Final Report-102

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:
1143-102

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

TABLES

APPENDICES

FIGURES

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 6.29.00

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:

Inspections/Review	Findings Reported	Inspector/Reviewer
Protocol 11/18,19,29,30/99	11/30/99	C. Brown
Phase Inspection 01/14/00	01/31/00	C. Brown
Final Report and Data Audit 05/01-03,08-12/00	05/12/00	C. Matos-Rosa
Post-Audit 06/22,23,26/00	06/26/00	C. Matos-Rosa

Quality Assurance Unit:

6/28/00

C. Matos-Rosa /Date

STUDY IDENTIFICATION

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

TherImmune Study Number:	1143-102
Test Articles:	Flutamide, Methyl Testosterone, Propylthiouracil, Ketoconazole, Pimozide, and Dibutylphthalate
Sponsor:	Environmental Protection Agency
Sponsor's Representative:	Kenneth H. Elstein, Project Officer Environmental Protection Agency RTP: MD-71 NHEERL Research Triangle Park, NC 27711 Phone: 919-541-3581 Fax: 919-541-1499
Study Director:	Meredith S. Rocca, Ph.D. TherImmune Research Corporation 15 Firstfield Road Gaithersburg, MD 20878 Phone: 301-330-3735
Study Timetable	
Study Initiation:	December 14, 1999
Experimental Start Date:	January 15, 2000
Experimental Termination:	February 15, 2000

STUDY PERSONNEL
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

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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 pimozide, 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, levitor 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	↓	↑	✓		
Methyl Testosterone	↓	↓	✓		
Propylthiouracil	↓	↑	✓	↑	↓
Ketoconazole	↓	↑SD			
Pimozide	↓	↑SD	✓ LE		
Dibutylphthalate	↓LE	↑LE	✓LE		↓LE

KEY: ↓ = significantly decreased compared to control mean
↑ = significantly increased compared to control mean
✓ = affected histopathology
LE = Long Evans only
SD = Sprague Dawley only
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. Although there were some differences between strains, when all endpoints were considered the variation in response to treatment was minimal, except for ketoconazole which had a greater effect on SD males and DBP which affected only LE males. As evidenced by changes observed in body weight, 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 15, 2000. The last terminal necropsies were performed on February 15, 2000.

TEST AND CONTROL ARTICLES

The control article, corn oil, and test articles, flutamide, methyl testosterone, propylthiouracil, ketoconazole, pimozide, 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
Pimozide	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 pimozide 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-four timed-pregnant female Hsd: Sprague Dawley® SD® Rats and twenty timed-pregnant female Long-Evans Hooded Rats, were received on December 14, 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 postnatal day (PND) 21.

Pups were weighed on PND 1 and weekly thereafter to identify runted 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. 1143-103).

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 4 and 3 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 1143-103. 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 23 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 mL 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.

Unscheduled Sacrifices and Deaths

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

Terminal Sacrifice

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 μl serum/animal was aliquoted into 1.7 ml siliconized microcentrifuge tubes,

stored at approximately -80°C, and later shipped on dry ice by express carrier to Dr. Ralph Cooper, US EPA, Durham, North Carolina. Approximately 550 μl serum/animal was aliquoted into 1.7 mL siliconized microcentrifuge tubes, stored at approximately -80°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 DBP-treated SD males. For organ to body weight ratios only, the null hypothesis was not rejected for ketoconazole (SD only), pimozide and DBP (SD only)treated Therefore, no post-hoc tests were performed for these groups.

"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. There were three unscheduled deaths, one LE male in each of the control, ketoconazole, and DBP-treated groups. There was no obvious case of death for two of the animals, although one was partially cannibalized. The DBP-treated male had a discolored lung which suggests that test article may have been aspirated. The deaths are not considered to be test article related. All other males survived to scheduled termination on PND 53 or 54.

Clinical Observations

Weekly clinical observations are summarized in Table 1 and presented individually in Appendix 1. The only adverse clinical observation was dyspnea in one ketoconazole-treated LE male and the rat was sacrificed as moribund. The observation was not considered to be related to the test article. At this time Sialodacryoadenitis virus (SDAV) had been diagnosed in rats in another area of the laboratory. Blood was collected from this male at termination and a serum sample from all the rats housed in cages of the animals that died, as well as, other randomly selected males were tested for SDAV antibodies. No animals in this study, or in studies in neighboring rooms, tested positive for SDAV. We conclude that SDAV was not present in this room and had no effect on this study.

Daily Body Weights

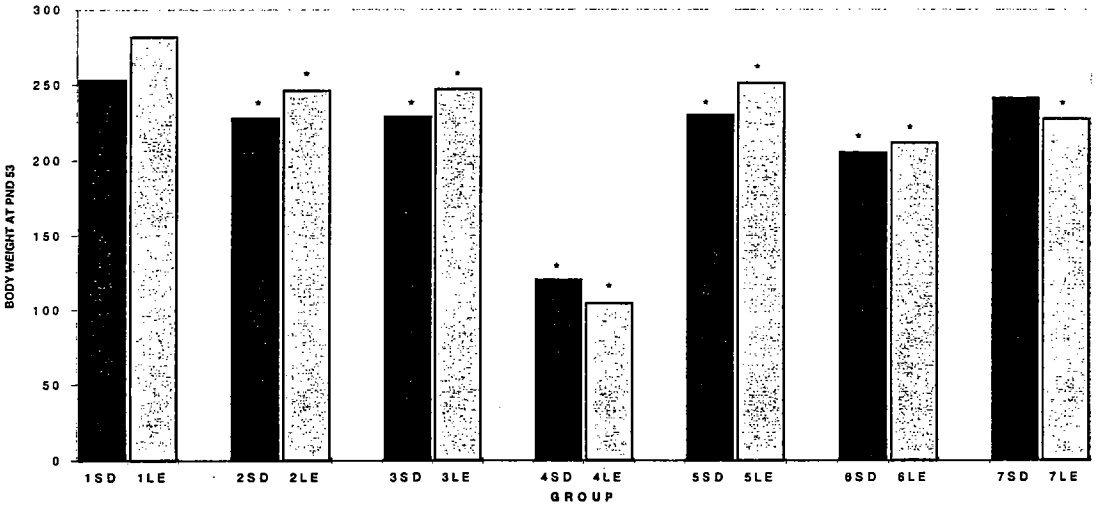
Body weights are shown in Figure 2, summarized in Table 2 and presented individually in Appendix 2. Mean body weight changes from PND 22 to necropsy are summarized in Table 3.

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 13.3% for SD and 13.5% for LE rats.

The PND 53 mean body weights for all treatment groups were lower than control males, except for DBP-treated SD males. The greatest effect was with PTU treatment. PTU-treated males had body weights which were only 47.6 and 37.1% of control mean body weights for SD and LE males respectively.

Figure 2: PND 53 Mean Body Weights



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

* = significantly different than control
5 = 100 mg/kg/day Ketoconazole
6 = 30 mg/kg/day Pimozide
7 = 1000 mg/kg/day Dibutylphthalate

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 preputial separation was greater for LE males (PND 50.17, 258.30

g) than for SD males (PND 43.00, 187.70 g). The age at complete preputial separation of PND 50 in LE males was a very unusual finding, as our historical control data shows that preputial separation is usually complete in untreated SD males on PND43.9 (7 recent studies, N = 370). When the data for this study and for the replicate study 1143-100 were further examined it became apparent that the difference in this group of LE males was that there was an extended time between the start and completion of separation. On this study both SD and LE males first started preputial separation on PND 41 and the mean day of the start of separation was 42.5 and 43.5 for SD and LE, respectively. The difference between the strains was that the LE males had a persistent thread of tissue between the glans and the prepuce which delayed complete separation. We considered the possibility that different technicians may have varied in reporting observations, but as the same technician examined all groups on any given day, this explanation was eliminated. We believe that the late completion of preputial separation in these LE males is due to biological variability.

Flutamide treatment completely inhibited preputial separation in both strains. No PTU-treated LE and only two (33%) of SD males achieved complete preputial separation. In SD males only, ketoconazole (PND 45.83) and pimozide (PND 50.17) also increased the mean age of complete preputial separation. One ketoconazole-treated LE male never achieved complete preputial separation, and although the mean age was not significantly different than controls, this mean is artificially low as the day after necropsy was used as the day of preputial separation for statistical purposes for these males. Two DBP-treated LE males (33%) never achieved complete preputial separation, and the mean age to complete preputial separation increased to 52.5 days in this group.

Methyl testosterone was the only treatment which decreased the age of preputial separation. Mean age at preputial separation was PND 37.33 and 33.50 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

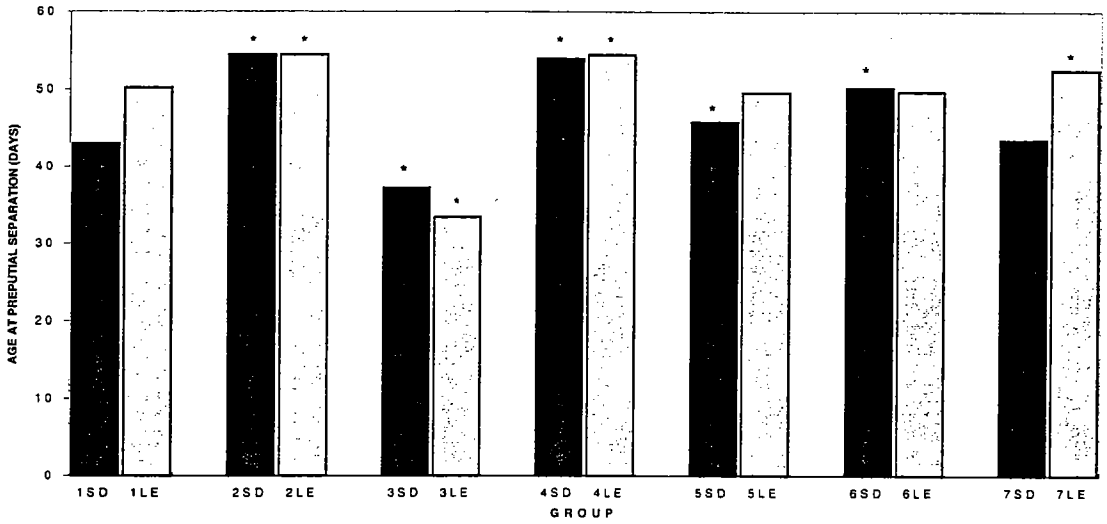
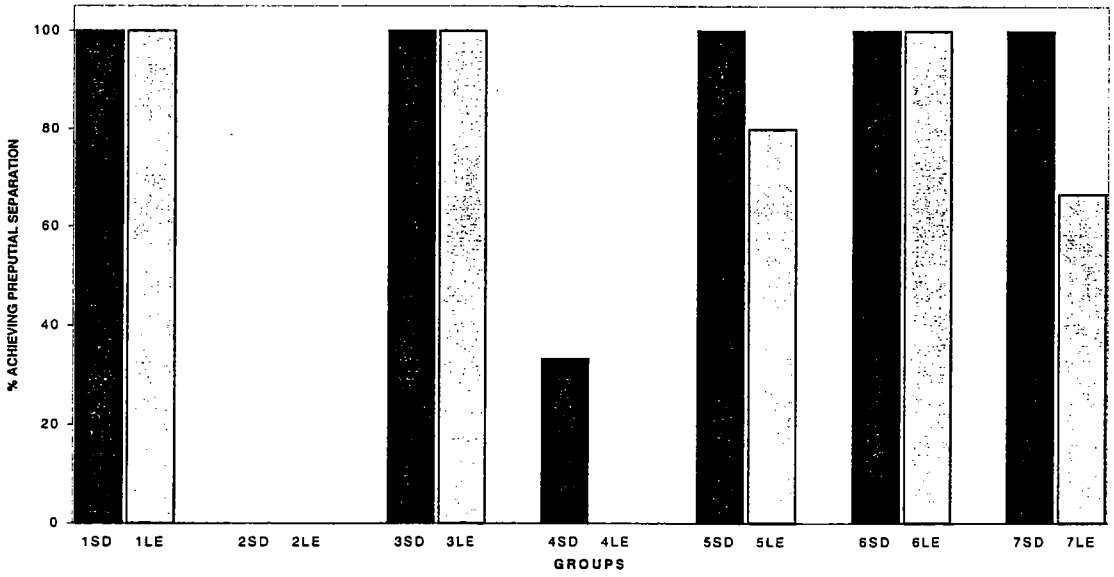


Figure 4: Percent Achieving Preputial Separation



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3 = 80 mg/kg/day Methyl Testosterone
4 = 240 mg/kg/day Propylthiouracil

* = significantly different than control

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, epididymis, ventral prostate, adrenal and thyroid. The testes were small in 83 and 55% of methyl testosterone and DBP-treated males, respectively. Twenty-five percent of flutamide-treated males had small epididymides. Small ventral prostates were observed in flutamide (67%), PTU (58%), and ketoconazole (9%) treated males. PTU treatment also caused enlarged thyroids in all males (100%). Enlarged adrenals were seen in 64% of ketoconazole-treated rats.

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 similar for both SD and LE males when both absolute organ weights and organ to body weights 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 increased by ketoconazole treatment. Kidneys weighed less in flutamide, PTU and pimozide-treated males. Methyl testosterone, PTU, and pimozide decreased pituitary 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.

Seminal vesicle and ventral prostate weights showed a similar pattern - the weight was decreased by flutamide, PTU, ketoconazole, pimozide and DBP (LE only) and increased by methyl testosterone. In contrast, testis weight was decreased by methyl testosterone, PTU, pimozide (LE only), and DBP (LE only) treatment and increased by flutamide in LE males. Epididymides weighed significantly less in flutamide, methyl testosterone (SD), PTU and

pimozide-treated rats compared to controls. The weight of levator ani and bulbocavernosus muscles were decreased in flutamide, PTU, pimozide and DBP (LE) treated rats and increased in methyl testosterone-treated LE males. The effects of DBP treatment on organ weights was only significant in LE males.

Figure 5: Organ Weights

Tissue	Flutamide		Methyl Testosterone		PTU		Ketocon-azole		Pimozide		DBP	
	Wt.	%	Wt.	%	Wt.	%	Wt.	%	Wt.	%	Wt.	%
Adrenals			↓LE		↓LE	↑LE	↑	↑LE	↓LE			
Kidneys	↓			↓SD	↓	↓SD			↓		↓LE	
Liver		↑			↓SD				↓SD			
Pituitary			↓		↓	↑			↓			
Seminal vesicles	↓	↓	↑	↑	↓	↓	↓		↓SD		↓LE	↓LE
Ventral prostate	↓	↓	↑	↑	↓	↓	↓SD		↓SD		↓LE	
Testes	↑LE	↑LE	↓	↓	↓	↑LE			↓LE		↓LE	↓LE
Epididymides	↓	↓	↓SD		↓	↑LE	↓LE		↓		↓LE	
Levator ani and bulbocavernosus	↓		↑LE	↑LE	↓	↓SD			↓		↓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	Ketocon-azole	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 4.80 and 6.65 μg/DL for SD and LE males respectively. TSH levels were 2.72 and 2.22 ng/mL for SD and LE males respectively. PTU treatment had significant effects on T4 and TSH levels. T4 levels were less than 18% of the mean control, while TSH levels were greater than nine times higher in PTU-treated males. DBP treatment resulted in a decrease in T4 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. 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, pituitary, and testes weights, but increased seminal vesicle, ventral prostate and levator ani and bulbocavernosus muscles (LE) 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 (LE) weights and never exhibited preputial separation, and had decreased weights of kidneys, epididymides, levator ani and bulbocavernosus muscles, seminal vesicles, and ventral prostate, when compared to control means, but increased testes weight (LE). 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, had significant results only in LE males. Treatment resulted in lower body weights, increased the age of preputial separation, and decreased kidney, semial vesicle, ventral prostate, testes, epididymides, and levator ani and bulbocavernosus muscles weights and T4 levels when compared to control means. Histology findings in LE males included seminiferous tubule degeneration, hypospermatogenesis, and hypospermia.

