLUSION**

Eighty-four juvenile male rats (42 Sprague-Dawley rats and 42 Long-Evans rats) were randomly assigned to seven groups and gavaged daily for at least 31 days. Text Table 1 summarizes the group designations and dosage levels. Following at least 31 days of dosing, all animals were killed by decapitation. Protocol specified tissues were collected at necropsy and preserved. Thyroid, testes and epididymides from all animals were processed through paraffin and rendered to H&E stained ~5-micron sections which were evaluated microscopically for pathological changes.

Flutamide, methyl testosterone, pimozide and dibutylphthalate caused morphologic changes in the male reproductive organs (testes and epididymides) consistent with their respective reported actions. For pimozide and dibutylphthalate, changes were present only in the Long Evans strain. For flutamide and methyl testosterone, changes were similar in both strains. No changes in the testes or epididymides were detected in the ketoconazole treated animals.

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Propylthiouracil caused morphologic changes in the thyroid glands consistent with its reported action. Secondary changes in the testes and epididymides were considered to be possibly consistent with the hypothyroid state of the test animals.

For all test articles except ketoconazole, the study design was sufficient to reproduce morphologic effects in target tissues of one or both strains of rats.

Study Pathologist:

<u>Mark T. Butt</u>	<u>6-15-00</u>
Mark T. Butt, DVM, DACVP	Date



Appendix 1:  
Reports Code Table

PATHOLOGY ASSOCIATES INTERNATIONAL  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE  
MALE RATS  
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

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Reports Code Table

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N	Tissues within normal histological limits
A	Autolysis precluding adequate evaluation
U	Tissues unavailable/unsuitable for evaluation
S	Tissues not applicable to animal
*	Tissues not examined/not required by protocol

---

1	minimal
2	mild
3	moderate
4	marked
( )	focal
[ ]	diffuse
< >	multifocal
P	Present
B	Neoplasm, Benign
M	Neoplasm, Malignant without Metastasis
C	Neoplasm, Malignant with Metastasis
X	Metastatic Site (+)
I	Bilateral
L	Unilateral
-	Diagnosis Not Applicable to Animal/Tissue

Appendix 2:  
Abbreviations List

PATHOLOGY ASSOCIATES INTERNATIONAL  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE  
MALE RATS  
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

Abbreviations List

# EX	Number Examined
1143100	1143-100
TK	Terminal Kill

II. Project Summary Tables

**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**PROJECT SUMMARY**  
 -----

STUDY ID : 1143-100  
 FATE: TK Sprague-Dawley

STUDY NUMBER: 1143100

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS  
 -----

GROUP:	1	2	3	4	5
	(1)	(2)	(3)	(4)	(5)
NUMBER OF ANIMALS:	6	6	6	6	6
	#	#	#	#	#
THYROID	# EX				
ULTIMOBANCHIAL CYST	0	0	1	0	0
FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY	0	0	0	6	0
COLLOID DEPLETION	0	0	0	6	0
TESTES	# EX				
NECROSIS	0	1	0	0	0
INTERSTITIAL CELL - HYPERPLASIA/HYPERTROPHY	0	6	0	0	0
SEMINIFEROUS TUBULES - DILATION	0	2	0	0	0
HYOSPERMATOGENESIS	0	0	6	2	0
INTERSTITIAL CELL - ATROPHY	0	0	6	3	0
SEMINIFEROUS TUBULES - DEGENERATION	0	0	0	0	1
EPIDIDYMIDES	# EX				
ATROPHY	0	6	0	0	0
HYOSPERMIA	0	0	6	1	0
GRANULOMA(S)	0	1	0	0	0
DEGENERATIVE GERM CELLS	0	0	6	4	0

(1) - Corn Oil 2.5 ml/kg/day  
 (2) - Flutamide 50 mg/kg/day  
 (3) - Methyl testosterone 80 mg/kg/day

(4) - Propylthiouracil (PTU) 240 mg/kg/day  
 (5) - Ketoconazole 100 mg/kg/day

LABCAT HP4.33

05-APR-2000

**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**PROJECT SUMMARY**  
 -----

STUDY ID : 1143-100  
 FATE: TK Sprague-Dawley

STUDY NUMBER: 1143100

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS  
 -----

GROUP:	6	7
	(1)	(2)
NUMBER OF ANIMALS:	6	6
	#	#
THYROID	6	6
# EX		
ULTIMOBANCHIAL CYST	0	0
FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY	0	0
COLLOID DEPLETION	0	0
TESTES	6	6
# EX		
NECROSIS	0	0
INTERSTITIAL CELL - HYPERPLASIA/HYPERTROPHY	0	0
SEMIFEROUS TUBULES - DILATION	0	0
HYOSPERMATOGENESIS	0	0
INTERSTITIAL CELL - ATROPHY	0	0
SEMIFEROUS TUBULES - DEGENERATION	0	0
EPIDIDYIMIDES	6	6
# EX		
ATROPHY	0	0
HYOSPERMIA	0	0
GRANULOMA(S)	0	0
DEGENERATIVE GERM CELLS	0	0

-----  
 (1) - Pimozide 30 mg/kg/day

(2) - Dibutylphthalate (DBP) 1000 mg/kg/day

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**PROJECT SUMMARY**  
 -----

STUDY ID : 1143-100  
 FATE: TK Long-Evans

STUDY NUMBER: 1143100

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS  
 -----

GROUP:	1	2	3	4	5
	(1)	(2)	(3)	(4)	(5)
NUMBER OF ANIMALS:	6	6	6	6	6
-----					
THYROID	#	#	#	#	#
# EX	6	6	6	6	6
ULTIMOBANCHIAL CYST	0	1	1	0	0
FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY	0	0	0	6	0
COLLOID DEPLETION	0	0	0	6	0
TESTES	#	#	#	#	#
# EX	6	6	6	6	6
INTERSTITIAL CELL - HYPERPLASIA/HYPERTROPHY	0	6	0	0	0
SEMINIFEROUS TUBULES - DILATION	0	3	0	0	0
HYOSPERMATOGENESIS	0	0	6	0	0
INTERSTITIAL CELL - ATROPHY	0	0	6	3	0
SEMINIFEROUS TUBULES - DEGENERATION	0	0	0	0	0
EPIDIDYIMIDES	#	#	#	#	#
# EX	6	6	6	6	6
ATROPHY	0	6	0	2	0
HYOSPERMIA	0	0	6	4	0
INFILTRATION CELLULAR, LYMPHOCYTE	0	0	0	0	1
DEGENERATIVE GERM CELLS	0	0	6	5	0

- (1) - Corn Oil 2.5 ml/kg/day  
 (2) - Flutamide 50 mg/kg/day  
 (3) - Methyl testosterone 80 mg/kg/day

- (4) - Propylthiouracil (PTU) 240 mg/kg/day  
 (5) - Ketoconazole 100 mg/kg/day

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**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

**PROJECT SUMMARY**

STUDY ID : 1143-100  
 FATE: TK Long-Evans

STUDY NUMBER: 1143100

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		6	7
		(1)	(2)
NUMBER OF ANIMALS:		6	6
		#	#
THYROID	# EX	6	6
ULTIMOBANCHIAL CYST		0	1
FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY		0	0
COLLOID DEPLETION		0	0
TESTES	# EX	6	6
INTERSTITIAL CELL - HYPERPLASIA/HYPERTROPHY		0	0
SEMINIFEROUS TUBULES - DILATION		0	0
HYOSPERMATOGENESIS		2	6
INTERSTITIAL CELL - ATROPHY		0	0
SEMINIFEROUS TUBULES - DEGENERATION		0	6
EPIDIDYIMIDES	# EX	6	6
ATROPHY		1	0
HYOSPERMIA		6	6
INFILTRATION CELLULAR, LYMPHOCYTE		0	0
DEGENERATIVE GERM CELLS		0	4

(1) - Pimozide 30 mg/kg/day

(2) - Dibutylphthalate (DBP) 1000 mg/kg/day

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III. Tabulated Animal Data

**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Sprague-Dawley

STUDY NUMBER: 1143100  
 GROUP: 1: Corn Oil 2.5 ml/kg/day  
 SEX: MALE

ANIMAL ID:	R15062	R15063	R15064	R15065	R15066	R15067
THYROID	N	N	N	N	N	N
TESTES	N	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N	N

-----  
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**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100 STUDY NUMBER: 1143100  
 FATE: TK Sprague-Dawley GROUP: 2: Flutamide 50 mg/kg/day  
SEX: MALE