Ketoconazole disrupts endocrine function by inhibiting cytochrome P_{450} enzymes which are necessary for steroidogenesis. Males treated with ketoconazole had lower body weights. Age at complete preputial separation was significantly increased in SD males only, but

the mean age of complete preputial separation is artificially low for LE males as one LE male never achieved complete preputial separation. Adrenal size and weights were increased in both strains. There were no adverse histopathological findings in the organs examined in ketoconazole-treated males.

Pimozide is a D_2 receptor antagonist, which suppresses the action of dopamine, resulting in an increase in prolactin secretion. Pimozide treatment resulted in severe weight loss (>13%) 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 in SD males only. The only histology finding was sporadic hypospermia in LE males.

PTU acts by inhibiting iodination of thyroid hormones. This inhibition disrupts growth and, indirectly, sexual maturation. PTU treatment severly decreased body weight and increased the age of complete preputial separation. Only two SD and no LE males achieved complete 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.

The day of complete preputial separation was delayed in control LE males compared to the replicate study 1143-100 and our historical control data for SD males. This resulted in the age to complete preputial separation not being significantly different in ketoconazole-treated LE males as compared to the control mean. It should be noted, however, that one ketoconazole-treated LE male never achieved complete preputial separation and combined with the effects on body and organ weights this screening protocol identified ketoconazole as an endocrine disruptor.

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 parameters examined, except ketoconazole and DBP. Ketoconazole had a greater effect on SD males, while DPB treatment had significant effects only in LE 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 ketoconazole which had a greater effect on SD males and DBP which affected only LE males. As evidenced by changes observed in body weight, 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:

Meredith S. Rocca 6-29-00

Meredith S. Rocca, Ph.D./ Date

Project Leader:

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 28								
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 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 49								
No. Observed		0	0	0	0	0	0	1
Found Dead		0	0	0	0	0	0	1 100%
PND 50								
No. Observed		12	12	12	12	12	12	11
Moribund Kill		0	0	0	0	1 8%	0	0
Found Dead		1 8%	0	0	0	0	0	0
Normal		11 92%	12 100%	12 100%	12 100%	11 92%	12 100%	11 100%
Dyspnea		0	0	0	0	1 8%	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
5 = 100 mg/kg/day Ketoconazole
6 = 30 mg/kg/day Pimozide
7 = 1000 mg/kg/day Dibutylphthalate
PND = Postnatal Day

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	49.22± 0.94 (6)	50.70± 0.91 (6)	50.35± 1.01 (6)	49.15± 0.51 (6)	49.27± 1.27 (6)	51.02± 0.98 (6)	51.55± 0.89 (6)
PND23	52.62± 0.93 (6)	*55.55± 0.92 (6)	54.47± 0.81 (6)	53.10± 0.60 (6)	52.88± 1.48 (6)	54.12± 1.06 (6)	**57.00± 1.07 (6)
PND24	58.97± 1.12 (6)	59.72± 0.96 (6)	59.42± 1.10 (6)	58.17± 1.00 (6)	57.22± 1.63 (6)	**46.92± 1.01 (6)	61.88± 0.79 (6)
PND25	63.13± 1.25 (6)	64.65± 0.77 (6)	66.17± 1.23 (6)	61.32± 1.43 (6)	63.27± 1.76 (6)	**52.48± 1.39 (6)	*66.92± 0.96 (6)
PND26	69.58± 1.12 (6)	70.20± 0.97 (6)	71.25± 1.16 (6)	68.95± 0.89 (6)	*66.22± 1.67 (6)	**59.85± 1.32 (6)	70.57± 0.73 (6)
PND27	74.10± 1.39 (6)	76.33± 0.75 (6)	*78.17± 1.44 (6)	72.93± 0.75 (6)	71.00± 1.39 (6)	**62.78± 1.60 (6)	74.42± 0.79 (6)
PND28	80.85± 1.54 (6)	82.22± 0.87 (6)	*84.95± 1.43 (6)	79.10± 0.92 (6)	77.40± 1.50 (6)	**67.80± 1.74 (6)	82.35± 0.79 (6)
PND29	86.63± 1.25 (6)	87.30± 1.16 (6)	**91.82± 1.55 (6)	84.05± 0.98 (6)	*82.42± 1.25 (6)	**70.93± 1.76 (6)	89.78± 0.96 (6)
PND30	92.77± 1.48 (6)	93.68± 1.55 (6)	*97.82± 1.65 (6)	90.32± 0.98 (6)	**87.05± 1.46 (6)	**75.35± 1.95 (6)	94.72± 1.04 (6)
PND31	99.27± 1.63 (6)	99.65± 1.43 (6)	*104.38± 1.40 (6)	94.62± 1.11 (6)	*93.88± 1.54 (6)	**82.82± 2.54 (6)	101.33± 1.37 (6)
PND32	108.10± 1.62 (6)	110.25± 2.23 (6)	112.38± 1.66 (6)	**100.65± 1.23 (6)	*101.80± 1.92 (6)	**89.15± 2.53 (6)	107.93± 1.31 (6)
PND33	115.08± 1.74 (6)	115.37± 2.05 (6)	118.50± 1.38 (6)	**102.83± 1.56 (6)	**106.78± 1.44 (6)	**95.00± 2.33 (6)	115.73± 1.74 (6)
PND34	122.90± 1.92 (6)	124.97± 2.05 (6)	126.70± 1.35 (6)	**106.50± 1.55 (6)	**115.05± 1.06 (6)	**102.13± 2.55 (6)	124.55± 1.88 (6)
PND35	129.27± 2.47 (6)	128.43± 2.57 (6)	133.53± 1.27 (6)	**109.63± 1.37 (6)	**119.83± 1.54 (6)	**106.28± 2.45 (6)	130.02± 2.12 (6)
PND36	137.33± 2.54 (6)	135.38± 2.76 (6)	140.05± 1.08 (6)	**110.80± 1.85 (6)	**127.42± 1.62 (6)	**113.90± 2.97 (6)	138.20± 1.97 (6)
PND37	145.45± 2.70 (6)	142.80± 2.70 (6)	146.07± 1.79 (6)	**114.93± 2.19 (6)	**133.88± 1.81 (6)	**121.62± 2.95 (6)	144.75± 1.75 (6)
PND38	154.92± 3.14 (6)	150.72± 3.05 (6)	154.22± 1.64 (6)	**116.52± 2.79 (6)	**142.13± 1.87 (6)	**129.05± 3.54 (6)	153.07± 2.27 (6)
PND39	161.63± 2.63 (6)	156.23± 2.81 (6)	160.13± 1.45 (6)	**118.50± 2.42 (6)	**147.62± 1.74 (6)	**134.97± 3.70 (6)	160.13± 1.28 (6)
PND40	167.73± 3.31 (6)	160.43± 3.64 (6)	164.25± 1.61 (6)	**116.63± 2.45 (6)	**153.55± 1.82 (6)	**139.90± 4.22 (6)	161.67± 2.26 (6)
PND41	174.48± 3.93 (6)	168.02± 3.43 (6)	170.30± 1.62 (6)	**116.63± 2.41 (6)	**160.20± 2.31 (6)	**146.68± 4.84 (6)	170.87± 2.63 (6)
PND42	180.68± 3.05 (6)	172.63± 4.29 (6)	177.83± 1.12 (6)	**118.75± 2.99 (6)	**166.60± 1.87 (6)	**156.18± 5.51 (6)	177.97± 2.50 (6)
PND43	188.25± 4.28 (6)	182.50± 4.44 (6)	182.75± 1.19 (6)	**119.52± 3.01 (6)	**172.35± 1.80 (6)	**161.88± 5.12 (6)	184.37± 2.27 (6)
PND44	194.02± 3.87 (6)	186.85± 4.10 (6)	187.87± 1.10 (6)	**118.40± 2.35 (6)	**177.97± 2.33 (6)	**169.15± 4.45 (6)	191.98± 3.13 (6)
PND45	200.28± 4.29 (6)	193.12± 3.97 (6)	194.32± 1.17 (6)	**120.72± 2.48 (6)	**183.82± 2.60 (6)	**174.90± 5.27 (6)	196.98± 3.33 (6)
PND46	210.95± 4.17 (6)	203.67± 5.08 (6)	202.68± 1.69 (6)	**123.25± 2.68 (6)	**194.60± 2.42 (6)	**184.77± 5.12 (6)	206.42± 3.52 (6)
PND47	217.05± 4.26 (6)	*205.43± 5.44 (6)	207.53± 1.75 (6)	**120.80± 2.66 (6)	**197.48± 2.98 (6)	**187.37± 5.35 (6)	210.65± 3.19 (6)
PND48	226.12± 4.23 (6)	*213.10± 5.01 (6)	*213.77± 2.05 (6)	**121.78± 3.28 (6)	**205.85± 3.27 (6)	**193.00± 6.18 (6)	219.33± 3.26 (6)
PND49	230.05± 5.01 (6)	*217.18± 5.88 (6)	220.60± 2.00 (6)	**123.10± 2.91 (6)	**210.97± 3.24 (6)	**198.38± 6.17 (6)	224.72± 2.44 (6)
PND50	235.37± 5.24 (6)	*221.22± 5.18 (6)	223.88± 2.55 (6)	**121.02± 2.92 (6)	**216.58± 3.71 (6)	**198.33± 7.87 (6)	227.35± 2.89 (6)
PND51	240.55± 5.79 (6)	226.52± 5.61 (6)	230.05± 3.44 (6)	**120.78± 3.05 (6)	**217.60± 4.06 (6)	**196.58± 8.83 (6)	230.72± 5.64 (6)
PND52	246.27± 5.16 (6)	**225.45± 7.29 (6)	*231.12± 3.24 (6)	**120.73± 2.71 (6)	**225.07± 3.45 (6)	**199.83± 8.36 (6)	235.07± 3.91 (6)
PND53	252.98± 7.05 (6)	**227.88± 8.63 (6)	*228.75± 6.00 (6)	**120.40± 3.54 (6)	**230.12± 4.43 (6)	**205.18± 8.61 (6)	241.20± 4.87 (6)
PND54	255.87±13.88 (3)	228.77±18.56 (3)	237.50±11.70 (3)	**113.03± 3.40 (3)	242.13± 5.74 (3)	**203.83±14.41 (3)	235.90± 8.89 (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
5 = 100 mg/kg/day Ketoconazole
6 = 30 mg/kg/day Pimozide
7 = 1000 mg/kg/day Dibutylphthalate
PND = Postnatal Day

TABLE 2
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	45.92± 1.04 (6)	46.25± 0.90 (6)	45.88± 1.02 (6)	45.55± 0.95 (6)	45.67 ± 1.15 (6)	46.37± 0.52 (6)	46.32± 0.85 (6)
PND23	49.88± 1.10 (6)	51.55± 1.08 (6)	50.05± 1.24 (6)	47.22± 1.20 (6)	49.87 ± 1.32 (6)	50.08± 0.94 (6)	50.48± 1.20 (6)
PND24	54.88± 1.10 (6)	56.38± 1.24 (6)	56.02± 1.37 (6)	51.77± 1.33 (6)	54.07 ± 1.74 (6)	**43.30± 0.61 (6)	56.07± 1.43 (6)
PND25	60.68± 1.48 (6)	62.63± 1.37 (6)	62.45± 1.59 (6)	58.95± 1.72 (6)	60.22 ± 2.00 (6)	**46.50± 1.26 (6)	61.55± 1.36 (6)
PND26	68.38± 1.12 (6)	69.55± 1.90 (6)	69.55± 1.69 (6)	65.90± 1.93 (6)	66.95 ± 2.17 (6)	**51.67± 1.59 (6)	67.88± 1.85 (6)
PND27	73.53± 1.28 (6)	74.48± 1.97 (6)	74.68± 1.75 (6)	70.73± 2.06 (6)	71.27 ± 2.32 (6)	**55.48± 2.38 (6)	72.92± 1.58 (6)
PND28	78.68± 1.20 (6)	81.42± 2.01 (6)	82.65± 1.87 (6)	75.90± 2.46 (6)	78.65 ± 2.49 (6)	**59.90± 1.38 (6)	79.33± 2.22 (6)
PND29	86.33± 1.33 (6)	87.88± 2.09 (6)	89.43± 1.93 (6)	*80.28± 2.41 (6)	83.28 ± 2.89 (6)	**63.37± 1.77 (6)	83.55± 1.88 (6)
PND30	93.30± 1.47 (6)	95.98± 2.35 (6)	96.25± 2.25 (6)	**85.52± 2.35 (6)	90.48 ± 3.17 (6)	**69.72± 1.81 (6)	90.35± 1.90 (6)
PND31	101.13± 2.15 (6)	102.25± 2.49 (6)	102.72± 2.14 (6)	**88.70± 3.08 (6)	98.02 ± 2.98 (6)	**73.40± 1.48 (6)	95.88± 2.19 (6)
PND32	109.50± 1.90 (6)	111.00± 2.44 (6)	111.07± 2.48 (6)	**91.62± 2.78 (6)	105.07 ± 3.43 (6)	**79.42± 2.11 (6)	103.02± 2.02 (6)
PND33	117.17± 2.41 (6)	118.00± 2.60 (6)	117.63± 2.77 (6)	**91.03± 3.32 (6)	111.90 ± 3.24 (6)	**85.70± 2.53 (6)	109.67± 2.13 (6)
PND34	124.72± 2.96 (6)	125.45± 2.70 (6)	125.42± 2.81 (6)	**95.03± 2.74 (6)	120.00 ± 3.70 (6)	**92.62± 2.72 (6)	117.07± 2.41 (6)
PND35	130.60± 4.02 (6)	130.63± 2.54 (6)	131.52± 3.09 (6)	**94.72± 3.66 (6)	127.67 ± 4.03 (6)	**100.85± 2.87 (6)	124.00± 2.81 (6)
PND36	141.25± 4.13 (6)	139.25± 3.47 (6)	139.28± 3.16 (6)	**96.18± 3.74 (6)	135.17 ± 3.57 (6)	**107.57± 2.33 (6)	*131.57± 2.70 (6)
PND37	149.65± 3.57 (6)	145.28± 3.55 (6)	148.65± 3.67 (6)	**97.63± 3.53 (6)	143.00 ± 4.17 (6)	**114.95± 3.06 (6)	*138.02± 3.46 (6)
PND38	158.47± 4.58 (6)	154.03± 4.59 (6)	155.90± 3.71 (6)	**100.40± 2.98 (6)	149.55 ± 5.00 (6)	**120.57± 3.05 (6)	**144.60± 2.87 (6)
PND39	166.97± 4.79 (6)	160.60± 4.80 (6)	162.92± 3.51 (6)	**100.53± 3.11 (6)	156.58 ± 5.14 (6)	**126.45± 3.06 (6)	**151.45± 3.13 (6)
PND40	174.00± 5.61 (6)	165.32± 4.54 (6)	165.77± 3.65 (6)	**100.30± 2.91 (6)	163.55 ± 4.95 (6)	**132.20± 3.04 (6)	**157.70± 2.51 (6)
PND41	183.73± 5.73 (6)	173.83± 4.20 (6)	173.58± 3.47 (6)	**101.53± 2.77 (6)	**169.67 ± 5.13 (6)	**137.43± 3.16 (6)	**165.58± 2.86 (6)
PND42	191.50± 5.70 (6)	179.85± 5.47 (6)	178.32± 3.88 (6)	**101.65± 2.88 (6)	**172.80 ± 7.35 (6)	**146.88± 4.06 (6)	**172.12± 3.21 (6)
PND43	200.22± 6.61 (6)	189.85± 6.03 (6)	187.85± 4.08 (6)	**103.22± 2.81 (6)	**179.97 ± 7.25 (6)	**154.52± 3.87 (6)	**177.83± 4.08 (6)
PND44	203.80± 5.93 (6)	194.77± 5.73 (6)	193.27± 4.01 (6)	**103.20± 2.62 (6)	*187.35 ± 7.40 (6)	**159.30± 3.49 (6)	**184.37± 3.82 (6)
PND45	213.73± 6.85 (6)	201.05± 6.11 (6)	199.18± 4.09 (6)	**103.53± 2.78 (6)	**194.22 ± 7.60 (6)	**166.83± 3.60 (6)	**188.80± 4.04 (6)
PND46	226.70± 7.32 (6)	212.38± 6.80 (6)	*207.63± 4.43 (6)	**105.27± 2.68 (6)	**203.05 ± 7.77 (6)	**174.68± 2.89 (6)	**199.27± 4.69 (6)
PND47	232.32± 8.13 (6)	215.20± 7.62 (6)	*214.33± 4.31 (6)	**104.23± 2.57 (6)	**205.92 ± 7.96 (6)	**183.17± 3.99 (6)	**204.12± 4.52 (6)
PND48	236.20±10.25 (6)	222.70± 7.21 (6)	219.22± 4.24 (6)	**104.73± 2.83 (6)	*212.77 ± 9.83 (6)	**189.37± 4.89 (6)	**209.32± 5.21 (6)
PND49	241.02±13.65 (6)	229.83± 7.85 (6)	227.97± 4.32 (6)	**106.28± 2.85 (6)	*214.87 ±11.66 (6)	**192.73± 4.75 (6)	*215.25± 6.08 (6)
PND50	260.86± 9.29 (5)	*236.93± 8.42 (6)	**232.00± 4.47 (6)	**106.37± 2.66 (6)	**220.92 ±14.58 (6)	**199.60± 3.65 (6)	**218.70± 4.85 (5)
PND51	270.16±10.32 (5)	**242.42± 8.20 (6)	**239.66± 4.99 (5)	**104.90± 2.27 (6)	**241.92 ± 8.68 (5)	**204.87± 4.05 (6)	**221.26± 7.11 (5)
PND52	275.04±10.42 (5)	**242.12± 8.92 (6)	**241.38± 5.49 (6)	**105.35± 2.93 (6)	*248.34 ± 8.23 (5)	**205.53± 7.67 (6)	**225.46± 8.88 (5)
PND53	281.94± 9.76 (5)	**246.20± 8.84 (6)	**247.07± 5.98 (6)	**104.72± 2.99 (6)	**251.18 ± 7.56 (5)	**211.72± 7.27 (6)	**227.52±11.00 (5)
PND54	305.90± 6.80 (2)	**243.50±12.72 (3)	**251.77± 1.98 (3)	**100.70± 0.90 (3)	279.85 ± 9.15 (2)	**225.30± 3.63 (3)	**233.50±16.94 (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
				Sprague Dawley			
	208.8±15.56 (6)	180.9±21.30 (6)	179.5±18.24 (6)	70.3± 8.01 (6)	182.9±15.18 (6)	154.3±21.09 (6)	189.1±15.49 (6)
				Long-Evans			
	241.1±24.05 (5)	202.7±21.61 (6)	202.7±13.91 (6)	59.7±5.50 (6)	210.4±20.13 (5)	167.1±18.23 (6)	185.6±25.83 (5)

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

GROUP: PERIOD	1	2	3	4	5	6	7
				Sprague Dawley			
AGE (DAYS)	43.00± 0.37 (6)	**54.50± 0.22 (6)a	**37.33± 1.09 (6)	**54.00± 0.37 (6)a	**45.83± 0.40 (6)	**50.17± 0.87 (6)	43.50± 0.34 (6)
WEIGHT (GRAMS)	187.70± 4.37 (6)	**231.57± 8.70 (6)a	**147.62± 6.79 (6)	**120.32± 3.45 (6)a	190.00± 1.30 (6)	193.68± 7.03 (6)	187.20± 2.87(6)
				Long-Evans			
AGE (DAYS)	50.17± 1.19 (6)	**54.50± 0.22 (6)a	**33.50± 0.34 (6)	**54.50± 0.22 (6)a	49.60± 1.17 (5)a	49.67± 0.99 (6)	*52.50± 1.18 (6)a
WEIGHT (GRAMS)	258.30± 13.59 (6)	248.97± 8.98 (6)a	**120.77± 3.80 (6)	**105.23± 2.76 (6)a	*228.98± 8.75 (5)a	*197.70± 7.47 (6)	*231.98± 7.96 (6)a

a This mean included censored data.

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 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	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Kidneys (Paired)							
No. of Observations	11	12	12	12	11	12	11
DILATED	0	1 8%	0	0	0	1 8%	0
NO GROSS FINDINGS	11 100%	11 92%	12 100%	12 100%	11 100%	11 92%	11 100%
Testes (Paired)							
No. of Observations	11	12	12	12	11	12	11
SMALL	0	0	10 83%	0	0	0	6 55%
SOFT	0	1 8%	0	0	0	0	0
UNEQUALLY SIZED	0	1 8%	0	0	0	0	0
NO GROSS FINDINGS	11 100%	11 92%	2 17%	12 100%	11 100%	12 100%	5 45%
Epididymides (Paired)							
No. of Observations	11	12	12	12	11	12	11
SMALL	0	3 25%	0	0	0	0	1 9%
NO GROSS FINDINGS	11 100%	9 75%	12 100%	12 100%	11 100%	12 100%	10 91%
Seminal Vesicle							
No. of Observations	11	12	12	12	11	12	11
ENLARGED	0	0	1 8%	0	0	0	0
SMALL	0	7 58%	0	7 58%	2 18%	0	3 27%
NO GROSS FINDINGS	11 100%	5 42%	11 92%	5 42%	9 82%	12 100%	8 73%

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

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
Levator Ani/Bulbocavernosus Muscles							
No. of Observations	11	12	12	12	11	12	11
SMALL	0	0	0	1 8%	0	0	0
NO GROSS FINDINGS	11 100%	12 100%	12 100%	11 92%	11 100%	12 100%	11 100%
Ventral Prostate							
No. of Observations	11	12	12	12	11	12	11
SMALL	0	8 67%	0	7 58%	1 9%	0	0
NO GROSS FINDINGS	11 100%	4 33%	12 100%	5 42%	10 91%	12 100%	11 100%
Adrenals							
No. of Observations	11	12	12	12	11	12	11
ENLARGED	0	0	0	0	7 64%	0	0
DARK AREA	0	1 8%	0	0	0	0	0
PALE	0	0	0	0	4 36%	0	0
NO GROSS FINDINGS	11 100%	11 92%	12 100%	12 100%	4 36%	12 100%	11 100%
Pituitary							
No. of Observations	11	12	12	12	11	12	11
SMALL	0	0	0	1 8%	0	0	0
NO GROSS FINDINGS	11 100%	12 100%	12 100%	11 92%	11 100%	12 100%	11 100%
Thyroid							
No. of Observations	11	12	12	12	11	12	11
ENLARGED	0	0	0	12 100%	0	0	0
GELATINOUS	0	0	0	0	0	1 8%	0
NO GROSS FINDINGS	11 100%	12 100%	12 100%	0	11 100%	11 92%	11 100%

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

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
Brain							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Spinal Cords							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Preputial Gland							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Esophagus							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Eye							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Harderian Gland							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Duodenum							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%

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

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
Jejunum							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Ileum							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Cecum							
No. of Observations	11	12	12	12	11	12	11
LUMEN GAS	0	0	1 8%	0	0	0	0
NO GROSS FINDINGS	11 100%	12 100%	11 92%	12 100%	11 100%	12 100%	11 100%
Colon							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Rectum							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Lacrimal Gland							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Larynx							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%

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

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
Heart							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Mandibular Lymph Node							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Mammary Gland							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Mesentery							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Nose							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Muscle							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Salivary Glands							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%

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

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
Pancreas							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Peripheral Nerve							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Pharynx							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Pituitary Gland							
No. of Observations	11	12	12	12	11	12	11
NO GROSS FINDINGS	11 100%	12 100%	12 100%	12 100%	11 100%	12 100%	11 100%
Other							
No. of Observations	11	12	12	12	11	12	11
INTESTINES-LUMEN GAS	0	0	1 8%	0	0	0	0
STOMACH-LUMEN GAS	0	0	1 8%	0	0	0	0
NO GROSS FINDINGS	11 100%	12 100%	11 92%	12 100%	11 100%	12 100%	11 100%

KEY: GROUP:
1 = 2.5 ml/kg/day Corn Oil
2 = 50 mg/kg/day Flutamide
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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 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)	258.0 ± 7.18 (6)	240.6 ±15.96 (6)	*229.8 ± 7.57 (6)	**119.4 ± 3.38 (6)	*232.2 ± 5.69 (6)	**205.3 ± 8.84 (6)	240.7 ± 6.16 (6)
ADRENALS(g)	0.047 ± 0.002 (6)	0.054 ± 0.004 (6)	0.051 ± 0.001 (6)	0.031 ± 0.003 (6)	*0.211 ± 0.121 (6)	0.041 ± 0.001 (6)	0.043 ± 0.006 (6)
EPIDIDYMIDES(g)	0.489 ± 0.013 (6)	**0.337 ± 0.026 (6)	*0.412 ± 0.022 (6)	**0.267 ± 0.029 (6)	0.447 ± 0.023 (6)	**0.387 ± 0.019 (6)	0.474 ± 0.021 (6)
KIDNEYS(g)	2.056 ± 0.066 (6)	*1.845 ± 0.099 (6)	2.194 ± 0.069 (6)	**0.886 ± 0.023 (6)	1.868 ± 0.066 (6)	**1.508 ± 0.063 (6)	2.049 ± 0.092 (6)
LEVATOR ANI AND BULBOCAVERNOSUS MUSCLES (g)	0.578 ± 0.021 (6)	**0.269 ± 0.017 (6)	0.681 ± 0.034 (6)	**0.124 ± 0.024 (6)	0.413 ± 0.030 (6)	**0.359 ± 0.058 (6)	0.460 ± 0.043 (6)
LIVER(g)	10.708 ± 0.532 (6)	11.039 ± 0.654 (6)	9.826 ± 0.568 (6)	**4.959 ± 0.159 (6)	10.520 ± 0.468 (6)	*8.906 ± 0.522 (6)	11.200 ± 0.561 (6)
PITUITARY(g)	0.009 ± 0.000 (6)	0.007 ± 0.001 (6)	*0.007 ± 0.001 (6)	**0.006 ± 0.001 (6)	0.007 ± 0.000 (6)	**0.006 ± 0.001 (6)	0.010 ± 0.001 (6)
SEMINAL VESICLES(g)	0.406 ± 0.041 (6)	**0.066 ± 0.014 (6)	**0.742 ± 0.104 (6)	**0.049 ± 0.016 (6)	*0.250 ± 0.025 (6)	**0.236 ± 0.045 (6)	0.371 ± 0.028 (6)
TESTES(g)	3.095 ± 0.076 (6)	3.336 ± 0.247 (6)	**0.940 ± 0.060 (6)	**1.915 ± 0.255 (6)	2.958 ± 0.093 (6)	2.501 ± 0.083 (6)	2.180 ± 0.312 (6)
VENTRAL PROSTATE(g)	0.219 ± 0.013 (6)	**0.040 ± 0.005 (6)	**0.395 ± 0.029 (6)	**0.045 ± 0.007 (6)	*0.137 ± 0.031 (6)	**0.124 ± 0.016 (6)	0.193 ± 0.036 (6)
				Long-Evans			
BODY(g)	275.5 ±10.37 (5)	**249.0 ± 8.98 (6)	**248.6 ± 6.14 (6)	**105.2 ± 2.76 (6)	256.2 ±10.10 (5)	**213.5 ± 7.90 (6)	**231.2 ±12.10 (5)
ADRENALS(g)	0.046 ± 0.005 (5)	0.050 ± 0.004 (6)	**0.033 ± 0.003 (6)	**0.024 ± 0.001 (6)	**0.114 ±0.022 (5)	*0.035 ± 0.003 (6)	0.044 ± 0.004 (5)
EPIDIDYMIDES(g)	0.458 ± 0.028 (5)	**0.228 ± 0.021 (6)	0.452 ± 0.020 (6)	**0.232 ± 0.007 (6)	**0.384 ± 0.023 (5)	**0.352 ± 0.021 (6)	**0.339 ± 0.011 (5)
KIDNEYS(g)	2.316 ± 0.153 (5)	**2.065 ± 0.082 (6)	2.281 ± 0.110 (6)	**0.830 ± 0.029 (6)	2.258 ± 0.118 (5)	**1.716 ± 0.027 (6)	**2.055 ± 0.121 (5)
LEVATOR ANI AND BULBOCAVERNOSUS MUSCLES(g)	0.475 ± 0.027 (5)	**0.278 ± 0.032 (6)	**0.711 ± 0.056 (6)	**0.180 ± 0.067 (6)	0.408 ± 0.052 (5)	*0.364 ± 0.049 (6)	**0.278 ± 0.025 (5)
LIVER(g)	11.859 ± 0.732 (5)	12.431 ± 0.390 (6)	**9.770 ± 0.564 (6)	**4.354 ± 0.278 (6)	12.160 ± 0.676 (5)	**9.447 ± 0.476 (6)	10.561 ± 0.702 (5)
PITUITARY(g)	0.008 ± 0.002 (5)	0.008 ± 0.001 (6)	0.006 ± 0.001 (6)	0.005 ± 0.001 (6)	0.006 ± 0.001 (5)	0.007 ± 0.002 (6)	0.008 ± 0.002 (5)
SEMINAL VESICLES(g)	0.320 ± 0.051 (5)	**0.068 ± 0.009 (6)	**0.742 ± 0.096 (6)	**0.077 ± 0.020 (6)	*0.193 ± 0.035 (5)	0.262 ± 0.049 (6)	**0.142 ± 0.017 (5)
TESTES(g)	2.605 ± 0.074 (5)	*2.930 ± 0.142 (6)	**0.638 ± 0.039 (6)	**1.723 ± 0.074 (6)	2.564 ± 0.105 (5)	**2.167 ± 0.098 (6)	**0.680 ± 0.031 (5)
VENTRAL PROSTATE(g)	0.179 ± 0.033 (5)	**0.039 ± 0.005 (6)	**0.365 ± 0.035 (6)	**0.039 ± 0.006 (6)	0.120 ± 0.010 (5)	0.132 ± 0.023 (6)	*0.101 ± 0.022 (5)

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
Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