ANIMAL ID:	R15074	R15075	R15076	R15077	R15078	R15079
THYROID	N	N	N	N	N	N
TESTES	-	-	-	-	-	-
NECROSIS	4L	-	-	-	-	-
INTERSTITIAL CELL - HYPERPLASIA/HYPERTROPHY	1L	11	21	21	11	21
SEMINIFEROUS TUBULES - DILATION	-	-	21	21	-	-
EPIDIDYMIDES	-	-	-	-	-	-
ATROPHY	21	11	11	11	11	11
GRANULOMA(S)	-	-	(3)	-	-	-
Non-Protocol Tissues:						
SEMINAL VESICLE	-	*	*	-	*	*
Non-Protocol Tissues:						
VENTRAL PROSTATE	-	-	*	-	-	-

-----  
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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Sprague-Dawley

STUDY NUMBER: 1143100  
 GROUP: 3: Methyl testosterone 80 mg/kg/day  
 SEX: MALE

ANIMAL ID:	R15086	R15087	R15088	R15089	R15090	R15091
THYROID	-	N	N	N	N	N
ULTIMOBANCHIAL CYST	P	-	-	-	-	-
TESTES	-	-	-	-	-	-
HYOSPERMATOGENESIS	4I	4I	4I	3I	3I	4I
INTERSTITIAL CELL - ATROPHY	3I	3I	3I	3I	3I	4I
EPIDIDYMIDES	-	-	-	-	-	-
HYOSPERMIA	4I	4I	4I	4I	4I	4I
DEGENERATIVE GERM CELLS	2I	2I	2I	2I	2I	2I
Non-Protocol Tissues:						
KIDNEYS	-	-	-	*	-	-

-----  
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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100 STUDY NUMBER: 1143100  
 FATE: TK Sprague-Dawley GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day  
SEX: MALE

ANIMAL ID:	R15098	R15099	R15100	R15101	R15102	R15103
<b>THYROID</b>	-	-	-	-	-	-
FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY	2I	3I	3I	3I	3I	3I
COLLOID DEPLETION	2I	2I	2I	2I	2I	2I
<b>TESTES</b>	-	N	-	-	-	N
HYOSPERMATOGENESIS	2I	-	3I	-	-	-
INTERSTITIAL CELL - ATROPHY	-	-	2I	1I	1I	-
<b>EPIDIDYMIDES</b>	-	N	-	N	-	-
HYOSPERMIA	-	-	4I	-	-	-
DEGENERATIVE GERM CELLS	2I	-	3I	-	1I	1I
<b>Non-Protocol Tissues:</b>						
SEMINAL VESICLE	*	-	*	*	*	*
<b>Non-Protocol Tissues:</b>						
VENTRAL PROSTATE	*	-	-	-	*	-
<b>Non-Protocol Tissues:</b>						
PITUITARY	-	-	-	-	-	*

-----  
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**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Sprague-Dawley

STUDY NUMBER: 1143100  
 GROUP: 5: Ketoconazole 100 mg/kg/day  
 SEX: MALE

ANIMAL ID:	R15110	R15111	R15112	R15113	R15114	R15115
THYROID	U	N	N	N	N	N
TESTES	-	N	N	N	N	N
SEMINIFEROUS TUBULES - DEGENERATION	11	-	-	-	-	-
EPIDIDYMIDES	N	N	N	N	N	N
Non-Protocol Tissues:						
ADRENALS	-	*	-	-	*	*

-----  
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**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Sprague-Dawley

STUDY NUMBER: 1143100  
 GROUP: 6: Pimozide 30 mg/kg/day  
 SEX: MALE

ANIMAL ID:	R15122	R15123	R15124	R15125	R15126	R15127
THYROID	N	N	N	N	N	N
TESTES	N	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N	N

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**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100 STUDY NUMBER: 1143100  
 FATE: TK Sprague-Dawley GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day  
SEX: MALE

ANIMAL ID:	R15134	R15135	R15136	R15137	R15138	R15139
THYROID	N	N	N	N	N	N
TESTES	N	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N	N
Non-Protocol Tissues:						
KIDNEYS	-	-	*	-	-	-

-----  
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**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Long-Evans

STUDY NUMBER: 1143100  
 GROUP: 1: Corn Oil 2.5 ml/kg/day  
 SEX: MALE

ANIMAL ID:	R15068	R15069	R15070	R15071	R15072	R15073
THYROID	N	N	N	N	N	N
TESTES	N	N	N	N	N	N
EPIDIDYIMIDES	N	N	N	N	N	N

-----  
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**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Long-Evans

STUDY NUMBER: 1143100  
 GROUP: 2: Flutamide 50 mg/kg/day  
 SEX: MALE

ANIMAL ID:	R15080	R15081	R15082	R15083	R15084	R15085
<b>THYROID</b>	N	N	N	N	-	N
ULTIMOBANCHIAL CYST	-	-	-	-	PI	-
<b>TESTES</b>	-	-	-	-	-	-
INTERSTITIAL CELL - HYPERPLASIA/HYPERTROPHY	2I	2I	1I	2I	1I	1I
SEMINIFEROUS TUBULES - DILATION	-	-	2I	1I	2I	-
<b>EPIDIDYMIDES</b>	-	-	-	-	-	-
ATROPHY	1I	1I	1I	1I	1I	1I
<b>Non-Protocol Tissues:</b>						
<b>SEMINAL VESICLE</b>	-	-	*	-	*	-
<b>Non-Protocol Tissues:</b>						
<b>VENTRAL PROSTATE</b>	-	-	-	*	-	-

-----  
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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THEIRIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Long-Evans

STUDY NUMBER: 1143100  
 GROUP: 3: Methyl testosterone 80 mg/kg/day  
 SEX: MALE

ANIMAL ID:	R15092	R15093	R15094	R15095	R15096	R15097
THYROID	-	N	N	N	N	N
ULTIMOBANCHIAL CYST	P	-	-	-	-	-
TESTES	-	-	-	-	-	-
HYOSPERMATOGENESIS	4I	4I	4I	4I	4I	4I
INTERSTITIAL CELL - ATROPHY	4I	4I	4I	4I	4I	4I
EPIDIDYIMIDES	-	-	-	-	-	-
HYOSPERMIA	4I	4I	4I	4I	4I	4I
DEGENERATIVE GERM CELLS	2I	2I	2I	2I	2I	2I
Non-Protocol Tissues:						
LIVER	*	-	-	-	-	-

-----  
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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Long-Evans

STUDY NUMBER: 1143100  
 GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day  
 SEX: MALE

ANIMAL ID:	R15104	R15105	R15106	R15107	R15108	R15109
THYROID	-	-	-	-	-	-
FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY	3I	3I	3I	3I	3I	3I
COLLOID DEPLETION	2I	2I	2I	2I	2I	2I
TESTES	-	N	N	-	N	-
INTERSTITIAL CELL - ATROPHY	1I	-	-	1I	-	1I
EPIDIDYMIDES	-	N	-	-	-	-
ATROPHY	1I	-	-	1I	-	-
HYOSPERMIA	2I	-	-	2I	2I	2I
DEGENERATIVE GERM CELLS	1I	-	2I	2I	1I	1I
Non-Protocol Tissues:						
SEMINAL VESICLE	-	-	-	-	*	*
Non-Protocol Tissues:						
VENTRAL PROSTATE	-	-	-	-	*	*

-----  
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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Long-Evans

STUDY NUMBER: 1143100  
 GROUP: 5: Ketoconazole 100 mg/kg/day  
 SEX: MALE

ANIMAL ID:	R15116	R15117	R15118	R15119	R15120	R15121
THYROID	N	N	N	N	N	N
TESTES	N	N	N	N	N	N
EPIDIDYMIDES	N	-	N	N	N	N
INFILTRATION CELLULAR, LYMPHOCYTE	-	11	-	-	-	-
Non-Protocol Tissues:						
ADRENALS	*	-	*	*	-	-
Non-Protocol Tissues:						
LIVER	*	-	-	-	-	-

-----  
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**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100  
 FATE: TK Long-Evans

STUDY NUMBER: 1143100  
 GROUP: 6: Pimozide 30 mg/kg/day  
 SEX: MALE

ANIMAL ID:	R15128	R15129	R15130	R15131	R15132	R15133
THYROID	N	N	N	N	N	N
TESTES	-	N	N	-	N	N
HYOSPERMATOGENESIS	1I	-	-	2I	-	-
EPIDIDYIMIDES	-	-	-	-	-	-
ATROPHY	1I	-	-	-	-	-
HYOSPERMIA	3I	2I	2I	3I	2I	2I
Non-Protocol Tissues:						
KIDNEYS	*	-	-	-	-	-

-----  
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**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**TABULATED ANIMAL DATA**  
 -----