GROUP:	1	2	3	4	5	6	7
				Sprague Dawley			
ADRENALS	0.018 ± 0.001 (6)	0.023 ± 0.003 (6)	0.023 ± 0.001 (6)	0.026 ± 0.003 (6)	0.096 ± 0.058 (6)	0.020 ± 0.001 (6)	0.018 ± 0.003 (6)
EPIDIDYMIDES	0.190 ± 0.007 (6)	**0.140 ± 0.005 (6)	0.181 ± 0.013 (6)	0.222 ± 0.022 (6)	0.193 ± 0.012 (6)	0.189 ± 0.005 (6)	0.197 ± 0.008 (6)
KIDNEYS	0.797 ± 0.016 (6)	0.770 ± 0.015 (6)	**0.955 ± 0.014 (6)	*0.743 ± 0.011 (6)	0.804 ± 0.013 (6)	0.737 ± 0.027 (6)	0.851 ± 0.027 (6)
LEVATOR ANI AND BULBOCAVERNOSUS MUSCLES	0.225 ± 0.010 (6)	0.112 ± 0.004 (6)	0.298 ± 0.017 (6)	**0.103 ± 0.020 (6)	0.177 ± 0.010 (6)	0.173 ± 0.023 (6)	0.190 ± 0.015 (6)
LIVER	4.140 ± 0.107 (6)	**4.609 ± 0.144 (6)	4.263 ± 0.139 (6)	4.156 ± 0.099 (6)	4.524 ± 0.134 (6)	4.325 ± 0.079 (6)	4.645 ± 0.147 (6)
PITUITARY	0.004 ± 0.000 (6)	0.003 ± 0.000 (6)	0.003 ± 0.000 (6)	**0.005 ± 0.000 (6)	0.003 ± 0.000 (6)	0.003 ± 0.000 (6)	0.004 ± 0.000 (6)
SEMINAL VESICLES	0.158 ± 0.017 (6)	**0.027 ± 0.006 (6)	**0.326 ± 0.050 (6)	**0.041 ± 0.014 (6)	0.108 ± 0.011 (6)	0.113 ± 0.017 (6)	0.154 ± 0.012 (6)
TESTES	1.205 ± 0.047 (6)	1.406 ± 0.114 (6)	**0.410 ± 0.026 (6)	1.588 ± 0.188 (6)	1.276 ± 0.043 (6)	1.222 ± 0.027 (6)	0.898 ± 0.125 (6)
VENTRAL PROSTATE	0.085 ± 0.005 (6)	**0.017 ± 0.003 (6)	**0.174 ± 0.016 (6)	**0.037 ± 0.006 (6)	0.059 ± 0.012 (6)	0.060 ± 0.006 (6)	0.079 ± 0.013 (6)
				Long-Evans			
ADRENALS	0.017 ± 0.002 (5)	0.020 ± 0.002 (6)	0.013 ± 0.001 (6)	*0.023 ± 0.001 (6)	**0.044 ± 0.007 (5)	0.017 ± 0.002 (6)	0.019 ± 0.001 (5)
EPIDIDYMIDES	0.167 ± 0.009 (5)	**0.091 ± 0.006 (6)	0.182 ± 0.008 (6)	**0.222 ± 0.011 (6)	0.150 ± 0.008 (5)	0.165 ± 0.006 (6)	0.148 ± 0.007 (5)
KIDNEYS	0.838 ± 0.036 (5)	0.832 ± 0.033 (6)	0.917 ± 0.034 (6)	0.788 ± 0.016 (6)	0.882 ± 0.035 (5)	0.808 ± 0.022 (6)	0.889 ± 0.024 (5)
LEVATOR ANI AND BULBOCAVERNOSUS MUSCLES	0.174 ± 0.014 (5)	0.111 ± 0.010 (6)	*0.285 ± 0.018 (6)	0.172 ± 0.065 (6)	0.159 ± 0.019 (5)	0.169 ± 0.020 (6)	0.120 ± 0.009 (5)
LIVER	4.299 ± 0.193 (5)	**5.015 ± 0.192 (6)	3.917 ± 0.145 (6)	4.119 ± 0.149 (6)	4.746 ± 0.192 (5)	4.422 ± 0.121 (6)	4.558 ± 0.119 (5)
PITUITARY	0.003 ± 0.001 (5)	0.003 ± 0.000 (6)	0.002 ± 0.000 (6)	**0.005 ± 0.001 (6)	0.002 ± 0.001 (5)	0.003 ± 0.001 (6)	0.003 ± 0.001 (5)
SEMINAL VESICLES	0.116 ± 0.017 (5)	**0.028 ± 0.004 (6)	**0.300 ± 0.040 (6)	*0.705 ± 0.021 (6)	0.075 ± 0.013 (5)	0.120 ± 0.020 (6)	*0.061 ± 0.007 (5)
TESTES	0.951 ± 0.046 (5)	**1.177 ± 0.040 (6)	**0.259 ± 0.019 (6)	**1.649 ± 0.101 (6)	1.002 ± 0.024 (5)	1.018 ± 0.042 (6)	**0.297 ± 0.020 (5)
VENTRAL PROSTATE	0.065 ± 0.011 (5)	**0.016 ± 0.002 (6)	**0.147 ± 0.013 (6)	*0.037 ± 0.006 (6)	0.047 ± 0.004 (5)	0.061 ± 0.010 (6)	0.044 ± 0.009 (5)

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
				Sprague Dawley			
T4, TOTAL (µg/dL)	4.80± 0.3 (6)	3.57± 0.57 (6)	3.63± 0.54 (6)	**0.01± 0.01 (6)	4.72± 0.42 (6)	4.35± 0.51 (6)	3.34± 0.47 (6)
TSH (ng/mL)	2.72± 0.8 (6)	2.07± 0.41 (6)	2.14± 0.42 (6)	**26.63± 1.70 (6)	2.84± 0.73 (6)	1.96± 0.43 (6)	2.37± 0.36 (6)
				Long-Evans			
T4, TOTAL (µg/dL)	6.65±0.3 (5)	5.59± 1.22 (6)	5.64± 0.41 (6)	**1.19± 0.75 (6)	6.16± 0.62 (5)	5.19± 0.54 (6)	**3.13± 0.93 (5)
TSH (ng/mL)	2.22±0.5 (5)	3.13± 1.37 (6)	1.79± 0.23 (6)	**23.32± 4.53 (6)	2.97± 0.56 (5)	1.64± 0.14 (6)	2.09± 0.32 (5)

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
R15230	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15231	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15232	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15233	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15234	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15235	Normal			PND 22
	Normal			PND 28
	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 — LONG-EVANS
PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15236	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15237	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15238	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15239	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Found Dead			PND 50
R15240	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15241	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Normal			PND 54
	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
R15242	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15243	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15244	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15245	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15246	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15247	Normal			PND 22
	Normal			PND 28
	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
R15248	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15249	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15250	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15251	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15252	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15253	Normal			PND 22
	Normal			PND 28
	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
R15254	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15255	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15256	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15257	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15258	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15259	Normal			PND 22
	Normal			PND 28
	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 LONG-EVANS
PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15260	Normal			
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15261	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15262	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15263	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15264	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15265	Normal			PND 22
	Normal			PND 28
	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
R15266	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15267	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15268	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15269	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15270	Normal			PND 22
	Normal	PND 28		
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15271	Normal			PND 22
	Normal			PND 28
	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 Female Rats

GROUP: 4 - 240 mg/kg/day Propylthiouracil LONG-EVANS
PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15272	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15273	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15274	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15275	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15276	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15277	Normal			PND 22
	Normal			PND 28
	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 SPRAGUE DAWLEY
PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15278	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15279	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15280	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15281	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15282	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15283	Normal			PND 22
	Normal			PND 28
	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
R15284	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15285	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15286	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15287	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15288	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Dyspnea			PND 50
	Moribund Kill			PND 50
R15289	Normal			PND 22
	Normal			PND 28
	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 SPRAGUE DAWLEY
PND 21-54

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15290	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15291	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15292	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15293	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15294	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15295	Normal			PND 22
	Normal			PND 28
	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
R15296	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15297	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15298	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15299	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15300	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15301	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

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

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

ANIMAL #	OBSERVATIONS	SEVERITY	LOCATION	TIME OCCURRED
R15302	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15303	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15304	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15305	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15306	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15307	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54

Appendix Continued

APPENDIX 1 (CONTINUED)
INDIVIDUAL 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
R15308	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Found Dead			PND 49
R15309	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15310	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 53
R15311	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15312	Normal			PND 22
	Normal			PND 28
	Normal			PND 36
	Normal			PND 43
	Normal			PND 50
	Terminal Kill			PND 54
R15313	Normal			PND 22
	Normal			PND 28
	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

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

ANIMAL #	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15230	51.7	54.5	62.1	65.6	72.2	78.7	85.5	91.5	98.8	106.4	115.0	122.9
R15231	48.7	51.3	58.3	62.8	68.4	73.1	80.6	85.1	92.1	98.2	107.1	114.7
R15232	47.8	51.8	57.3	61.8	67.8	71.5	77.0	84.1	91.0	98.0	105.5	113.2
R15233	49.9	53.5	60.4	66.5	71.9	75.6	83.1	88.7	94.1	100.8	109.0	116.0
R15234	51.5	55.4	61.0	64.1	71.7	76.3	83.0	86.9	92.7	97.4	108.6	113.3
R15235	45.7	49.2	54.7	58.0	65.5	69.4	75.9	83.5	87.9	94.8	103.4	110.4
R15236	44.0	48.4	52.0	57.3	64.7	70.6	75.5	83.8	90.3	95.8	106.3	113.5
R15237	43.1	46.7	52.3	56.5	65.4	69.5	74.5	81.0	87.7	93.4	101.9	107.4
R15238	43.9	47.5	53.6	58.7	68.5	73.5	79.7	87.1	95.3	102.4	112.6	120.4
R15239	49.2	53.3	58.8	65.1	71.3	77.9	80.8	88.1	93.6	103.8	109.4	117.0
R15240	47.5	51.5	56.1	62.9	70.4	75.7	80.0	88.6	96.1	105.9	112.9	122.9
R15241	47.8	51.9	56.5	63.6	70.0	74.0	81.6	89.4	96.8	105.5	113.9	121.8
MEAN	47.6	51.3	56.9	61.9	69.0	73.8	79.8	86.5	93.0	100.2	108.8	116.1
S.D.	2.89	2.78	3.35	3.44	2.70	3.13	3.41	3.02	3.45	4.56	4.19	5.02
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15230 - R15235 are Sprague Dawley
Animals R15236 - R15241 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

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
R15230	130.8	140.5	149.2	157.6	169.7	173.0	181.7	190.3	191.8	205.4	208.9	216.6
R15231	121.6	129.2	137.7	145.4	155.2	161.9	167.9	175.4	179.4	189.3	195.3	200.6
R15232	121.5	126.5	134.2	142.7	151.6	158.9	163.0	171.7	176.7	182.4	189.7	198.6
R15233	125.8	129.3	137.3	147.0	154.6	163.9	170.1	178.6	186.1	194.7	200.2	206.9
R15234	120.1	127.7	133.8	141.1	150.1	157.2	166.1	168.9	179.8	179.8	186.9	191.2
R15235	117.6	122.4	131.8	138.9	148.3	154.9	157.6	162.0	170.3	177.9	183.1	187.8
R15236	121.2	124.8	138.3	146.5	156.0	163.4	169.9	180.8	189.2	196.3	204.4	212.1
R15237	112.6	114.5	123.1	134.5	138.8	147.8	150.9	160.7	168.7	174.0	181.0	185.8
R15238	128.7	132.7	144.4	154.6	166.8	172.0	180.0	189.1	196.0	207.5	211.1	220.7
R15239	123.3	131.3	141.1	148.5	155.5	163.1	170.7	178.5	185.7	192.8	193.0	205.6
R15240	131.5	141.6	150.4	159.3	169.8	181.9	191.0	202.0	209.6	220.0	220.8	233.5
R15241	131.0	138.7	150.2	154.5	163.9	173.6	181.5	191.3	199.8	210.7	212.5	224.7
MEAN	123.8	129.9	139.3	147.6	156.7	164.3	170.9	179.1	186.1	194.2	198.9	207.0
S.D.	5.90	7.82	8.27	7.71	9.36	9.44	11.24	12.45	12.08	14.43	12.76	15.08
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15230 - R15235 are Sprague Dawley
Animals R15236 - R15241 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

ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
R15230	227.1	233.2	241.9	249.1	255.2	258.5	262.8	275.4	a
R15231	211.3	219.1	226.5	230.0	236.4	241.3	246.9	255.2	a
R15232	208.2	215.5	222.5	224.4	227.1	233.5	242.0	249.8	a
R15233	217.2	221.6	229.9	238.4	244.0	251.9	255.0	262.6	275.6
R15234	203.5	210.5	225.9	224.3	230.3	240.0	245.4	251.6	262.9
R15235	198.4	202.4	210.0	214.1	219.2	218.1	225.5	223.3	229.1
R15236	227.1	231.8	242.6	247.5	259.9	268.6	270.9	282.6	a
R15237	196.7	199.7	213.8	216.0	225.7	232.0	237.0	244.7	a
R15238	235.7	238.7	249.2	260.5	268.9	277.6	283.0	292.9	a
R15239	216.3	220.6	197.1	185.8	--	--	--	--	--
R15240	246.5	252.4	261.0	271.1	278.7	293.2	297.5	300.6	312.7
R15241	237.9	250.7	253.5	265.2	271.1	279.4	286.8	288.9	299.1
MEAN	218.8	224.7	231.2	235.5	247.0	254.0	259.3	266.1	275.9
S.D.	16.16	17.13	19.06	24.68	20.79	23.51	22.87	23.84	32.60
N	12	12	12	12	11	11	11	11	5

Appendix Continued
-- Data Unavailable
a Terminal Kill

Key: Animals R15230 - R15235 are Sprague Dawley
Animals R15236 - R15241 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

ANIMAL #	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15242	54.2	59.3	63.8	67.6	73.4	78.7	84.9	88.9	97.7	102.6	115.9	120.2
R15243	47.3	53.0	57.3	63.2	67.1	76.7	81.0	86.7	92.9	97.7	108.9	114.2
R15244	51.1	56.7	59.7	64.8	71.4	76.5	83.0	89.4	96.5	103.4	113.0	118.3
R15245	49.9	54.2	58.3	63.0	67.7	73.0	78.7	81.8	87.2	93.8	100.2	106.0
R15246	50.9	54.3	58.3	63.2	70.9	76.7	83.0	88.4	92.3	99.8	112.8	117.3
R15247	50.8	55.8	60.9	66.1	70.7	76.4	82.7	88.6	95.5	100.6	110.7	116.2
R15248	44.1	48.9	55.1	59.4	64.9	68.9	76.6	83.8	92.1	98.1	107.6	113.6
R15249	46.9	52.4	57.8	64.2	71.3	76.2	84.3	88.8	97.2	102.5	111.6	118.8
R15250	46.4	51.4	56.5	64.9	71.1	74.6	83.1	89.9	98.3	103.1	115.5	123.1
R15251	48.0	52.9	57.6	63.0	72.4	77.2	84.2	89.9	100.8	106.1	112.7	119.6
R15252	43.2	48.3	51.2	57.8	62.8	68.9	74.0	80.2	86.3	93.1	101.0	107.8
R15253	48.9	55.4	60.1	66.5	74.8	81.1	86.3	94.7	101.2	110.6	117.6	125.1
MEAN	48.5	53.6	58.1	63.6	69.9	75.4	81.8	87.6	94.8	101.0	110.6	116.7
S.D.	3.14	3.14	3.12	2.80	3.54	3.61	3.64	3.96	4.80	4.94	5.47	5.64
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15242 - R15247 are Sprague Dawley
Animals R15248 - R15253 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

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
R15242	131.1	134.8	140.1	149.0	157.4	160.2	167.5	175.9	180.1	191.2	194.5	198.9
R15243	120.5	123.5	129.4	139.6	148.1	150.8	155.5	162.0	166.3	175.1	180.3	188.2
R15244	128.5	133.1	140.6	149.4	156.5	164.2	170.1	174.5	183.1	194.7	197.3	202.9
R15245	117.7	118.3	124.5	131.6	137.6	145.5	145.5	154.4	156.7	165.4	170.3	176.1
R15246	126.5	130.9	139.4	143.9	155.3	159.9	163.0	173.3	181.3	186.8	191.3	198.5
R15247	125.5	130.0	138.3	143.3	149.4	156.8	161.0	168.0	168.3	181.8	187.4	194.1
R15248	122.1	125.9	134.7	139.7	149.1	151.8	158.9	164.8	173.1	181.8	183.2	190.4
R15249	124.4	130.8	137.8	145.7	154.3	160.5	162.6	173.2	176.1	185.6	191.2	194.8
R15250	131.2	135.4	144.2	156.5	169.8	176.5	180.7	188.7	200.4	210.9	215.2	224.5
R15251	128.9	133.0	141.9	147.6	152.0	158.4	162.8	175.9	178.7	190.6	200.0	204.4
R15252	114.4	121.0	126.1	131.6	137.0	145.1	150.8	160.3	161.7	169.0	176.5	182.7
R15253	131.7	137.7	150.8	150.6	162.0	171.3	176.1	180.1	189.1	201.2	202.5	209.5
MEAN	125.2	129.5	137.3	144.0	152.4	158.4	162.9	170.9	176.2	186.2	190.8	197.1
S.D.	5.60	6.07	7.59	7.48	9.26	9.46	9.94	9.46	12.09	12.94	12.35	12.73
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15242 - R15247 are Sprague Dawley
Animals R15248 - R15253 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

ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
R15242	212.1	214.1	221.1	228.7	229.6	234.7	218.4	225.8	a
R15243	197.1	197.1	205.4	212.0	215.3	218.8	225.7	233.9	a
R15244	216.8	219.2	225.5	230.6	234.1	239.4	243.5	243.4	a
R15245	183.3	183.8	192.7	193.7	200.5	204.4	196.3	190.9	194.6
R15246	211.7	214.6	220.9	227.4	230.6	238.8	244.6	251.3	258.4
R15247	201.0	203.8	213.0	210.7	217.2	223.0	224.2	222.0	233.3
R15248	202.9	202.3	210.6	217.1	220.0	227.8	234.2	240.6	a
R15249	204.6	203.2	206.9	214.3	220.3	224.7	227.3	239.2	a
R15250	239.3	242.8	251.7	259.0	266.1	270.3	279.7	283.5	a
R15251	218.5	224.5	230.8	243.6	252.5	254.0	231.1	222.9	224.2
R15252	191.3	193.2	207.7	210.3	217.1	222.2	223.4	232.7	238.8
R15253	217.7	225.2	228.5	234.7	245.6	255.5	257.0	258.3	267.5
MEAN	208.0	210.3	217.9	223.5	229.1	234.5	233.8	237.0	236.1
S.D.	14.73	16.29	15.35	17.49	18.27	18.40	20.92	22.53	25.93
N	12	12	12	12	12	12	12	12	6

Appendix Continued
a Terminal Kill

Key: Animals R15242 - R15247 are Sprague Dawley
Animals R15248 - R15253 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

ANIMAL #	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15254	49.5	55.0	59.6	67.0	72.4	78.4	85.1	91.6	97.0	102.2	110.9	117.9
R15255	46.7	51.4	55.4	62.3	66.7	72.9	80.4	86.2	92.5	99.8	106.6	113.9
R15256	52.6	56.6	61.7	69.1	74.0	81.6	88.9	95.0	101.4	107.4	112.8	119.4
R15257	51.1	54.9	60.1	65.7	70.8	77.6	84.8	90.9	96.9	104.3	113.5	120.8
R15258	53.3	56.1	62.5	69.7	74.0	82.4	88.8	97.0	103.6	109.2	119.1	123.2
R15259	48.9	52.8	57.2	63.2	69.6	76.1	81.7	90.2	95.5	103.4	111.4	115.8
R15260	49.5	53.8	60.6	67.9	75.2	80.5	88.7	96.4	104.7	110.7	120.4	128.0
R15261	46.2	50.4	54.7	60.4	68.1	74.1	80.8	89.1	94.3	100.7	108.3	113.1
R15262	43.5	47.3	53.3	58.9	64.6	69.5	76.2	82.7	90.4	96.4	102.8	108.6
R15263	44.9	48.8	53.6	59.5	67.3	71.5	81.1	86.1	91.2	99.1	108.1	115.6
R15264	43.2	46.6	53.9	61.2	68.1	73.4	81.9	90.7	96.5	102.6	114.2	121.4
R15265	48.0	53.4	60.0	66.8	74.0	79.1	87.2	91.6	100.4	106.8	112.6	119.1
MEAN	48.1	52.3	57.7	64.3	70.4	76.4	83.8	90.6	97.0	103.6	111.7	118.1
S.D.	3.33	3.37	3.40	3.85	3.49	4.17	4.08	4.27	4.68	4.32	4.98	5.13
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15254 - R15259 are Sprague Dawley
Animals R15260 - R15265 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

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
R15254	125.7	132.3	140.8	145.0	152.8	159.2	158.2	165.9	176.4	180.8	185.2	190.8
R15255	122.7	129.4	135.9	140.1	150.0	155.2	162.4	170.8	177.1	185.1	188.2	193.9
R15256	127.8	134.8	140.5	143.6	151.0	159.5	167.2	165.6	176.8	177.7	184.5	192.4
R15257	127.2	134.6	141.0	149.1	157.3	161.0	167.0	171.3	181.9	183.7	191.0	197.3
R15258	132.3	138.4	143.7	152.7	160.6	166.2	168.4	176.0	180.3	184.9	190.7	198.2
R15259	124.5	131.7	138.4	145.9	153.6	159.7	162.3	172.2	174.5	184.3	187.6	193.3
R15260	137.9	143.9	152.2	164.2	171.5	176.5	181.3	187.9	194.7	203.8	208.0	213.4
R15261	121.3	126.9	134.3	141.1	149.6	153.2	158.8	164.5	172.1	177.6	183.0	186.6
R15262	118.4	122.8	129.8	140.2	145.8	156.8	158.2	166.8	168.5	180.8	183.8	192.4
R15263	122.0	127.0	136.4	144.5	151.9	158.1	160.1	170.1	172.8	180.8	188.6	193.8
R15264	126.1	133.8	141.2	152.7	158.2	168.1	170.4	177.2	182.5	193.8	198.9	206.7
R15265	126.8	134.7	141.8	149.2	158.4	164.8	165.8	175.0	179.3	190.3	197.3	202.2
MEAN	126.1	132.5	139.7	147.4	155.1	161.5	165.0	171.9	178.1	185.3	190.6	196.8
S.D.	5.18	5.62	5.53	6.88	6.75	6.44	6.64	6.55	6.68	7.51	7.42	7.47
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15254 - R15259 are Sprague Dawley
Animals R15260 - R15265 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

ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
R15254	200.2	204.8	212.1	220.5	227.1	234.4	238.6	238.2	a
R15255	201.6	207.4	214.3	219.5	222.4	231.5	232.8	222.9	a
R15256	198.2	204.1	207.2	214.6	213.8	213.8	217.9	205.3	a
R15257	208.0	211.4	220.0	227.2	226.8	235.8	238.7	246.9	254.3
R15258	207.7	214.0	219.0	225.3	232.0	236.0	232.3	235.8	243.2
R15259	200.4	203.5	210.0	216.5	221.2	228.8	226.4	223.4	215.0
R15260	224.3	232.5	237.2	245.0	250.5	257.7	262.7	271.8	a
R15261	193.3	202.8	207.7	214.5	221.0	229.4	231.5	231.3	a
R15262	199.3	206.2	211.8	219.4	223.7	231.9	223.3	233.1	a
R15263	205.9	211.1	216.2	227.6	226.7	237.9	241.3	246.6	254.7
R15264	210.2	214.9	218.9	230.2	231.9	241.4	243.8	249.0	252.6
R15265	212.8	218.5	223.5	231.1	238.2	239.9	245.7	250.6	248.0
MEAN	205.2	210.9	216.5	224.3	227.9	234.9	236.3	237.9	244.6
S.D.	8.25	8.47	8.28	8.75	9.50	10.14	11.81	16.95	15.16
N	12	12	12	12	12	12	12	12	6

Appendix Continued
a Terminal Kill

Key: Animals R15254 - R15259 are Sprague Dawley
Animals R15260 - R15265 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

ANIMAL #	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15266	50.1	55.6	57.6	59.4	67.6	73.0	79.1	83.5	90.9	97.4	103.6	106.4
R15267	47.1	51.1	54.8	59.8	68.4	71.1	79.1	82.4	88.9	93.3	98.9	102.4
R15268	49.8	52.9	56.2	60.4	69.5	71.5	75.9	82.9	89.8	95.3	99.2	102.0
R15269	48.5	53.6	58.9	57.1	66.0	71.7	78.4	82.4	88.9	91.6	100.1	100.2
R15270	48.9	52.5	60.1	65.5	69.8	74.9	79.2	84.4	88.5	92.1	97.1	97.9
R15271	50.5	52.9	61.4	65.7	72.4	75.4	82.9	88.7	94.9	98.0	105.0	108.1
R15272	49.0	51.8	56.4	65.2	71.4	77.3	82.6	86.4	92.5	97.6	99.0	100.8
R15273	46.5	47.0	49.5	60.9	68.5	73.4	77.4	80.6	86.4	87.8	91.3	92.3
R15274	46.9	49.0	55.5	61.3	70.3	74.8	83.2	88.1	91.7	98.4	100.7	100.1
R15275	44.3	46.8	50.2	55.4	61.3	65.8	70.1	73.4	80.7	81.9	87.3	86.0
R15276	42.8	45.4	49.7	54.2	60.8	65.6	70.6	75.9	78.5	81.8	83.9	80.9
R15277	43.8	43.3	49.3	56.7	63.1	67.5	71.5	77.3	83.3	84.7	87.5	86.1
MEAN	47.4	50.2	55.0	60.1	67.4	71.8	77.5	82.2	87.9	91.7	96.1	96.9
S.D.	2.59	3.79	4.33	3.89	3.85	3.81	4.65	4.72	4.89	6.22	6.89	8.64
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15266 - R15271 are Sprague Dawley
Animals R15272 - R15277 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

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
R15266	107.3	111.9	114.3	117.0	119.1	124.6	121.3	119.0	125.0	122.3	122.0	124.0
R15267	106.4	111.5	108.4	116.8	119.3	119.9	115.6	117.6	120.1	120.2	118.2	120.4
R15268	107.5	112.7	117.9	120.4	124.7	123.0	124.8	125.4	125.7	129.2	123.8	124.4
R15269	104.5	106.4	108.1	111.6	112.8	114.4	115.0	111.9	116.8	115.4	117.8	121.1
R15270	100.9	104.5	105.6	105.7	104.9	108.7	107.3	108.4	105.5	107.5	107.6	109.0
R15271	112.4	110.8	110.5	118.1	118.3	120.4	115.8	117.5	119.4	122.5	121.0	125.4
R15272	104.7	108.2	107.6	108.0	109.8	110.4	109.7	110.0	108.4	110.6	107.5	109.1
R15273	94.6	94.4	93.1	91.7	96.1	96.4	98.6	98.3	98.0	101.5	102.6	100.7
R15274	101.4	102.6	107.9	108.3	108.8	110.1	108.5	110.5	112.5	112.9	113.3	114.5
R15275	90.2	88.7	90.1	90.2	95.0	94.5	94.8	97.4	96.7	97.0	98.5	97.1
R15276	87.5	85.2	87.2	89.7	92.7	94.2	92.8	96.2	95.2	97.1	95.4	98.3
R15277	91.8	89.2	91.2	97.9	100.0	97.6	97.4	96.8	99.1	100.2	101.9	101.5
MEAN	100.8	102.2	103.5	106.3	108.5	109.5	108.5	109.1	110.2	111.4	110.8	112.1
S.D.	7.93	10.11	10.28	11.35	10.78	11.42	10.59	9.95	11.26	10.89	9.84	10.88
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15266 - R15271 are Sprague Dawley
Animals R15272 - R15277 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

ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
R15266	129.3	125.9	130.7	131.3	125.4	127.0	128.3	128.7	a
R15267	124.3	122.5	123.3	123.2	121.9	120.2	121.8	121.6	a
R15268	127.2	125.3	125.7	124.8	126.8	125.1	124.8	127.2	a
R15269	120.9	118.9	121.2	122.0	119.3	118.9	121.0	115.7	113.8
R15270	111.2	108.5	106.8	110.2	107.5	107.1	108.7	105.4	106.8
R15271	126.6	123.7	123.0	127.1	125.2	126.4	119.8	123.8	118.5
R15272	110.5	110.8	112.4	113.3	111.6	109.5	111.0	109.2	a
R15273	102.6	102.5	102.4	104.4	106.1	103.0	102.1	103.0	a
R15274	116.0	113.1	114.6	116.6	116.7	114.0	117.4	117.1	a
R15275	100.0	98.2	99.4	100.3	100.9	100.4	100.7	96.6	98.9
R15276	99.6	98.5	99.1	100.1	101.9	101.4	100.0	100.5	101.5
R15277	102.9	102.3	100.5	103.0	101.0	101.1	100.9	101.9	101.7
MEAN	114.3	112.5	113.3	114.7	113.7	112.8	113.0	112.6	106.9
S.D.	11.28	10.59	11.42	11.06	10.06	10.41	10.39	11.21	7.78
N	12	12	12	12	12	12	12	12	6

Appendix Continued
a Terminal Kill

Key: Animals R15266 - R15271 are Sprague Dawley
Animals R15272 - R15277 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

ANIMAL #	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15278	49.9	53.7	58.0	65.0	68.1	71.3	79.7	83.6	89.4	94.9	104.0	109.4
R15279	45.3	49.7	53.0	59.0	62.2	65.7	72.6	77.5	82.0	87.8	93.5	100.4
R15280	51.8	56.1	61.6	68.9	71.0	76.0	81.1	86.3	92.1	98.9	106.7	109.9
R15281	45.4	47.6	51.7	57.3	60.3	69.5	73.0	80.6	84.3	91.7	100.2	107.9
R15282	51.6	53.2	58.7	64.2	67.4	70.9	78.2	82.4	87.3	95.7	105.0	107.9
R15283	51.6	57.0	60.3	65.2	68.3	72.6	79.8	84.1	87.2	94.3	101.4	105.2
R15284	46.5	50.6	54.7	62.9	67.7	73.2	82.8	87.6	92.4	101.6	106.4	114.0
R15285	43.6	47.2	51.2	59.1	64.1	67.9	75.3	77.3	83.4	91.3	96.5	104.1
R15286	42.0	45.9	47.6	52.4	58.6	63.3	69.7	73.8	79.8	87.5	95.0	103.2
R15287	50.0	55.1	60.0	67.2	74.6	80.3	87.4	93.5	101.5	107.4	118.0	125.0
R15288	44.9	50.9	54.5	59.1	68.2	70.8	78.3	83.0	93.4	101.0	107.0	111.6
R15289	47.0	49.5	56.4	60.6	68.5	72.1	78.4	84.5	92.4	99.3	107.5	113.5
MEAN	47.5	51.4	55.6	61.7	66.6	71.1	78.0	82.9	88.8	96.0	103.4	109.3
S.D.	3.40	3.64	4.27	4.68	4.53	4.46	4.84	5.22	6.04	5.95	6.72	6.44
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15278 - R15283 are Sprague Dawley
Animals R15284 - R15289 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

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
R15278	115.4	120.2	131.8	137.5	146.8	147.2	157.6	165.5	169.3	175.5	180.8	188.2
R15279	111.9	114.0	122.1	127.0	136.1	141.1	146.5	152.3	157.5	166.2	169.8	175.6
R15280	118.5	124.5	129.9	135.2	141.4	150.0	155.6	164.6	169.8	175.7	181.5	188.5
R15281	114.5	118.2	125.7	133.3	141.5	149.2	156.5	162.1	167.9	175.6	179.9	184.4
R15282	117.4	123.2	130.8	139.2	148.1	153.3	155.6	162.8	168.2	173.8	183.9	189.9
R15283	112.6	118.9	124.2	131.1	138.9	144.9	149.5	153.9	166.9	167.3	171.9	176.3
R15284	123.7	130.7	139.8	145.5	153.5	160.6	168.4	176.9	184.2	187.1	196.7	204.7
R15285	109.9	116.0	125.7	131.9	137.1	140.5	147.2	156.2	162.6	168.8	175.5	181.0
R15286	109.4	115.4	125.0	132.8	137.1	144.6	152.6	159.2	165.3	168.1	178.1	187.7
R15287	132.5	139.9	147.7	159.4	169.1	175.1	179.8	190.0	196.9	205.7	211.7	219.2
R15288	119.4	130.6	134.3	141.3	145.7	156.4	162.2	164.3	146.7	158.5	162.9	168.2
R15289	125.1	133.4	138.5	147.1	154.8	162.3	171.1	171.4	181.1	191.6	199.2	204.5
MEAN	117.5	123.8	131.3	138.4	145.8	152.1	158.6	164.9	169.7	176.2	182.7	189.0
S.D.	6.86	8.21	7.64	8.89	9.63	10.12	10.15	10.52	12.94	12.95	13.72	14.34
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15278 - R15283 are Sprague Dawley
Animals R15284 - R15289 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

ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
R15278	197.2	205.3	208.5	206.0	212.8	216.5	224.3	229.8	a
R15279	188.0	188.5	195.6	203.9	209.7	213.6	220.8	225.3	a
R15280	197.2	199.2	207.7	215.5	221.3	206.3	213.9	211.6	a
R15281	196.4	200.0	208.4	215.5	223.3	227.5	234.5	240.5	249.8
R15282	202.0	203.4	217.3	222.3	228.1	231.6	235.6	240.4	245.7
R15283	186.8	188.5	197.6	202.6	204.3	210.1	221.3	233.1	230.9
R15284	202.3	191.5	193.1	206.9	217.6	229.5	235.1	238.0	a
R15285	193.4	199.0	203.3	210.8	221.9	227.9	235.9	241.5	a
R15286	192.1	202.3	207.8	212.5	222.3	228.7	238.1	241.8	a
R15287	233.3	238.3	253.0	254.8	265.0	271.6	278.0	278.9	289.0
R15288	180.7	185.5	190.2	169.9	157.6	--	--	--	--
R15289	216.5	218.9	229.2	234.3	241.1	251.9	254.6	255.7	270.7
MEAN	198.8	201.7	209.3	212.9	218.8	228.7	235.6	239.7	257.2
S.D.	14.14	14.72	17.49	20.09	24.94	19.01	17.86	17.15	22.76
N	12	12	12	12	12	11	11	11	5

Appendix Continued
-- Data Unavailable
a Terminal Kill

Key: Animals R15278 - R15283 are Sprague Dawley
Animals R15284 - R15289 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

ANIMAL #	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15290	53.8	56.8	48.5	55.3	64.3	67.1	72.5	75.9	81.2	89.7	97.3	102.9
R15291	50.0	53.3	45.9	50.6	59.2	57.9	62.4	68.5	71.8	79.9	85.6	92.8
R15292	47.3	50.1	43.0	47.2	54.7	58.9	63.6	63.7	68.3	76.0	83.5	89.6
R15293	52.7	56.7	49.9	56.3	62.0	66.7	72.1	72.9	79.5	88.8	95.7	101.4
R15294	49.9	52.7	45.9	51.4	59.1	61.6	66.8	71.2	75.1	76.2	83.0	90.4
R15295	52.4	55.1	48.3	54.1	59.8	64.5	69.4	73.4	76.2	86.3	89.8	92.9
R15296	45.7	47.9	40.7	44.6	44.9	44.9	55.6	56.1	62.7	67.8	71.3	75.2
R15297	44.3	46.9	42.3	45.1	52.6	54.6	57.6	63.7	66.9	72.4	78.7	85.7
R15298	48.1	51.3	44.3	43.0	49.8	54.7	57.7	62.7	70.0	75.1	78.8	87.0
R15299	46.9	50.1	44.3	48.6	55.8	61.6	63.8	69.2	74.8	78.9	85.6	91.2
R15300	46.7	53.0	44.2	51.5	54.5	58.8	63.2	65.9	73.6	73.5	84.5	92.2
R15301	46.5	51.3	44.0	46.2	52.4	58.3	61.5	62.6	70.3	72.7	77.6	82.9
MEAN	48.7	52.1	45.1	49.5	55.8	59.1	63.9	67.2	72.5	78.1	84.3	90.4
S.D.	3.04	3.15	2.71	4.39	5.47	6.08	5.52	5.71	5.29	6.92	7.45	7.48
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15290 - R15295 are Sprague Dawley
Animals R15296 - R15301 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

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
R15290	110.1	113.4	121.3	130.3	137.7	144.1	145.7	155.1	164.9	169.8	176.1	180.6
R15291	103.8	107.0	112.2	122.9	128.5	134.3	139.2	147.1	158.0	161.4	167.0	173.7
R15292	99.1	100.3	108.2	115.1	121.3	129.7	135.7	142.0	152.8	155.8	164.5	172.9
R15293	108.3	113.5	123.1	128.0	139.1	144.5	151.0	160.0	170.0	175.2	180.1	190.4
R15294	95.5	101.4	114.2	121.8	130.4	136.6	145.9	149.8	160.0	168.7	176.6	179.9
R15295	96.0	102.1	104.4	111.6	117.3	120.6	121.9	126.1	131.4	140.4	150.6	151.9
R15296	83.8	91.0	98.7	104.6	110.1	114.6	119.5	125.3	131.8	140.9	145.4	153.7
R15297	89.0	97.7	105.7	109.2	117.2	122.8	129.6	133.0	140.7	147.6	154.2	161.3
R15298	91.2	99.2	107.1	117.5	123.0	127.6	135.1	139.2	150.0	158.1	161.9	170.2
R15299	99.7	106.9	113.0	120.6	127.1	131.5	138.5	145.3	154.8	161.7	165.5	174.4
R15300	101.3	110.8	114.6	124.9	130.0	136.4	139.9	145.6	159.2	166.6	169.3	177.3
R15301	90.7	99.5	106.3	112.9	116.0	125.8	130.6	136.2	144.8	152.2	159.5	164.1
MEAN	97.4	103.6	110.7	118.3	124.8	130.7	136.1	142.1	151.5	158.2	164.2	170.9
S.D.	7.91	6.85	7.06	7.84	8.90	9.09	9.49	10.70	12.30	11.27	10.66	11.35
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15290 - R15295 are Sprague Dawley
Animals R15296 - R15301 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

ANIMAL #	PND 46	PND 47	PND 48	PND 49	PND 50	PND 51	PND 52	PND 53	PND 54
R15290	192.3	196.9	204.0	208.1	211.4	217.7	223.4	226.9	a
R15291	182.6	189.4	192.5	198.0	200.7	207.7	207.1	212.2	a
R15292	177.3	181.8	191.9	195.4	175.5	167.6	175.7	181.3	a
R15293	201.1	197.6	205.3	211.0	213.9	197.9	196.4	200.4	201.2
R15294	189.9	195.0	200.0	207.6	215.3	215.7	219.3	228.7	230.0
R15295	165.4	163.5	164.3	170.2	173.2	172.9	177.1	181.6	180.3
R15296	164.4	168.4	172.0	172.9	186.7	193.4	193.9	198.4	a
R15297	168.7	176.6	178.3	186.6	191.8	191.1	172.2	181.6	a
R15298	176.5	187.9	196.2	199.2	204.8	211.2	217.6	224.9	a
R15299	182.4	191.3	201.2	203.8	207.2	212.1	217.8	221.1	226.5
R15300	181.5	194.2	199.7	201.7	208.9	213.0	217.9	225.6	230.9
R15301	174.6	180.6	188.8	192.2	198.2	208.4	213.8	218.7	218.5
MEAN	179.7	185.3	191.2	195.6	199.0	200.7	202.7	208.5	214.6
S.D.	11.04	11.24	13.16	13.19	14.35	16.61	18.97	18.92	20.08
N	12	12	12	12	12	12	12	12	6

Appendix Continued
a Terminal Kill

Key: Animals R15290 - R15295 are Sprague Dawley
Animals R15296 - R15301 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

ANIMAL #	PND 22	PND 23	PND 24	PND 25	PND 26	PND 27	PND 28	PND 29	PND 30	PND 31	PND 32	PND 33
R15302	52.0	56.9	60.8	66.8	70.8	74.1	81.2	88.8	93.5	102.2	109.6	115.8
R15303	47.4	52.4	58.4	63.3	68.1	72.0	79.7	86.3	90.5	96.2	103.3	110.8
R15304	53.3	58.8	63.2	69.5	73.4	77.3	83.7	93.4	97.8	103.9	112.0	120.4
R15305	53.4	60.1	63.2	68.8	71.0	76.1	84.6	91.0	96.4	105.6	110.0	120.9
R15306	51.7	57.0	62.8	65.1	70.8	73.8	81.1	89.8	94.6	100.9	105.4	111.6
R15307	51.5	56.8	62.9	68.0	69.3	73.2	83.8	89.4	95.5	99.2	107.3	114.9
R15308	49.6	54.6	60.7	65.6	73.0	76.7	86.0	89.3	96.4	101.3	108.4	115.4
R15309	46.8	50.4	57.3	61.9	68.7	74.1	80.7	85.2	91.8	98.9	104.3	111.5
R15310	45.6	51.1	57.1	63.0	71.2	75.3	83.6	84.9	92.6	98.1	103.0	109.5
R15311	45.8	49.3	52.8	58.8	64.3	70.8	76.2	83.2	90.0	96.6	103.7	109.8
R15312	46.9	51.8	57.4	63.5	69.3	74.5	78.7	83.4	88.8	94.4	105.0	111.9
R15313	43.2	45.7	51.1	56.5	60.8	66.1	70.8	75.3	82.5	86.0	93.7	99.9
MEAN	48.9	53.7	59.0	64.2	69.2	73.7	80.8	86.7	92.5	98.6	105.5	112.7
S.D.	3.41	4.31	4.06	3.93	3.57	3.02	4.20	4.77	4.24	5.13	4.73	5.54
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15302 - R15307 are Sprague Dawley
Animals R15308 - R15313 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 34	PND 35	PND 36	PND 37	PND 38	PND 39	PND 40	PND 41	PND 42	PND 43	PND 44	PND 45
R15302	126.7	134.0	142.7	149.5	159.4	162.8	169.3	180.8	184.2	191.3	199.1	207.5
R15303	120.7	123.7	133.6	140.2	145.4	157.0	154.0	162.0	169.4	175.9	181.5	186.2
R15304	128.7	135.4	142.4	150.3	157.9	164.2	166.1	174.2	185.6	188.9	202.0	205.9
R15305	129.3	134.3	142.2	144.8	155.5	161.7	161.5	172.2	175.5	185.9	191.0	193.8
R15306	117.7	124.8	132.1	141.0	148.0	157.7	157.6	167.7	174.6	182.8	191.9	193.6
R15307	124.2	127.9	136.2	142.7	152.2	157.4	161.5	168.3	178.5	181.4	186.4	194.9
R15308	124.0	131.4	140.1	150.6	154.1	162.4	166.0	178.1	183.5	192.1	197.1	203.4
R15309	121.4	129.4	137.1	142.6	149.6	156.8	161.9	167.1	177.2	186.3	190.7	196.2
R15310	115.3	123.8	130.3	133.0	139.7	148.4	153.6	162.4	165.6	173.6	179.3	182.9
R15311	117.7	122.9	131.8	139.8	144.1	151.4	158.1	166.0	173.2	173.1	179.3	184.7
R15312	117.1	124.8	128.8	136.3	145.8	149.8	158.1	162.5	171.6	177.6	188.4	189.8
R15313	106.9	111.7	121.3	125.8	134.3	139.9	148.5	157.4	161.6	164.3	171.4	175.8
MEAN	120.8	127.0	134.9	141.4	148.8	155.8	159.7	168.2	175.0	181.1	188.2	192.9
S.D.	6.38	6.61	6.51	7.31	7.49	7.20	5.95	6.98	7.39	8.42	9.07	9.64
N	12	12	12	12	12	12	12	12	12	12	12	12

Appendix Continued

Key: Animals R15302 - R15307 are Sprague Dawley
Animals R15308 - R15313 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
R15302	218.7	220.6	229.7	234.8	237.2	255.3	253.3	263.2	a
R15303	198.5	200.8	209.7	217.8	218.9	228.7	233.8	241.8	a
R15304	215.6	218.1	228.2	228.3	234.8	212.8	227.9	231.4	a
R15305	204.8	203.6	218.7	222.7	224.9	226.9	227.7	237.7	237.9
R15306	200.5	208.9	214.7	222.9	223.8	228.2	231.0	230.4	219.6
R15307	200.4	211.9	215.0	221.8	224.5	232.4	236.7	242.7	250.2
R15308	216.3	222.8	228.5	239.1	--	--	--	--	--
R15309	206.0	208.3	214.9	216.6	228.8	235.4	242.9	252.0	a
R15310	195.5	199.3	202.7	213.4	220.7	201.6	200.1	203.7	a
R15311	195.1	198.5	202.9	207.8	213.9	228.5	233.9	237.3	244.7
R15312	200.5	205.5	214.9	220.6	227.6	234.0	241.9	245.8	255.6
R15313	182.2	190.3	192.0	194.0	202.5	206.8	208.5	198.8	200.2
MEAN	202.8	207.4	214.3	220.0	223.4	226.4	230.7	235.0	234.7
S.D.	10.38	9.76	11.42	11.90	9.62	14.86	15.12	19.09	21.00
N	12	12	12	12	11	11	11	11	6

-- Data Unavailable
a Terminal Kill

Key: Animals R15302 - R15307 are Sprague Dawley
Animals R15308 - R15313 are Long-Evans
PND = Postnatal Day

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)
	GROUP: 1 - 2.5 ML/KG/DAY CORN OIL	
R15230	205.4	43
R15231	179.4	42
R15232	176.7	42
R15233	194.7	43
R15234	186.9	44
R15235	183.1	44
	GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE	
R15242	NS	NS
R15243	NS	NS
R15244	NS	NS
R15245	NS	NS
R15246	NS	NS
R15247	NS	NS
	GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE	
R15254	140.8	36
R15255	122.7	34
R15256	165.6	41
R15257	167.0	40
R15258	143.7	36
R15259	145.9	37
	GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL	
R15266	128.7	53
R15267	NS	NS
R15268	NS	NS
R15269	NS	NS
R15270	NS	NS
R15271	123.8	53
	GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE	
R15278	188.2	45
R15279	188.5	47
R15280	188.5	45
R15281	196.4	46
R15282	189.9	45
R15283	188.5	47
	GROUP: 6 - 30 MG/KG/DAY PIMOZIDE	
R15290	208.1	49
R15291	189.4	47
R15292	175.7	52
R15293	200.4	53
R15294	215.3	50
R15295	173.2	50
	GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE	
R15302	191.3	43
R15303	175.9	43
R15304	188.9	43
R15305	193.8	45
R15306	191.9	44
R15307	181.4	43

Appendix Continued

NS = NO 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)
	GROUP: 1 - 2.5 ML/KG/DAY CORN OIL	
R15236	231.8	47
R15237	244.7	53
R15238	268.9	50
R15239	220.6	47
R15240	312.7	54
R15241	271.1	50
	GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE	
R15248	NS	NS
R15249	NS	NS
R15250	NS	NS
R15251	NS	NS
R15252	NS	NS
R15253	NS	NS
	GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE	
R15260	128.0	33
R15261	113.1	33
R15262	108.6	33
R15263	122.0	34
R15264	133.8	35
R15265	119.1	33
	GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL	
R15272	NS	NS
R15273	NS	NS
R15274	NS	NS
R15275	NS	NS
R15276	NS	NS
R15277	NS	NS
	GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE	
R15284	217.6	50
R15285	203.3	48
R15286	NS	NS
R15287	253.0	48
R15288	MK	MK
R15289	229.2	48
	GROUP: 6 - 30 MG/KG/DAY PIMOZIDE	
R15296	186.7	50
R15297	178.3	48
R15298	204.8	50
R15299	182.4	46
R15300	225.6	53
R15301	208.4	51
	GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE	
R15308	228.5	48
R15309	252.0	54
R15310	220.7	50
R15311	NS	NS
R15312	245.8	53
R15313	NS	NS

NS = NO PREPUTIAL SEPARATION WAS SEEN
MK = ANIMAL WAS MORIBUND KILLED BEFORE PREPUTIAL SEPARATION WAS SEEN

APPENDIX 4

INDIVIDUAL DAILY PREPUTIAL SEPARATION DATA

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

ANIMAL ID	POSTNATAL DAY 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
GROUP: 1 - 2.5 ML/KG/DAY CORN OIL																																
R15230	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y										
R15231	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y										
R15232	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y	Y										
R15233	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y									
R15234	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	Y	Y	Y								
R15235	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	Y	Y	Y								
GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE																																
R15242	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	
R15243	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	
R15244	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	
R15245	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
R15246	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
R15247	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
GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE																																
R15254	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																
R15255	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																		
R15256	N	N	N	N	N	N	N	N	N	N	N	N	N	P	T	T	T	T	Y	Y	Y											
R15257	N	N	N	N	N	N	N	N	N	N	N	N	N	T	T	T	T	Y	*	Y	Y											
R15258	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																
R15259	N	N	N	N	N	N	N	N	N	N	N	N	P	T	Y	Y	Y															
GROUP: 4 - 240MG/KG/DAY PROPYLTHIOURACIL																																
R15266	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	Y	
R15267	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	
R15268	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	T	
R15269	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
R15270	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
R15271	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	Y	Y

Appendix Continued

Y = Yes, prepuce separated N = No, prepuce not separated

P = Prepuce partially separated T = Persistent thread of tissue between glans and prepuce

* = Animal was not observed for preputial separation on this day.