STUDY ID : 1143-100 STUDY NUMBER: 1143100  
 FATE: TK Long-Evans GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day  
SEX: MALE

ANIMAL ID:	R15140	R15141	R15142	R15143	R15144	R15145
THYROID	N	N	N	N	N	-
ULTIMOBANCHIAL CYST	-	-	-	-	-	P
TESTES	-	-	-	-	-	-
HYOSPERMATOGENESIS	4I	4I	4I	3I	4I	4I
SEMINIFEROUS TUBULES - DEGENERATION	3I	4I	3I	2I	4I	4I
EPIDIDYMIDES	-	-	-	-	-	-
HYOSPERMIA	4I	4I	4I	4I	4I	4I
DEGENERATIVE GERM CELLS	3I	-	-	3I	2I	1I
Non-Protocol Tissues:						
SEMINAL VESICLE	-	-	*	-	*	-

-----  
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#### IV. Correlation of Gross and Microscopic Findings

**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 1: Corn Oil 2.5 ml/kg/day

No Gross Observations for any animal in this group

-----  
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**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
 -----

STUDY ID: 1143-100	STUDY NUMBER: 1143100
SEX: MALE	GROUP: 2: Flutamide 50 mg/kg/day
Animal ID: R15074	Pathologist: MTB
Animal Fate: TK Sprague-Dawley	

Reference to Necropsy Record:	Related Histopathology:
TESTES - DARK, LEFT, GRAY	TESTES - NECROSIS

Animal ID: R15075	Pathologist: MTB
Animal Fate: TK Sprague-Dawley	

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required

Animal ID: R15076	Pathologist: MTB
Animal Fate: TK Sprague-Dawley	

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required
VENTRAL PROSTATE - SMALL	VENTRAL PROSTATE - Histopathology Not Required

Animal ID: R15078	Pathologist: MTB
Animal Fate: TK Sprague-Dawley	

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required

Animal ID: R15079	Pathologist: MTB
Animal Fate: TK Sprague-Dawley	

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL	SEMINAL VESICLE - Histopathology Not Required

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**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**TherImmune RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 2: Flutamide 50 mg/kg/day

Animal ID: R15082  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL, BILATERAL

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required

Animal ID: R15083  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
EPIDIDYMIDES - SMALL, BILATERAL  
  
VENTRAL PROSTATE - SMALL

Related Histopathology:  
EPIDIDYMIDES - ATROPHY  
  
VENTRAL PROSTATE - Histopathology Not Required

Animal ID: R15084  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL, BILATERAL

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
 -----

STUDY ID: 1143-100

STUDY NUMBER: 1143100

SEX: MALE

GROUP: 3: Methyl testosterone 80 mg/kg/day

Animal ID: R15089

Pathologist: MTB

Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:

KIDNEYS - CYST, LEFT, CORTEX, ONE, CLEAR, 1X1MM

Related Histopathology:

KIDNEYS - Histopathology Not Required

Animal ID: R15091

Pathologist: MTB

Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:

TESTES - SMALL, BILATERAL

Related Histopathology:

TESTES - HYOSPERMATOGENESIS

THYROID - ENLARGED, MODERATE

THYROID - No Corollary change detected

Animal ID: R15092

Pathologist: MTB

Animal Fate: TK Long-Evans

Reference to Necropsy Record:

LIVER - ACCESSORY LOBE, MEDIAN LOBE AT CLEFT, ONE, TAN,  
10X5X3

Related Histopathology:

LIVER - Histopathology Not Required

TESTES - SMALL, BILATERAL

TESTES - HYOSPERMATOGENESIS

Animal ID: R15093

Pathologist: MTB

Animal Fate: TK Long-Evans

Reference to Necropsy Record:

TESTES - SMALL, BILATERAL

Related Histopathology:

TESTES - HYOSPERMATOGENESIS

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**TherImmune RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 3: Methyl testosterone 80 mg/kg/day

Animal ID: R15095  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
TESTES - SMALL, BILATERAL

Related Histopathology:  
TESTES - HYOSPERMATOGENESIS

-----  
Animal ID: R15097  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
TESTES - SMALL, BILATERAL

Related Histopathology:  
TESTES - HYOSPERMATOGENESIS

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION  
IN JUVENILE MALE RATS  
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

-----  
**CORRELATION OF GROSS & MICRO**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day

Animal ID: R15098  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL, BILATERAL  
  
THYROID - ENLARGED, BILATERAL  
  
VENTRAL PROSTATE - SMALL

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required  
  
THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY  
  
VENTRAL PROSTATE - Histopathology Not Required

Animal ID: R15100  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL, BILATERAL  
  
THYROID - ENLARGED, MODERATE

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required  
  
THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

Animal ID: R15101  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL, BILATERAL  
  
THYROID - ENLARGED, SEVERE

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required  
  
THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

Animal ID: R15102  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL  
  
VENTRAL PROSTATE - SMALL

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required  
  
VENTRAL PROSTATE - Histopathology Not Required

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
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STUDY ID: 1143-100  
 SEX: MALE  
 STUDY NUMBER: 1143100  
 GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day

Animal ID: R15103  
 Animal Fate: TK Sprague-Dawley  
 Pathologist: MTB

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BOTH	SEMINAL VESICLE - Histopathology Not Required
PITUITARY - SOFT CYST, 1, CLEAR, 1X1MM	PITUITARY - Histopathology Not Required
THYROID - ENLARGED, SEVERE	THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

Animal ID: R15104  
 Animal Fate: TK Long-Evans  
 Pathologist: MTB

Reference to Necropsy Record:	Related Histopathology:
THYROID - ENLARGED, SEVERE	THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

Animal ID: R15105  
 Animal Fate: TK Long-Evans  
 Pathologist: MTB

Reference to Necropsy Record:	Related Histopathology:
THYROID - ENLARGED, BILATERAL, SEVERE	THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

Animal ID: R15106  
 Animal Fate: TK Long-Evans  
 Pathologist: MTB

Reference to Necropsy Record:	Related Histopathology:
THYROID - ENLARGED, BILATERAL, SEVERE	THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day

Animal ID: R15107  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
THYROID - ENLARGED, SEVERE, BOTH

Related Histopathology:  
THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

Animal ID: R15108  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL, BILATERAL

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required

VENTRAL PROSTATE - SMALL

VENTRAL PROSTATE - Histopathology Not Required

THYROID - ENLARGED, SEVERE

THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

Animal ID: R15109  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL, BILATERAL

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required

VENTRAL PROSTATE - SMALL

VENTRAL PROSTATE - Histopathology Not Required

THYROID - ENLARGED, BILATERAL, SEVERE

THYROID - FOLLICULAR CELLS - HYPERPLASIA/HYPERTROPHY

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 5: Ketoconazole 100 mg/kg/day

Animal ID: R15111  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

Reference to Necropsy Record:  
ADRENALS - ENLARGED, BILATERAL, 4X3X3MM

Related Histopathology:  
ADRENALS - Histopathology Not Required

Animal ID: R15114  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

Reference to Necropsy Record:  
ADRENALS - ENLARGED, BILATERAL, 4X4X4MM  
  
ADRENALS - PALE, BILATERAL, GREY

Related Histopathology:  
ADRENALS - Histopathology Not Required  
  
ADRENALS - Histopathology Not Required

Animal ID: R15115  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

Reference to Necropsy Record:  
ADRENALS - ENLARGED, 5X4X3MM

Related Histopathology:  
ADRENALS - Histopathology Not Required

Animal ID: R15116  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
LIVER - ACCESSORY LOBE, MEDIAN LOBE, ONE, TAN, 13X5X4MM  
  
ADRENALS - ENLARGED, BILATERAL, 5X3X3MM

Related Histopathology:  
LIVER - Histopathology Not Required  
  
ADRENALS - Histopathology Not Required

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**CORRELATION OF GROSS & MICRO**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 5: Ketoconazole 100 mg/kg/day

Animal ID: R15118  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
ADRENALS - ENLARGED, BILATERAL, 4X3X3MM

Related Histopathology:  
ADRENALS - Histopathology Not Required

-----  
Animal ID: R15119  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
ADRENALS - ENLARGED, BILATERAL, 4X3X3MM

Related Histopathology:  
ADRENALS - Histopathology Not Required

ADRENALS - PALE, BILATERAL, GREY

ADRENALS - Histopathology Not Required

-----  
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PATHOLOGY ASSOCIATES INTERNATIONAL  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION  
IN JUVENILE MALE RATS  
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

-----  
**CORRELATION OF GROSS & MICRO**  
-----

STUDY ID: 1143-100

STUDY NUMBER: 1143100

SEX: MALE

GROUP: 6: Pimozide 30 mg/kg/day

Animal ID: R15128

Pathologist: MTB

Animal Fate: TK Long-Evans

Reference to Necropsy Record:

KIDNEYS - CYST, LEFT, ONE, CLEAR, 1X1MM

Related Histopathology:

KIDNEYS - Histopathology Not Required

-----  
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ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION  
IN JUVENILE MALE RATS  
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day

Animal ID: R15136  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

Reference to Necropsy Record:  
KIDNEYS - CYST, RIGHT, ONE, CLEAR, 1X1MM

Related Histopathology:  
KIDNEYS - Histopathology Not Required

Animal ID: R15141  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
TESTES - SMALL, BILATERAL

Related Histopathology:  
TESTES - SEMINIFEROUS TUBULES - DEGENERATION

Animal ID: R15142  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
SEMINAL VESICLE - SMALL, BILATERAL

Related Histopathology:  
SEMINAL VESICLE - Histopathology Not Required

Animal ID: R15144  
Animal Fate: TK Long-Evans

Pathologist: MTB

Reference to Necropsy Record:  
TESTES - SMALL, BILATERAL

Related Histopathology:  
TESTES - SEMINIFEROUS TUBULES - DEGENERATION

SEMINAL VESICLE - SMALL, BILATERAL

SEMINAL VESICLE - Histopathology Not Required

V. Comment Report

**PATHOLOGY ASSOCIATES INTERNATIONAL**  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION  
IN JUVENILE MALE RATS  
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

-----  
**COMMENT REPORT**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 1: Corn Oil 2.5 ml/kg/day

No Comments for any animal in this group

-----  
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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**COMMENT REPORT**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 2: Flutamide 50 mg/kg/day

Animal ID: R15074  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

TISSUE COMMENTS:

TESTES - THE ENTIRE TESTIS IS NECROTIC AND INFARCTED. THIS SUGGESTS AN INTERRUPTION IN THE BLOOD SUPPLY TO THIS TESTIS. THIS CHANGE IS LIKELY UNRELATED TO THE TEST ARTICLE.  
EPIDIDYMIDES - THE ATROPHY IS CHARACTERIZED BY A REDUCTION IN SIZE OF TUBULAR LINING CELLS AND THE OVERALL SIZE OF THE TUBULES.

-----  
Animal ID: R15076  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

TISSUE COMMENTS:

TESTES - THE SEMINIFEROUS TUBULE DILATATION HAS NO APPARENT EFFECT ON SPERMATOGENESIS.

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION  
IN JUVENILE MALE RATS  
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

-----  
**COMMENT REPORT**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 3: Methyl testosterone 80 mg/kg/day

No Comments for any animal in this group

-----  
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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**COMMENT REPORT**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day

Animal ID: R15100  
Animal Fate: TK Sprague-Dawley

Pathologist: MTB

TISSUE COMMENTS:  
TESTES - THE CHANGES IN THE TESTES MAY BE DUE TO DELAYED MATURATION AS OPPOSED TO AN ACTUAL TOXIC EFFECT.

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**COMMENT REPORT**  
-----

STUDY ID: 1143-100

STUDY NUMBER: 1143100

SEX: MALE

GROUP: 5: Ketoconazole 100 mg/kg/day

Animal ID: R15110

Pathologist: MTB

Animal Fate: TK Sprague-Dawley

**TISSUE COMMENTS:**

TESTES - SCATTERED TUBULES (10%) CONTAIN BASOPHILIC SPERMATOGONIA AND LACK PRODUCTIVE SPERMATOGENESIS.

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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION  
IN JUVENILE MALE RATS  
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100

-----  
**COMMENT REPORT**  
-----

STUDY ID: 1143-100  
SEX: MALE

STUDY NUMBER: 1143100  
GROUP: 6: Pimozide 30 mg/kg/day

No Comments for any animal in this group

-----  
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**PATHOLOGY ASSOCIATES INTERNATIONAL**  
**ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION**  
**IN JUVENILE MALE RATS**  
**THEIRIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-100**

-----  
**COMMENT REPORT**  
-----

STUDY ID: 1143-100

STUDY NUMBER: 1143100

SEX: MALE

GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day

Animal ID: R15137

Pathologist: MTB

Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:

THYROID - INFLAMMATION IN THE SURROUNDING TISSUE SUGGESTS A POSSIBLE GAVAGE ACCIDENT.

-----  
Animal ID: R15138

Pathologist: MTB

Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:

THYROID - INFLAMMATION IN THE SURROUNDING TISSUE SUGGESTS A GAVAGE ACCIDENT.

-----  
Animal ID: R15140

Pathologist: MTB

Animal Fate: TK Long-Evans

TISSUE COMMENTS:

EPIDIDYMNIDES - THE EPIDIDYMAL CHANGES ARE DUE TO THE IMMATURETY OF THE TESTES.

-----  
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(END OF REPORT)

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VI. Quality Assurance Statement



**Pathology Associates International**  
A Company of Science Applications International Corporation



**Pathology Report**

**Assessment of Pubertal Development and Thyroid Function  
in Juvenile Male Rats**

TherImmune Research Corporation Study Number: 1143-100

**QUALITY ASSURANCE STATEMENT**

This histopathology project has been inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Environmental Protection Agency (EPA-FIFRA). The pathology report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU.

<u>Date of Inspection</u>	<u>Phase Inspected</u>	<u>Date Findings Reported to PAI Management/Study Pathologist</u>
02/25/00	Tissue Trimming	02/25/00
03/31;04/05/00	Individual Animal Data	04/05/00
03/31;04/05/00	Draft Pathology Report	04/05/00
06/15/00	Final Pathology Report	06/15/00

Karen E. Butler  
Karen E. Butler  
Quality Assurance Officer

6/15/00  
Date

15 Worman's Mill Court, Suite I • Frederick, Maryland 21701 • (301) 663-1644 • (301) 663-8994 FAX

## APPENDIX 8

## INDIVIDUAL SERUM T4 AND TSH LEVELS

## ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (SPRAGUE DAWLEY)

ANIMAL ID	T4, TOTAL (UG/DL)	TSH (NG/ML)
<u>GROUP: 1 - 2.5 ML/KG/DAY CORN OIL</u>		
R15062	7.08	1.32
R15063	4.44	2.64
R15064	3.80	2.00
R15065	4.58	3.17
R15066	5.33	3.72
R15067	4.46	7.54
<u>GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE</u>		
R15074	2.81	2.73
R15075	4.24	2.15
R15076	3.54	2.50
R15077	5.51	2.83
R15078	7.09	4.15
R15079	5.05	1.48
<u>GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE</u>		
R15086	5.54	2.26
R15087	4.08	1.43
R15088	3.74	3.22
R15089	5.42	6.75
R15090	4.79	2.49
R15091	4.59	3.04
<u>GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL</u>		
R15098	0.00	25.23
R15099	0.00	40.74
R15100	0.00	29.15
R15101	0.01	23.81
R15102	0.00	30.69
R15103	0.00	22.87
<u>GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE</u>		
R15110	6.00	4.11
R15111	5.69	3.87
R15112	4.58	2.70
R15113	7.42	1.63
R15114	5.31	4.20
R15115	4.56	2.21
<u>GROUP: 6 - 30 MG/KG/DAY PIMOZIDE</u>		
R15122	5.15	2.49
R15123	4.88	3.75
R15124	5.64	2.55
R15125	6.41	2.91
R15126	5.25	3.31
R15127	6.31	5.45
<u>GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE</u>		
R15134	4.05	1.68
R15135	4.88	2.80
R15136	3.80	2.74
R15137	7.15	6.29
R15138	3.68	0.49
R15139	2.76	0.98

Appendix Continued



APPENDIX 8 (CONTINUED)  
INDIVIDUAL SERUM T4 AND TSH

ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG-EVANS)