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

ANIMAL ID	POSTNATAL DAY 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
GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE																																
R15278	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							
R15279	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					
R15280	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							
R15281	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						
R15282	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							
R15283	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	P	Y	Y	Y					
GROUP: 6 - 30 MG/KG/DAY PIMOZIDE																																
R15290	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	Y	Y	Y			
R15291	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	P	P	Y	Y	Y					
R15292	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	P	Y	Y	
R15293	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	Y
R15294	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	P	T	T	T	Y	Y	Y		
R15295	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	P	T	Y	Y	Y		
GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE																																
R15302	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	T	Y	Y	Y									
R15303	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y									
R15304	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y									
R15305	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							
R15306	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y								
R15307	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y									

Appendix Continued

Y = Yes, prepuce separated
N = No, prepuce not separated
P = Prepuce partially 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	POSTNATAL DAY 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
GROUP: 1 - 2.5 ML/KG/DAY CORN OIL																																
R15236	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	T	T	Y	Y	Y						
R15237	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	P	P	T	T	T	T	T	T	T	T	Y	
R15238	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	Y	Y	Y		
R15239	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	T	T	Y	Y	Y					
R15240	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	P	T	T	T	T	T	T	T	T	T	Y
R15241	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	T	T	T	T	T	T	T	T	Y	Y	Y		
GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE																																
R15248	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	
R15249	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	
R15250	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	
R15251	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
R15252	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
R15253	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
GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE																																
R15260	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																			
R15261	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																			
R15262	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																			
R15263	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																		
R15264	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																	
R15265	N	N	N	N	N	N	N	N	N	N	Y	Y	Y																			
GROUP: 4 - 240MG/KG/DAY PROPYLTHIOURACIL																																
R15272	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	
R15273	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	
R15274	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	
R15275	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
R15276	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
R15277	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
N = No, prepuce not separated
P = Prepuce partially 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	POSTNATAL DAY 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
GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE																																
R15284	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		
R15285	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				
R15286	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	
R15287	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				
R15288	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				
R15289	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				
GROUP: 6 - 30 MG/KG/DAY PIMOZIDE																																
R15296	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		
R15297	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	Y	Y	Y				
R15298	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	Y	Y	Y		
R15299	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						
R15300	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	Y	Y
R15301	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	Y	Y	Y	
GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE																																
R15308	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	Y						
R15309	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	
R15310	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		
R15311	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	Y	T	T	T	T	T	T
R15312	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	Y	Y
R15313	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	T

Y = Yes, prepuce separated
N = No, prepuce not separated
P = Prepuce partially 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

ANIMAL ID	FATE	POSTNATAL DAY	LOCATION	OBSERVATION
R15230	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15231	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15232	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15233	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15234	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15235	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15236	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15237	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15238	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15239	Found Dead	50	Large Intestine (lower)	DARK BROWN, BLACK
R15240	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15241	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS

Appendix Continued

Key: Animals R15230 - R15235 are Sprague Dawley
Animals R15236 - R15341 are Long-Evans

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

GROUP: 2 - 50 mg/kg/day Flutamide

ANIMAL ID	FATE	POSTNATAL DAY	LOCATION	OBSERVATION
R15242	Terminal Kill	53	Testes (Paired)	UNEQUALLY SIZED, RIGHT, SMALL; SOFT, Right
			Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
R15243	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
R15244	Terminal Kill	53	Epididymides (Paired)	SMALL, Bilateral
			Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
R15245	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
R15246	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
R15247	Terminal Kill	54	Epididymides (Paired)	SMALL, Bilateral
			Ventral Prostate	SMALL
R15248	Terminal Kill	53	Ventral Prostate	SMALL
R15249	Terminal Kill	53	Kidneys (Paired)	DILATED PELVIS, LEFT;
			Adrenals	DARK AREA, LEFT, ONE BLACK
R15250	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15251	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
R15252	Terminal Kill	54	Epididymides (Paired)	SMALL, Bilateral
R15253	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL

Appendix Continued

Key: Animals R15242 - R15247 are Sprague Dawley
Animals R15248 - R15353 are Long-Evans

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

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

ANIMAL ID	FATE	POSTNATAL DAY	LOCATION	OBSERVATION
R15254	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15255	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
R15256	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
R15257	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
R15258	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15259	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
			Cecum	LUMEN GAS, MODERATE AMOUNT
			Other	STOMACH-LUMEN GAS, MODERATE AMOUNT; INTESTINES-LUMEN GAS, MODERATE AMOUNT
R15260	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
R15261	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
R15262	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
			Seminal Vesicle	ENLARGED, BILATERAL, MODERATELY
R15263	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
R15264	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
R15265	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral

Appendix Continued

Key: Animals R15254 - R15259 are Sprague Dawley
Animals R15260 - R15365 are Long-Evans

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

GROUP: 4 - 240 mg/kg/day Propylthiouracil

ANIMAL ID	FATE	POSTNATAL DAY	LOCATION	OBSERVATION
R15266	Terminal Kill	53	Thyroid	ENLARGED, Moderate
R15267	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
			Levator Ani/ Bulbocavernosus Muscle	SMALL
			Ventral Prostate	SMALL
			Thyroid	ENLARGED, BILATERAL, SEVERE
R15268	Terminal Kill	53	Thyroid	ENLARGED, SEVERE
R15269	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
			Pituitary	SMALL
			Thyroid	ENLARGED, BILATERAL, SEVERE
R15270	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
			Thyroid	ENLARGED, SEVERE
R15271	Terminal Kill	54	Thyroid	ENLARGED, BILATERAL, SEVERE
R15272	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
			Thyroid	ENLARGED, SEVERE
R15273	Terminal Kill	53	Thyroid	ENLARGED, SEVERE
R15274	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
			Thyroid	ENLARGED, SEVERE;
R15275	Terminal Kill	54	Thyroid	ENLARGED, SEVERE
R15276	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
			Thyroid	ENLARGED, BILATERAL, SEVERE
R15277	Terminal Kill	54	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
			Thyroid	ENLARGED, BILATERAL, SEVERE

Appendix Continued

Key: Animals R15266 - R15271 are Sprague Dawley
Animals R15272 - R15377 are Long-Evans

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	POSTNATAL DAY	LOCATION	OBSERVATION
R15278	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
			Ventral Prostate	SMALL
			Adrenals	ENLARGED, BILATERAL,4x4x3mm; PALE, BILATERAL, GREY
R15279	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15280	Terminal Kill	53	Adrenals	ENLARGED, BILATERAL,4x4x4mm; PALE, BILATERAL, GREY
R15281	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15282	Terminal Kill	54	Adrenals	ENLARGED, Moderate
R15283	Terminal Kill	54	Adrenals	ENLARGED, BILATERAL, MODERATELY
R15284	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15285	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15286	Terminal Kill	53	Seminal Vesicle	SMALL, Bilateral
			Adrenals	ENLARGED,BILATERAL,3x3x3mm; PALE, GREY
R15287	Terminal Kill	54	Adrenals	ENLARGED,BILATERAL,6x5x4mm; PALE, BILATERAL, GREY
R15288	Moribund Kill	50	Seminal Vesicle	SMALL, BILATERAL
			Adrenals	ENLARGED,BILATERAL,5x5x5mm;
R15289	Terminal Kill	54	Adrenals	ENLARGED,BILATERAL,4X4X3MM

Appendix Continued

Key: Animals R15278 - R15283 are Sprague Dawley
Animals R15284 - R15389 are Long-Evans

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

GROUP: 6 - 30 mg/kg/day Pimozide

ANIMAL ID	FATE	POSTNATAL DAY	LOCATION	OBSERVATION
R15290	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15291	Terminal Kill	53	Thyroid	GELATINOUS
R15292	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15293	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15294	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15295	Terminal Kill	54	Kidneys (Paired)	DILATED, RIGHT PELVIS, MODERATELY
R15296	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15297	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15298	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15299	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15300	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15301	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS

Appendix Continued

Key: Animals R15290 - R15295 are Sprague Dawley
Animals R15296 - R15301 are Long-Evans

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

GROUP: 7 - 1000 mg/kg/day Dibutylphthalate

ANIMAL ID	FATE	POSTNATAL DAY	LOCATION	OBSERVATION
R15302	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15303	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15304	Terminal Kill	53		NO ORGANS WITH GROSS FINDINGS
R15305	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15306	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
R15307	Terminal Kill	54		NO ORGANS WITH GROSS FINDINGS
R15308	Found Dead	49	Lungs	DISCOLORED, RED, PINK
R15309	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
			Seminal Vesicle	SMALL, Bilateral
R15310	Terminal Kill	53	Testes (Paired)	SMALL, Bilateral
R15311	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
R15312	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
			Epididymides (Paired)	SMALL, Bilateral
			Seminal Vesicle	SMALL, Bilateral
R15313	Terminal Kill	54	Testes (Paired)	SMALL, Bilateral
			Seminal Vesicle	SMALL, Bilateral

Key: Animals R15302 - R15307 are Sprague Dawley
Animals R15308 - R15313 are Long-Evans

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				STRAIN: SPRAGUE DAWLEY		
ANIMAL ID:	R15230	R15231	R15232	R15233	R15234	R15235
BODY WEIGHT (g)	275.4	255.2	249.8	275.6	262.9	229.1
Liver (g)	12.369	10.987	9.674	11.884	10.382	8.953
% BODY WEIGHT	4.491	4.305	3.873	4.312	3.949	3.908
Kidneys (Paired) (g)	2.264	2.141	2.074	2.104	1.960	1.794
% BODY WEIGHT	0.822	0.839	0.830	0.763	0.746	0.783
Testes (Paired) (g)	3.236	2.750	3.226	3.161	3.017	3.182
% BODY WEIGHT	1.175	1.078	1.291	1.147	1.148	1.389
Epididymides (Paired) (g)	0.536	0.482	0.508	0.485	0.442	0.480
% BODY WEIGHT	0.195	0.189	0.203	0.176	0.168	0.210
Seminal Vesicle (g)	0.540	0.272	0.337	0.395	0.387	0.503
% BODY WEIGHT	0.196	0.107	0.135	0.143	0.147	0.220
Levator Ani plus Bulbocavernosus Muscles(g)	0.645	0.486	0.577	0.575	0.585	0.600
% BODY WEIGHT	0.234	0.190	0.231	0.209	0.223	0.262
Ventral Prostate (g)	0.208	0.253	0.245	0.209	0.231	0.168
% BODY WEIGHT	0.076	0.099	0.098	0.076	0.088	0.073
Adrenals (g)	0.0544	0.0499	0.0391	0.0502	0.0459	0.0438
% BODY WEIGHT	0.0198	0.0196	0.0157	0.0182	0.0175	0.0191
Pituitary (g)	0.0088	0.0097	0.0085	0.0103	0.0080	0.0081
% BODY WEIGHT	0.0032	0.0038	0.0034	0.0037	0.0030	0.0035

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: 1 - 2.5 mL/kg/day Corn Oil				STRAIN: LONG-EVANS	
ANIMAL ID:	R15236	R15237	R15238	R15240	R15241
BODY WEIGHT (g)	282.6	244.7	292.9	258.4	299.1
Liver (g)	11.820	9.286	13.821	12.335	12.032
% BODY WEIGHT	4.183	3.795	4.719	4.774	4.023
Kidneys (Paired) (g)	2.247	1.766	2.550	2.389	2.629
% BODY WEIGHT	0.795	0.722	0.871	0.925	0.879
Testes (Paired) (g)	2.768	2.490	2.385	2.753	2.627
% BODY WEIGHT	0.979	1.018	0.814	1.065	0.878
Epididymides (Paired) (g)	0.460	0.361	0.444	0.508	0.518
% BODY WEIGHT	0.163	0.148	0.152	0.197	0.173
Seminal Vesicle (g)	0.211	0.210	0.314	0.404	0.463
% BODY WEIGHT	0.075	0.086	0.107	0.156	0.155
Levator Ani plus Bulbocavernosus Muscles(g)	0.392	0.519	0.433	0.520	0.513
% BODY WEIGHT	0.139	0.212	0.148	0.201	0.172
Ventral Prostate (g)	0.146	0.184	0.136	0.124	0.306
% BODY WEIGHT	0.052	0.075	0.046	0.048	0.102
Adrenals (g)	0.0376	0.0417	0.0393	0.0456	0.0669
% BODY WEIGHT	0.0133	0.0170	0.0134	0.0176	0.0224
Pituitary(g)	0.0018[a]	0.0068	0.0061	0.0103	0.0079
% BODY WEIGHT	0.0006[a]	0.0028	0.0021	0.0040	0.0026

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: 2 - 50 mg/kg/day Flutamide				STRAIN: SPRAGUE-DAWLEY		
ANIMAL ID:	R15242	R15243	R15244	R15245	R15246	R15247
BODY WEIGHT (g)	225.8	233.9	243.4	194.6	312.7	233.3
Liver (g)	10.608	11.477	11.227	9.708	13.846	9.370
% BODY WEIGHT	4.698	4.907	4.613	4.989	4.428	4.016
Kidneys (Paired) (g)	1.791	1.866	1.891	1.454	2.214	1.854
% BODY WEIGHT	0.793	0.798	0.777	0.747	0.708	0.795
Testes (Paired) (g)	2.531	4.016	3.958	2.805	3.185	3.520
% BODY WEIGHT	1.121	1.717	1.626	1.441	1.019	1.509
Epididymides (Paired) (g)	0.338	0.337	0.344	0.284	0.448	0.271
% BODY WEIGHT	0.150	0.144	0.141	0.146	0.143	0.116
Seminal Vesicle (g)	0.044	0.050	0.044	0.038	0.094	0.124
% BODY WEIGHT	0.019	0.021	0.018	0.020	0.030	0.053
Levator Ani plus Bulbocavernosus Muscles(g)	0.290	0.262	0.263	0.198	0.325	0.278
% BODY WEIGHT	0.128	0.112	0.108	0.102	0.104	0.119
Ventral Prostate (g)	0.037	0.064	0.027	0.042	0.039	0.029
% BODY WEIGHT	0.016	0.027	0.011	0.022	0.012	0.012
Adrenals(g)	0.0539	0.0508	0.0556	0.0695	0.0525	0.0399
% BODY WEIGHT	0.0239	0.0217	0.0228	0.0357	0.0168	0.0171
Pituitary (g)	0.0084	0.0063	0.0085	0.0076	0.0092	0.0048
% BODY WEIGHT	0.0037	0.0027	0.0035	0.0039	0.0029	0.0021