ANIMAL ID	T4, TOTAL (UG/DL)	TSH (NG/ML)
<u>GROUP: 1 - 2.5 ML/KG/DAY CORN OIL</u>		
R15068	7.18	2.68
R15069	4.08	2.55
R15070	6.06	5.44
R15071	6.63	3.35
R15072	7.71	5.11
R15073	7.04	4.20
<u>GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE</u>		
R15080	4.72	1.70
R15081	5.04	2.66
R15082	5.71	3.56
R15083	7.10	3.56
R15084	8.12	15.96
R15085	7.38	3.78
<u>GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE</u>		
R15092	7.41	1.70
R15093	5.28	5.26
R15094	4.93	4.54
R15095	8.81	1.58
R15096	6.22	4.41
R15097	5.34	4.50
<u>GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL</u>		
R15104	0.00	33.45
R15105	0.00	31.63
R15106	0.00	32.03
R15107	0.10	25.09
R15108	0.00	30.84
R15109	0.00	21.04
<u>GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE</u>		
R15116	6.66	4.34
R15117	4.87	2.52
R15118	5.58	1.84
R15119	4.84	2.72
R15120	5.78	2.40
R15121	6.19	2.84
<u>GROUP: 6 - 30 MG/KG/DAY PIMOZIDE</u>		
R15128	4.61	2.88
R15129	5.18	1.94
R15130	5.98	4.29
R15131	7.71	2.43
R15132	6.27	1.56
R15133	6.07	2.13
<u>GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE</u>		
R15140	3.15	1.93
R15141	4.40	2.42
R15142	3.48	1.52
R15143	4.37	2.03
R15144	4.04	3.03
R15145	2.83	1.87

APPENDIX 9  
INDIVIDUAL DAY OF DEATH  
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (SPRAGUE DAWLEY)

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ANIMAL ID	DAY OF DEATH
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GROUP: 1 - 2.5 ML/KG/DAY CORN OIL

R15062	53
R15063	53
R15064	53
R15065	54
R15066	54
R15067	54

GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE

R15074	53
R15075	53
R15076	53
R15077	54
R15078	54
R15079	54

GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE

R15086	53
R15087	53
R15088	53
R15089	54
R15090	54
R15091	54

GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL

R15098	53
R15099	53
R15100	53
R15101	54
R15102	54
R15103	54

GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE

R15110	53
R15111	53
R15112	53
R15113	54
R15114	54
R15115	54

GROUP: 6 - 30 MG/KG/DAY PIMOZIDE

R15122	53
R15123	53
R15124	53
R15125	54
R15126	54
R15127	54

GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE

R15134	53
R15135	53
R15136	53
R15137	54
R15138	54
R15139	54

Appendix CONTINUED

APPENDIX 9 (CONTINUED)  
INDIVIDUAL DAY OF DEATH

## ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG-EVANS)

<u>ANIMAL ID</u>	<u>DAY OF DEATH</u>
<u>GROUP: 1 - 2.5 ML/KG/DAY CORN OIL</u>	
R15068	53
R15069	53
R15070	53
R15071	54
R15072	54
R15073	54
<u>GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE</u>	
R15080	53
R15081	53
R15082	53
R15083	54
R15084	54
R15085	54
<u>GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE</u>	
R15092	53
R15093	53
R15094	53
R15095	54
R15096	54
R15097	54
<u>GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL</u>	
R15104	53
R15105	53
R15106	53
R15107	54
R15108	54
R15109	54
<u>GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE</u>	
R15116	53
R15117	53
R15118	53
R15119	54
R15120	54
R15121	54
<u>GROUP: 6 - 30 MG/KG/DAY PIMOZIDE</u>	
R15128	53
R15129	53
R15130	53
R15131	54
R15132	54
R15133	54
<u>GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE</u>	
R15140	53
R15141	53
R15142	53
R15143	54
R15144	54
R15145	54

APPENDIX 10  
STATISTICAL ANALYSES  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

Experiment R1143-100 - Sprague Dawley Juvenile Male Rats  
Body and Organ Weights

Table 1  
Test of Homogeneity of Variance Over All Groups  
Brown-Forsyth Version of Levene's Test

Dependent	ProbF
term	0.4321
liver	0.1493
kidney	0.2615
testes	0.1301
epid	0.8439
seminal	0.7406
levwt	0.2540
prost	0.4275
prep	0.1619
adren	0.3517
pit	0.6678
t4	0.1757
tsh	0.1011

Experiment R1143-100 - Sprague Dawley Juvenile Male Rats  
Body and Organ Weights

Table 2  
Analysis of Covariance: Test for FND22 x Dose Interaction

Dependent	ProbF
term	0.1199
liver	0.0920
kidney	0.5741
testes	0.2881
epid	0.3248
seminal	0.7268
levwt	0.6974
prost	0.9444
prep	0.1300
adren	0.7272
pit	0.8888
t4	0.3470
tsh	0.1108

Experiment R1143-100 - Sprague Dawley Juvenile Male Rats  
Body and Organ Weights

Table 3  
Results of MANCOVA for All Endpoints

Hypothesis	ProbF
Control_vs_Dose2	<.0001
Control_vs_Dose3	<.0001
Control_vs_Dose4	<.0001
Control_vs_Dose5	0.0031
Control_vs_Dose6	0.0002
Control_vs_Dose7	0.0250

Experiment R1143-100 - Sprague Dawley Juvenile Male Rats  
Ratio Data  
Table 4

Ratios: Test of Homogeneity of Variance Over All Groups  
Ratios: Brown-Forsyth Version of Levene's Test

Dependent	ProbF
liver	0.2695
kidney	0.6079
testes	0.1434
epid	0.1177
seminal	0.1381
levwt	0.2599
prost	0.4077
adren	0.4131
pit	0.8425

Experiment R1143-100 - Sprague Dawley Juvenile Male Rats  
Ratio Data  
Table 5

Analysis of Covariance: Test for Weaning Body Weight x Dose Inter

Dependent	ProbF
liver	0.5540
kidney	0.1597
testes	0.1273
epid	0.0638
seminal	0.8309
levwt	0.7898
prost	0.9490
adren	0.5380
pit	0.8467

Experiment R1143-100 - Sprague Dawley Juvenile Male Rats  
Ratio Data  
Table 6

Ratios: Results of MANCOVA

Hypothesis	ProbF
Control_vs_Dose2	<.0001
Control_vs_Dose3	<.0001
Control_vs_Dose4	<.0001
Control_vs_Dose5	0.0005
Control_vs_Dose6	0.0246
Control_vs_Dose7	0.0087

TABLE (1143-100)  
 ADJUSTED MEANS FROM COVARIANCE ANALYSIS  
 ASSESSMENT OF PUBERTYL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (SPRAGUE-DAWLEY)

	DOSE GROUP							
	CORN OIL	FLUAMIDE	METHYL TESTOSTERONE	PROPYLTHIOURACIL	KETOCONAZOLE	PIMOZIDE	DIETHYLPHTHALATE	
ADRENAL	0.042	0.048	0.045	**0.027	**0.073	0.044	0.046	
EPIDIDYMIDES	0.494	**0.280	**0.397	**0.244	+0.430	**0.402	0.457	
KIDNEY	2.099	1.945	*2.332	**0.843	1.958	**1.635	2.006	
LEVATOR MUSCLES WT	0.667	**0.257	0.717	**0.104	0.527	**0.376	0.567	
LIVER	11.132	**12.741	10.967	**4.483	11.312	**9.693	*12.296	
PITUITARY	0.008	*0.010	0.007	0.006	0.007	0.006	0.008	
PREPUCE SEPARATION	42.829	**56.624	**36.193	**54.710	**46.725	**53.047	44.872	
VENTRAL PROSTATE	0.223	*0.107	*0.353	**0.082	0.136	0.121	0.233	
SEMINAL	0.541	**0.081	*0.714	**0.056	**0.267	**0.214	*0.389	
T4, TOTAL	4.755	4.847	4.535	**0.239	5.470	5.848	4.242	
TERM	259.895	254.188	*243.522	**113.729	244.282	**219.425	246.283	
TESTES	3.053	*3.705	**0.833	**1.843	2.875	*2.581	2.645	
TSH	3.101	2.411	2.990	**26.176	3.058	3.045	1.926	

TABLE (1143-100)  
 ADJUSTED MEANS FROM PAIRWISE ANALYSIS OF COVARIANCE (ORGAN-TO-BODY WEIGHT RATIOS)  
 ASSESSMENT OF PUBERTYL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (SPRAGUE-DAWLEY)

	DOSE GROUP						
	CORN OIL	FLUTAMIDE	METHYL TESTOSTERONE	PROPIPIHOURACIL	KETONAZOLE	PHOZIDE	DIETHYLENTHALATE
ADRENAL	0.016	0.019	0.019	*0.024	**0.030	0.020	0.019
EPIDIDYMIDES	0.189	**0.111	*0.162	*0.215	0.175	0.185	0.185
KIDNEY	0.809	0.765	**0.958	*0.744	0.803	*0.744	0.815
LEVATOR MUSCLES WT	0.257	**0.102	0.294	**0.092	0.215	**0.171	0.229
LIVER	4.285	**5.009	4.502	*3.956	*4.633	4.418	**5.010
PITUITARY	0.003	*0.004	0.003	**0.005	0.003	0.003	0.003
VENTRAL PROSTATE	0.086	0.043	*0.145	0.070	0.055	0.056	0.094
SEMINAL	0.212	**0.032	**0.295	**0.055	**0.112	**0.097	*0.161
TESTES	1.176	**1.456	**0.342	**1.622	1.177	1.174	1.074



TABLE (1143-100)  
 SUMMARY OF BODY WEIGHT AND PREPUCE SEPARATION  
 ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (SPRAGUE-DAWLEY)

	DOSE GROUP					
	CORN OIL	FLUTAMIDE	METHYL TESTOSTERONE	PROPYLTHIOURACIL	KETOCANALOLE	DIETHYLPHTHALATE
BODY WT ON DAY OF SEP	184.92 ± 3.73 (6)**255.10 ± 3.25 (6)	**139.72 ± 7.03 (6)	**114.10 ± 1.72 (6)	*198.45 ± 4.72 (6)**212.87 ± 3.00 (6)	188.47 ± 3.10 (6)	

Experiment R1143-100 - Long Evans Juvenile Male Rats  
Body and Organ Weights

Table 1  
Test of Homogeneity of Variance Over All Groups  
Brown-Forsyth Version of Levene's Test

Dependent	ProbF
term	0.7038
liver	0.3255
kidney	0.9105
testes	0.1868
epid	0.8607
seminal	0.7255
levwt	0.6197
prost	0.5434
prep	0.2777
adren	0.1362
pit	0.5296
t4	0.8699
tsh	0.6533

Experiment R1143-100 - Long Evans Juvenile Male Rats  
Body and Organ Weights

Table 2  
Analysis of Covariance: Test for PND22 x Dose Interaction

Dependent	ProbF
term	0.6669
liver	0.3110
kidney	0.1834
testes	0.8127
epid	0.3875
seminal	0.4753
levwt	0.7679
prost	0.4129
prep	0.4784
adren	0.3619
pit	0.8201
t4	0.7152
tsh	0.8068

Experiment R1143-100 - Long Evans Juvenile Male Rats  
Body and Organ Weights

Table 3  
Results of MANCOVA for All Endpoints

Hypothesis	ProbF
Control_vs_Dose2	<.0001
Control_vs_Dose3	<.0001
Control_vs_Dose4	<.0001
Control_vs_Dose5	0.0568
Control_vs_Dose6	0.0004
Control_vs_Dose7	<.0001

## Experiment R1143-100 - Long Evans Juvenile Male Rats

## Ratio Data

## Table 4

Ratios: Test of Homogeneity of Variance Over All Groups  
Ratios: Brown-Forsyth Version of Levene's Test

Dependent	ProbF
liver	0.3671
kidney	0.8272
testes	0.0944
epid	0.2230
seminal	0.4601
levwt	0.6392
prost	0.3797
adren	0.2112
pit	0.2026

## Experiment R1143-100 - Long Evans Juvenile Male Rats

## Ratio Data

## Table 5

Analysis of Covariance: Test for Weaning Body Weight x Dose Inter

Dependent	ProbF
liver	0.6503
kidney	0.4890
testes	0.7665
epid	0.5695
seminal	0.6007
levwt	0.7787
prost	0.6341
adren	0.3562
pit	0.4452

## Experiment R1143-100 - Long Evans Juvenile Male Rats

## Ratio Data

## Table 6

Ratios: Results of MANCOVA

Hypothesis	ProbF
Control_vs_Dose2	<.0001
Control_vs_Dose3	<.0001
Control_vs_Dose4	<.0001
Control_vs_Dose5	0.0312
Control_vs_Dose6	0.0439
Control_vs_Dose7	<.0001

TABLE (1143-100)  
 ADJUSTED MEANS FROM ANALYSIS OF COVARIANCE  
 ASSESSMENT OF PUBERTYL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG EVANS)  
 DOSE GROUP

	CORN OIL	FLUTAMIDE	METHYL TESTOSTERONE	PROPYLPIROURACIL	KETOCANAZOLE	PIMOZIDE	DIBUTYLPHTHALATE
ADRENAL	0.047	0.050	0.040	*0.025	*0.071	0.058	0.048
EPIDIDYIMIDES	0.509	**0.308	0.499	**0.247	*0.393	**0.315	*0.398
KIDNEY	2.339	*2.082	2.359	**0.865	2.138	**1.760	2.250
LEVATOR MUSCLES WT	0.659	**0.396	0.641	**0.155	**0.488	**0.420	**0.383
LIVER	12.345	12.407	*11.170	**4.179	11.869	**9.898	11.623
PITUITARY	0.008	0.008	0.007	*0.006	0.007	0.007	0.007
PREPUCE SEPARATION	44.748	**54.470	**32.371	**53.007	*48.190	**52.017	**50.529
VENTRAL PROSTATE	0.183	**0.057	**0.307	**0.063	0.139	0.157	*0.131
SEMINAL	0.410	**0.092	*0.667	**0.122	0.240	*0.193	*0.189
T4, TOTAL	6.305	6.212	6.202	**0.005	5.619	5.864	*3.665
TERM	293.642	*258.329	*259.127	**109.284	**252.124	**218.873	*259.529
TESTES	2.754	3.278	**0.551	**1.855	2.564	**1.887	**0.843
TSH	3.734	3.892	3.289	**28.510	2.681	2.414	*2.081

TABLE (1143-100)  
 ADJUSTED MEANS FROM PAIRWISE ANALYSIS OF COVARIANCE (ORGAN-TO-BODY WEIGHT RATIOS)  
 ASSESSMENT OF PUBERTYL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG EVANS)  
 DOSE GROUP

	CORN OIL	FLUTAMIDE	METHYL TESTOSTERONE	PROPYLTHIOURACIL	KETOCONAZOLE	FINOZIDE	DIBUTYLPHTHALATE
ADRENAL	0.016	0.019	0.155	0.024	*0.028	*0.027	0.018
EPIDIDYIMIDES	0.173	**0.118	0.192	**0.229	0.155	0.142	0.152
KIDNEY	0.798	0.805	**0.908	0.795	0.848	0.804	*0.868
LEVATOR MUSCLES WT	0.226	**0.152	0.247	**0.143	0.193	0.189	**0.147
LIVER	4.213	**4.794	4.294	**3.842	**4.702	*4.515	*4.475
PITUITARY	0.003	0.003	0.003	**0.006	0.003	0.003	0.003
VENTRAL PROSTATE	0.062	**0.022	**0.118	0.057	0.055	0.072	0.050
SEMINAL TESTES	0.142	0.036	*0.261	0.153	0.099	0.089	0.076
	0.938	**1.269	**0.213	**1.721	1.017	0.859	**0.329

TABLE (1143-100)  
 SUMMARY OF BODY WEIGHT AND PREPUCE SEPARATION  
 ASSESSMENT OF FUGERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG EVANS)

DOSE GROUP	DOSE GROUP						
	CORN OIL	FLUTAMIDE	METHYL TESTOSTERONE	PROPYLTHIOURACIL	KETOCANAZOLE	PIMOZIDE	DIBUTYLPIPTHALATE
BODY WT ON DAY OF SEP	218.85 ± 7.03 (6)**	259.10 ± 8.44 (6)	117.32 ± 5.45 (6)	110.57 ± 2.73 (6)	214.57 ± 7.63 (6)	207.35 ± 8.29 (6)	238.30 ± 9.77 (6)

APPENDIX 11  
PROTOCOL  
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

# TherImmune

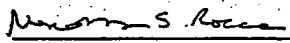
## Research Corporation

### STUDY PROTOCOL

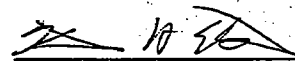
### Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

**APPROVED:**

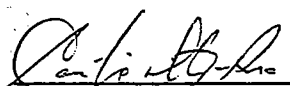
**TherImmune Research Corporation:**

 12-14-99  
Meredith S. Rocca, Ph.D. Date  
Study Director

**EPA:**

 12/15/99  
Kenneth H. Elstein Date  
Project Officer

**REVIEWED:**

 12/17/99  
Cecilia Matos-Rosa Date  
Quality Assurance Auditor



EPA Requisition No. AC5001  
EPA Reference No. QT-RT-99-002276

TherImmune No. 1143-100

**PROTOCOL**

**I. Study Title**

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

**II. Purpose**

The purpose of this protocol is to quantify the effects of environmental compounds on pubertal development and thyroid function in the intact juvenile male rat. The larger goal is to use this study and its replicate (1143-102) to: 1) provide preliminary validation of the protocol for future EPA studies and 2) assess intra-laboratory and inter-strain variation.

**III. Study Location**

TherImmune Research Corporation (TherImmune)  
15 Firstfield Road  
Gaithersburg, Maryland 20878  
Phone: 301-330-3737  
Fax: 301-330-3738

**IV. Sponsor and Address**

Environmental Protection Agency  
Kenneth H. Elstein, Project Officer  
Phone: 919-541-3581 Fax: 919-541-1499  
Julio E. Lopez, Contracting/Ordering Officer  
Phone: 919-541-4474 Fax: 919-541-4273  
RTP: MD-71 NHEERL  
Research Triangle Park, NC 27711

**V. TherImmune Staff**

- |                               |   |
|-------------------------------|---|
| A. Principal Investigator     | Gary W. Wolfe, Ph.D., D.A.B.T.                                |
| B. Study Director             | Meredith S. Rocca, Ph.D.                                      |
| C. Pathologist                | John M. Fletcher, D.V.M., M.P.H.,<br>D.A.C.V.P., D.A.C.V.P.M. |
| D. Quality Assurance Director | James Carignan, B.S.  |
| E. Veterinarian               | Edward T. Greenstein, D.V.M., A.C.L.A.M.                      |

**VI. Regulatory Compliance**

This study will be conducted in accordance with the EPA FIFRA Good Laboratory Practice Standards, 40 CFR Part 160.

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**VII. Quality Assurance**

The protocol, in-life phases, and the final report will be audited by Quality Assurance in accordance with TherImmune Standard Operating Procedures. Data will be examined for completeness, consistency, and proper documentation.

**VIII. Proposed Study Timetable**

Initiation of Dosing:	January 8, 2000
Last Terminal Sacrifice:	February 8, 2000
Progress Report:	December 31, 1999
Draft Report	March 17, 2000
Final Report:	May 19, 2000

**IX. Test Articles****A. Identification**

Vehicle:	Corn oil
Test Article 1:	Vinclozolin
Test Article 2:	Methyl testosterone
Test Article 3:	Propylthiouracil (PTU)
Test Article 4:	Ketoconazole
Test Article 5:	Pimozide
Test Article 6:	Dibutylphthalate (DBP)

**B. Purity**

Purity will be provided by the supplier.

**C. Characteristics**

Information on the methods of synthesis and stability, as well as data on composition or other characteristics which define the test articles, is on file with the manufacturer.

**D. Reserve Samples**

1. A sample of each reagent as provided by the vendor in the following quantities:  
100 mg each of vinclozolin, methyl testosterone, propylthiouracil, and ketoconazole  
1 g each of pimozide and dibutylphthalate
2. 1 ml of the initial stock solution made from the reagent (if applicable).
3. 1 ml of the first and last dosing solutions administered to the animals.

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Samples shall be stored according to the manufacturer's recommendations to minimize degradation. Samples shall be stored for at least six months after the final report is issued, or sent to the Sponsor on request.

## X. Husbandry

### A. Housing

Animals will be housed in polycarbonate boxes with Sani-Chip Hardwood laboratory bedding as follows:

Pregnant/lactating females: 1/cage  
Juvenile males 3/cage, if possible

### B. Food

Teklad 7012 Certified Rodent Diet will be provided *ad libitum*. Fresh food will be provided weekly.

Feed is analyzed by the manufacturer for concentrations of specified heavy metals, aflatoxin, chlorinated hydrocarbons, organophosphates, and specified nutrients. Specified nutrients analyses are on file at TherImmune.

### C. Water

Tap water will be provided *ad libitum* via an automatic watering system or water bottles. The water is routinely analyzed for contaminants and specific microbes. The results of these analyses are on file at TherImmune.

### D. Contaminants

The Study Director and/or Sponsor have considered possible interfering substances potentially present in animal feed and water, including the test material itself or possible structurally related materials as well as the items listed in (B) and (C) above. None of these contaminants are reasonably expected to be present in animal feed or water at levels sufficient to interfere with this study.

### E. Environment

The targeted temperature range is 20- 24° C with a relative humidity of 40-50%. Temperature and humidity are monitored continuously. A 14-hour light/10-hour dark cycle (lights on at 0500 h, off at 1900 h), will be maintained. Ten or greater air changes/hour will be maintained.

### F. Acclimation

Pregnant females will be acclimated to the facility for approximately 7 days prior to expected parturition. Animals will be observed for general health and suitability for testing during this period. Animals that are diseased or unsuitable for testing will be removed from the study.

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### XI. Experimental Design - Production of Juvenile Animals

This section describes procedures for producing the juvenile animals which will be used as study animals on protocols 1143-100 and 1143-101. Briefly, one set of timed pregnant females will arrive at TherImmune on Gestation Day (GD) 12 and will be used for both protocols. The females will be allowed to deliver and rear pups. At weaning, the male pups will be used on this protocol and the female pups on protocol 1143-101.

#### A. Animals

##### 1. Strain/Source

Hsd: Sprague Dawley®SD® Rats  
Harlan Sprague Dawley, Inc., Indianapolis, IN

Long-Evans Hooded Rats  
Harlan Sprague Dawley, Inc., Indianapolis, IN

##### 2. Number/Sex

20 timed pregnant Sprague-Dawley females  
20 timed pregnant Long-Evans females

##### 3. Identification

Females will be identified by individual ear tag and cage label.

##### 4. Justification

Rats will be used because of the extensive historical data base.

#### B. Observation of Animals

##### 1. Clinical Observations

Clinical observations for mortality and morbidity will be performed twice daily by cage-side observation.

##### 2. Litter Observations

###### a. Parturition

Pregnant females will be observed at least twice daily for signs of parturition.

###### b. Body Weights

Pups will be weighed on post-natal day PND 1 and weekly thereafter. (The objective is to identify runt pups and unthrifty litters; pups will not be individually identified.)

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c. Culling

On PND 3 or 4, litters will be culled to 8 to 10 pups (approximately equal numbers of male and female pups, when possible). Culled pups will be euthanized with sodium pentobarbital overdose.

d. Weaning

Pups will be weaned on PND 21.

3. Terminal Sacrifice/Necropsy - Dams and Untreated Pups

a. Unscheduled Sacrifices and Deaths

Moribund dams will be anesthetized via carbon dioxide inhalation and discarded without necropsy.

Moribund pups will be sacrificed with sodium pentobarbital overdose or carbon dioxide inhalation, and discarded without necropsy.

Animals found dead will be discarded without necropsy.

b. Scheduled Sacrifices

After total litter loss or litter weaning on PND 21, dams will be anesthetized via carbon dioxide inhalation and discarded without necropsy.

Culled pups will be euthanized with sodium pentobarbital overdose, and discarded without necropsy.

C. Selection of Study Animals

On PND 21, male pups will be weighed to the nearest 0.1 g, weight ranked and assigned to groups using computer-generated random numbers. At the time of randomization, the weight variation of each male used should not exceed 12 grams above or below the mean weight, and the mean body weights for each group will not be statistically different. Unthrifty or runt pups will not be selected.

Procedures for selected males are described in Section XII.

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Unselected male pups may be returned to the animal colony or sacrificed by carbon dioxide inhalation and discarded without necropsy. Female pups will be used on Protocol 1143-101.

## XII. Experimental Design - Treatment and Assessment of Juvenile Animals

The procedures described below will be performed on both strains of rats concurrently to compare inter-strain variability.

### A. Animals

1. **Number/Sex**  
 42 Sprague-Dawley males  
 42 Long-Evans males
2. **Identification**  
 Individual ear tag and cage label.

### B. Group Designation and Dosage Levels

Group	Treatment	Dosage (per kg/day)	# of males per strain
1	Corn Oil	2.5 ml	6
2	Vinclozolin	100 mg	6
3	Methyl testosterone	80 mg	6
4	Propylthiouracil (PTU)	240 mg	6
5	Ketoconazole	100 mg	6
6	Pimozide	30 mg	6
7	Dibutylphthalate (DBP)	1000 mg	6

### C. Dosing Procedures

1. **Method of Administration**  
 Oral gavage, using an 18-gauge gavage needle (1" long, with a 2.25 mm ball) and a 1 cc glass tuberculin syringe for each treatment.
2. **Frequency**  
 Daily, between 0700 and 0900 h, PND 23 through 53 or 54

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**3. Volume**

2.5 ml/kg body weight, adjusted on a daily basis.

**4. Formulations**

Test articles will be suspended in corn oil.

**5. Absorption**

Toxic or pathologic effects will serve as evidence of absorption.

**D. Observation of Animals**

**1. Clinical Observations**

Clinical observations for mortality and morbidity will be performed twice daily by cage-side observation.

**2. Physical Examinations**

Detailed clinical observations will be performed weekly.

**3. Body Weights**

Rats will be weighed daily. Body weight on the day of complete preputial separation will also be noted.

**4. Food Consumption**

Not required.

**5. Water Consumption**

Not required.

**6. Preputial Separation**

Males will be examined daily for preputial separation beginning on PND 23. The appearance of partial, complete, or a persistent thread of tissue between the glans and prepuce will be recorded on the days observed. The day of complete preputial separation will be used for analysis.

**E. Termination**

**1. Unscheduled Sacrifices and Deaths**

Necropsies will be conducted on all moribund animals and on all animals not surviving to termination. Moribund animals will be weighed and killed by decapitation. Trunk blood and tissues will be collected as described below. Animals will be necropsied as close as possible to the time of death.

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## 2. Terminal Sacrifice

Between 1300 and 1700 h on PND 53 or 54, all surviving animals will be killed by decapitation. Decapitation shall occur in a room separate from the housing area and within 15 seconds of removing the animal from its cage.

## F. Postmortem Procedures

### 1. Serum Collection and Analysis

Trunk blood (supplemented by cardiac puncture, if necessary) will be collected immediately after decapitation. Serum will be separated by centrifugation.

A minimum of 500  $\mu$ l/animal will be aliquoted into 1.7 ml siliconized microcentrifuge tubes, stored at  $-20^{\circ}$  C, and shipped by express carrier to:

Dr. Ralph Cooper  
US EPA/NHEERL/RTD, MD-72  
2525 NC Highway 54  
Durham, NC 27713.

A minimum of 550  $\mu$ l/animal will be aliquoted into 1 ml microcentrifuge tubes, stored at  $-20^{\circ}$  C, and delivered to Ani Lytics (Gaithersburg, MD) for T4 and TSH analysis. Low, medium and high internal RIA standards will be used for each assay.

### 2. Gross Necropsy

All animals will be subjected to a full gross necropsy, which includes examination of the external surface of the body, all orifices, and the cranial, thoracic, and abdominal cavities and their contents.

### 3. Organ Weights

Connective tissue and fat shall be carefully removed from the following tissues using small surgical scissors such that the fluid in the accessory sex glands is retained. The following organs will be weighed immediately after dissection to avoid drying of the trimmed tissues.

- (1) paired testes
- (2) paired epididymides
- (3) thyroid
- (4) liver
- (5) kidney
- (6) adrenals
- (7) pituitary



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- (8) ventral prostate
- (9) seminal vesicle
- (10) levator ani plus bulbocavernosus muscles

#### 4. Tissue Preservation

The thyroid, epididymides and testes will be placed in Bouin's fixative for approximately 24 hours, after which they shall be rinsed and stored in 70% ethanol.

#### 5. Histopathology

The preserved thyroid, epididymides and testes from all animals will be embedded in paraffin, stained with hematoxylin and eosin, and examined microscopically by a pathologist at Pathology Associates International.

## XII. Final Report

\*At termination of the study, a final report which includes the following information (as appropriate) will be prepared and submitted:

### A. Abstract

### B. Experimental Design and Methods

### C. Results

1. mortality
2. clinical observations
3. body weights
4. age and weight at complete preputial separation
5. gross pathology
6. organ weights and organ/body ratios
7. histopathology
8. serum T4 and TSH

### D. Statistical Analyses

Data shall be analyzed using multivariate analysis of covariance (MANCOVA), using body weight at weaning as a covariate. If the treatment x body weight at interaction is not significant, then the intercepts shall be tested for difference among treatments using a two-tailed test. If serum hormone levels, or any other data, display heterogeneity of variance, then appropriate data transformations (i.e. log transformation) shall be employed.

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**E. Statistical Evaluation (as deemed appropriate)**

1. age and weight at complete preputial separation
2. body weight
3. organ weights and organ/body weight ratios
4. serum T4 and TSH

**F. Tables (including mean, standard error, and sample size)**

1. mean age and weight at complete preputial separation
2. mean daily body weight
3. mean body weight change from PND 21 to necropsy
4. summary of clinical signs for each test group to include a list of each findings and number of animals affected
5. mean serum T4 and TSH
6. mean organ weights and organ to body weight ratios
7. summary incidence of gross pathology findings
8. summary incidence of histopathology findings

**G. Appendices**

1. day of death for each animal
2. individual age and weight at complete preputial separation
3. individual body weights
4. individual clinical signs for each animal to include the week of observation of each sign, a description of each sign and its subsequent course
5. individual serum T4 and TSH
6. individual organ weights and organ to body weight ratios
7. individual gross pathology findings
8. individual histopathology findings

**XIII. Record Retention**

All study records, study protocols, final reports, protocol and report revisions, and any written letters, memorandums or communications concerning the conduct of the study shall be retained at the TherImmune Archive for at least one year from study completion. Documentation of any transfer of study records, specimens, and reports will be maintained by TherImmune for a period of one year.

**XIV. Amendments**

Amendments to this protocol will be approved by the EPA Project Officer, justified, dated, and signed by the Study Director. Amendments will include a statement noting the impact, if any, on the study.

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**XV. Deviations**

Deviations from the GLP Regulations, Protocol, and Standard Operating Procedures will be immediately reported to the TherImmune Study Director. The Study Director will note in the study records any deviation, the effect of the deviation on the study, any corrective action taken, and will inform the EPA Project Officer.

## PROTOCOL AMENDMENT

TherImmune No.: 1143-100	
AMENDMENT NUMBER:   <sup>بمقتضى</sup> 144 1.21 00	
STUDY TITLE: Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats	
DISTRIBUTION:	
STUDY DIRECTORS/Wolfe and Rocca OPERATIONS DIRECTOR/Morgan FACILITY MANAGER/Blackford TECHNICAL SUPERVISOR/Hatcher VETERINARIAN/Greenstein QUALITY ASSURANCE/Carignan SPONSOR/Elstein HEALTH AND SAFETY OFFICER/Blackford ANALYTICAL CHEM/NA SALES-MARKETING/Zemo	STUDY NOTEBOOK/Musselman (2) CENTRAL FILE/Wolfe DOSE PREPARATION/Nyakiti IACUC CHAIR/Rocca PROJECT LEADER /Borst/Pepperl NECROPSY/Hackett PAI/Delaney (3) HEAD TECH/Musselman CONTRACTS/Allen
ORIGINAL FILED IN QA	
SPONSOR AUTHORIZATION: 1/4/00 e-mail from Kenneth Elstein	

## 1. Subject: Test Articles (IX, A) and Group Designation and Dosage Levels (XII, B)

Flutamide at a dosage of 50 mg/kg will be substituted for vinclozilin.

Justification: Vinclozilin is not commercially available.

## Approval:

Meredith S. Rocca 1.6.00  
Meredith S. Rocca, Ph.D. Date

## PROTOCOL AMENDMENT

TherImmune No.: 1143-100	
AMENDMENT NUMBER: 2	
STUDY TITLE: Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats	
DISTRIBUTION:	
STUDY DIRECTORS/Wolfe and Rocca OPERATIONS DIRECTOR/Morgan FACILITY MANAGER/Blackford TECHNICAL SUPERVISOR/Hatcher VETERINARIAN/Greenstein QUALITY ASSURANCE/Carignan SPONSOR/Elstein HEALTH AND SAFETY OFFICER/Blackford ANALYTICAL CHEM/NA SALES-MARKETING/Zemo	STUDY NOTEBOOK/Muselman (2) CENTRAL FILE/Wolfe DOSE PREPARATION/Nyakiti IACUC CHAIR/Rocca PROJECT LEADER /Borst/Pepperl NECROPSY/Hackett PAI/Delaney (3) HEAD TECH/Muselman CONTRACTS/Allen
ORIGINAL FILED IN QA	
SPONSOR AUTHORIZATION: 1/24/00 e-mail from Kenneth Elstein	

## 1. Subject: Organ Weights (XII, F, 3)

The thyroids will not be weighed. The thyroids with parathyroids, trachea and esophagus attached will be submitted for histology.

**Justification:** Thyroids weights were deemed unnecessary as hormone profiles and histology will provide more meaningful data on thyroid effects.

## 2. Subject: Serum Collection (XII, F, 1)

All serum samples will be aliquoted into 1.7 ml siliconized microcentrifuge tubes and stored at  $-80^{\circ}\text{C}$ .

**Justification:** One type of tube is being used for both serum samples for consistency. Samples are being stored at a lower temperature for better preservation.

## Approval:

Meredith S. Rocca 1.26.00  
Meredith S. Rocca, Ph.D. Date