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: 2 - 50 mg/kg/day Flutamide				STRAIN: LONG-EVANS		
ANIMAL ID:	R15248	R15249	R15250	R15251	R15252	R15253
BODY WEIGHT (g)	240.6	239.2	283.5	224.2	238.8	267.5
Liver (g)	12.100	12.292	14.091	12.921	11.677	11.503
% BODY WEIGHT	5.029	5.139	4.970	5.763	4.890	4.300
Kidneys (Paired) (g)	1.860	2.074	2.298	2.185	1.791	2.181
% BODY WEIGHT	0.773	0.867	0.811	0.975	0.750	0.815
Testes (Paired) (g)	3.184	2.939	3.349	2.579	2.461	3.065
% BODY WEIGHT	1.323	1.229	1.181	1.150	1.031	1.146
Epididymides (Paired) (g)	0.221	0.206	0.253	0.177	0.191	0.317
% BODY WEIGHT	0.092	0.086	0.089	0.079	0.080	0.119
Seminal Vesicle (g)	0.100	0.043	0.049	0.070	0.063	0.085
% BODY WEIGHT	0.042	0.018	0.017	0.031	0.026	0.032
Levator Ani plus Bulbocavernosus Muscles(g)	0.289	0.250	0.406	0.271	0.165	0.287
% BODY WEIGHT	0.120	0.105	0.143	0.121	0.069	0.107
Ventral Prostate (g)	0.049	0.017	0.049	0.043	0.030	0.046
% BODY WEIGHT	0.020	0.007	0.017	0.019	0.013	0.017
Adrenals(g)	0.0434	0.0421	0.0478	0.0624	0.0389	0.0627
% BODY WEIGHT	0.0180	0.0176	0.0169	0.0278	0.0163	0.0234
Pituitary (g)	0.0049	0.0078	0.0096	0.0090	0.0089	0.0091
% BODY WEIGHT	0.0020	0.0033	0.0034	0.0040	0.0037	0.0034

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:	R15254	R15255	R15256	R15257	R15258	R15259
BODY WEIGHT (g)	238.2	222.9	205.3	254.3	243.2	215.0
Liver (g)	11.393	9.195	8.681	11.357	10.233	8.097
% BODY WEIGHT	4.783	4.125	4.228	4.466	4.208	3.766
Kidneys (Paired) (g)	2.293	2.268	1.928	2.335	2.303	2.035
% BODY WEIGHT	0.963	1.017	0.939	0.918	0.947	0.947
Testes (Paired) (g)	0.739	0.822	0.915	1.018	1.143	1.005
% BODY WEIGHT	0.310	0.369	0.446	0.400	0.470	0.467
Epididymides (Paired) (g)	0.373	0.405	0.393	0.354	0.441	0.505
% BODY WEIGHT	0.157	0.182	0.191	0.139	0.181	0.235
Seminal Vesicle (g)	0.653	0.693	0.519	0.517	0.891	1.180
% BODY WEIGHT	0.274	0.311	0.253	0.203	0.366	0.549
Levator Ani plus Bulbocavernosus Muscles(g)	0.731	0.624	0.571	0.652	0.707	0.802
% BODY WEIGHT	0.307	0.280	0.278	0.256	0.291	0.373
Ventral Prostate (g)	0.357	0.467	0.345	0.342	0.357	0.502
% BODY WEIGHT	0.150	0.210	0.168	0.134	0.147	0.233
Adrenals (g)	0.0479	0.0549	0.0533	0.0506	0.0518	0.0485
% BODY WEIGHT	0.0201	0.0246	0.0260	0.0199	0.0213	0.0226
Pituitary (g)	0.0072	0.0082	0.0063	0.0087	0.0028	0.0060
% BODY WEIGHT	0.0030	0.0037	0.0031	0.0034	0.0012	0.0028

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		
ANIMAL ID:	R15260	R15261	R15262	R15263	R15264	R15265
BODY WEIGHT (g)	271.8	231.3	233.1	254.7	252.6	248.0
Liver (g)	11.589	8.882	7.895	10.396	10.795	9.061
% BODY WEIGHT	4.264	3.840	3.387	4.082	4.274	3.654
Kidneys (Paired) (g)	2.782	2.287	2.111	2.182	2.008	2.315
% BODY WEIGHT	1.024	0.989	0.906	0.857	0.795	0.933
Testes (Paired) (g)	0.516	0.617	0.730	0.547	0.750	0.670
% BODY WEIGHT	0.190	0.267	0.313	0.215	0.297	0.270
Epididymides (Paired) (g)	0.500	0.446	0.438	0.416	0.389	0.520
% BODY WEIGHT	0.184	0.193	0.188	0.163	0.154	0.210
Seminal Vesicle (g)	0.954	0.666	1.019	0.573	0.404	0.837
% BODY WEIGHT	0.351	0.288	0.437	0.225	0.160	0.338
Levator Ani plus Bulbocavernosus Muscle(g)	0.895	0.609	0.601	0.755	0.571	0.835
% BODY WEIGHT	0.329	0.263	0.258	0.296	0.226	0.337
Ventral Prostate (g)	0.491	0.426	0.336	0.298	0.380	0.258
% BODY WEIGHT	0.181	0.184	0.144	0.117	0.150	0.104
Adrenals (g)	0.0274	0.0439	0.0312	0.0340	0.0343	0.0269
% BODY WEIGHT	0.0101	0.0190	0.0134	0.0133	0.0136	0.0108
Pituitary (g)	0.0048	0.0054	0.0063	0.0080	0.0063	0.0030
% BODY WEIGHT	0.0018	0.0023	0.0027	0.0031	0.0025	0.0012

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		
ANIMAL ID:	R15266	R15267	R15268	R15269	R15270	R15271
BODY WEIGHT (g)	128.7	121.6	127.2	113.8	106.8	118.5
Liver (g)	5.408	5.399	5.049	4.765	4.649	4.484
% BODY WEIGHT	4.202	4.440	3.969	4.187	4.353	3.784
Kidneys (Paired) (g)	0.951	0.864	0.921	0.892	0.785	0.904
% BODY WEIGHT	0.739	0.711	0.724	0.784	0.735	0.763
Testes (Paired) (g)	2.178	1.402	2.596	1.572	1.151	2.588
% BODY WEIGHT	1.692	1.153	2.041	1.381	1.078	2.184
Epididymides (Paired) (g)	0.291	0.237	0.283	0.221	0.183	0.385
% BODY WEIGHT	0.226	0.195	0.222	0.194	0.171	0.325
Seminal Vesicle (g)	0.037	0.017	0.073	0.024	0.024	0.120
% BODY WEIGHT	0.029	0.014	0.057	0.021	0.022	0.101
Levator Ani plus Bulbocavernosus Muscle(g)	0.072	0.137	0.176	0.144	0.033	0.184
% BODY WEIGHT	0.056	0.113	0.138	0.127	0.031	0.155
Ventral Prostate (g)	0.053	0.025	0.061	0.047	0.020	0.061
% BODY WEIGHT	0.041	0.021	0.048	0.041	0.019	0.051
Adrenals (g)	0.0326	0.0299	0.0245	0.0420	0.0209	0.0339
% BODY WEIGHT	0.0253	0.0246	0.0193	0.0369	0.0196	0.0286
Pituitary (g)	0.0076	0.0064	0.0043	0.0070	0.0038	0.0061
% BODY WEIGHT	0.0059	0.0053	0.0034	0.0062	0.0036	0.0051

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		
ANIMAL ID:	R15272	R15273	R15274	R15275	R15276	R15277
BODY WEIGHT (g)	109.2	103.0	117.1	98.9	101.5	101.7
Liver (g)	4.467	4.204	5.664	3.800	3.993	3.995
% BODY WEIGHT	4.091	4.082	4.837	3.842	3.934	3.928
Kidneys (Paired) (g)	0.905	0.822	0.918	0.821	0.773	0.738
% BODY WEIGHT	0.829	0.798	0.784	0.830	0.762	0.726
Testes (Paired) (G	1.804	1.670	1.449	1.964	1.627	1.825
% BODY WEIGHT	1.652	1.621	1.237	1.986	1.603	1.794
Epididymides (Paired) (g)	0.210	0.240	0.217	0.243	0.223	0.257
% BODY WEIGHT	0.192	0.233	0.185	0.246	0.220	0.253
Seminal Vesicle (g)	0.032	0.099	0.048	0.167	0.062	0.052
% BODY WEIGHT	0.029	0.096	0.041	0.169	0.061	0.051
Levator Ani plus Bulbocavernosus Muscles(g)	0.146	0.510	0.117	0.133	0.077	0.094
% BODY WEIGHT	0.134	0.495	0.100	0.134	0.076	0.092
Ventral Prostate (g)	0.037	0.032	0.040	0.058	0.018	0.048
% BODY WEIGHT	0.034	0.031	0.034	0.059	0.018	0.047
Adrenals (g)	0.0292	0.0216	0.0210	0.0238	0.0234	0.0266
% BODY WEIGHT	0.0267	0.0210	0.0179	0.0241	0.0231	0.0262
Pituitary (g)	0.0049	0.0065	0.0032	0.0051	0.0047	0.0069
% BODY WEIGHT	0.0045	0.0063	0.0027	0.0052	0.0046	0.0068

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: SPRAGUE DAWLEY	
ANIMAL ID:	R15278	R15279	R15280	R15281	R15282	R15283
BODY WEIGHT (g)	229.8	225.3	211.6	249.8	245.7	230.9
Liver (g)	10.815	11.142	8.553	11.665	11.143	9.802
% BODY WEIGHT	4.706	4.945	4.042	4.670	4.535	4.245
Kidneys (Paired) (g)	1.861	1.821	1.687	2.065	2.054	1.719
% BODY WEIGHT	0.810	0.808	0.797	0.827	0.836	0.744
Testes (Paired) (g)	3.067	2.606	3.023	2.984	3.265	2.801
% BODY WEIGHT	1.335	1.157	1.429	1.195	1.329	1.213
Epididymides (Paired) (g)	0.430	0.373	0.514	0.458	0.508	0.398
% BODY WEIGHT	0.187	0.166	0.243	0.183	0.207	0.172
Seminal Vesicle (g)	0.137	0.315	0.242	0.263	0.278	0.264
% BODY WEIGHT	0.060	0.140	0.114	0.105	0.113	0.114
Levator Ani plus Bulbocavernosus Muscle(g)	0.319	0.411	0.339	0.474	0.508	0.429
% BODY WEIGHT	0.139	0.182	0.160	0.190	0.207	0.186
Ventral Prostate (g)	0.089	0.129	0.107	0.134	0.286	0.079
% BODY WEIGHT	0.039	0.057	0.051	0.054	0.116	0.034
Adrenals (g)	0.0940	0.0780	0.8160	0.0888	0.1211	0.0653
% BODY WEIGHT	0.0409	0.0346	0.3856	0.0355	0.0493	0.0283
Pituitary (g)	0.0084	0.0067	0.0069	0.0055	0.0083	0.0075
% BODY WEIGHT	0.0037	0.0030	0.0033	0.0022	0.0034	0.0032

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
ANIMAL ID:	R15284	R15285	R15286	R15287	R15289
BODY WEIGHT (g)	238.0	241.5	241.8	289.0	270.7
Liver (g)	12.502	11.070	10.180	13.201	13.845
% BODY WEIGHT	5.253	4.584	4.210	4.568	5.115
Kidneys (Paired) (g)	2.373	2.095	1.879	2.520	2.425
% BODY WEIGHT	0.997	0.867	0.777	0.872	0.896
Testes (Paired) (g)	2.349	2.634	2.292	2.841	2.703
% BODY WEIGHT	0.987	1.091	0.948	0.983	0.999
Epididymides (Paired) (g)	0.346	0.382	0.356	0.362	0.475
% BODY WEIGHT	0.145	0.158	0.147	0.125	0.175
Seminal Vesicle (g)	0.160	0.274	0.076	0.214	0.242
% BODY WEIGHT	0.067	0.113	0.031	0.074	0.089
Levator Ani plus Bulbocavernosus Muscles(g)	0.352	0.445	0.296	0.356	0.592
% BODY WEIGHT	0.148	0.184	0.122	0.123	0.219
Ventral Prostate (g)	0.123	0.110	0.104	0.105	0.156
% BODY WEIGHT	0.052	0.046	0.043	0.036	0.058
Adrenals (g)	0.0748	0.0769	0.0859	0.1662	0.1674
% BODY WEIGHT	0.0314	0.0318	0.0355	0.0575	0.0618
Pituitary (g)	0.0020	0.0069	0.0057	0.0108	0.0059
% BODY WEIGHT	0.0008	0.0029	0.0024	0.0037	0.0022

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				STRAIN: SPRAGUE DAWLEY		
ANIMAL ID:	R15290	R15291	R15292	R15293	R15294	R15295
BODY WEIGHT (g)	226.9	212.2	181.3	201.2	230.0	180.3
Liver (g)	10.010	9.228	7.813	8.333	10.654	7.398
% BODY WEIGHT	4.412	4.349	4.309	4.142	4.632	4.103
Kidneys (Paired) (g)	1.766	1.344	1.430	1.569	1.555	1.384
% BODY WEIGHT	0.778	0.633	0.789	0.780	0.676	0.768
Testes (Paired) (g)	2.604	2.538	2.323	2.656	2.700	2.182
% BODY WEIGHT	1.148	1.196	1.281	1.320	1.174	1.210
Epididymides (Paired) (g)	0.391	0.394	0.331	0.425	0.445	0.335
% BODY WEIGHT	0.172	0.186	0.183	0.211	0.193	0.186
Seminal Vesicle (g)	0.252	0.235	0.164	0.137	0.441	0.185
% BODY WEIGHT	0.111	0.111	0.090	0.068	0.192	0.103
Levator Ani plus Bulbocavernosus Muscles(g)	0.486	0.256	0.198	0.273	0.557	0.384
% BODY WEIGHT	0.214	0.121	0.109	0.136	0.242	0.213
Ventral Prostate (g)	0.139	0.167	0.089	0.079	0.166	0.104
% BODY WEIGHT	0.061	0.079	0.049	0.039	0.072	0.058
Adrenals (g)	0.0436	0.0413	0.0384	0.0442	0.0396	0.0406
% BODY WEIGHT	0.0192	0.0195	0.0212	0.0220	0.0172	0.0225
Pituitary (g)	0.0079	0.0073	0.0041	0.0023	0.0098	0.0033
% BODY WEIGHT	0.0035	0.0034	0.0023	0.0011	0.0043	0.0018

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				STRAIN: LONG-EVANS		
ANIMAL ID:	R15296	R15297	R15298	R15299	R15300	R15301
BODY WEIGHT (g)	198.4	181.6	224.9	226.5	230.9	218.5
Liver (g)	9.071	7.784	10.289	9.084	11.181	9.272
% BODY WEIGHT	4.572	4.286	4.575	4.011	4.842	4.243
Kidneys (Paired) (g)	1.688	1.616	1.731	1.699	1.813	1.750
% BODY WEIGHT	0.851	0.890	0.770	0.750	0.785	0.801
Testes (Paired) (g)	1.777	2.092	2.208	2.471	2.109	2.347
% BODY WEIGHT	0.896	1.152	0.982	1.091	0.913	1.074
Epididymides (Paired) (g)	0.303	0.290	0.351	0.402	0.349	0.417
% BODY WEIGHT	0.153	0.160	0.156	0.177	0.151	0.191
Seminal Vesicle (g)	0.142	0.111	0.259	0.423	0.277	0.361
% BODY WEIGHT	0.072	0.061	0.115	0.187	0.120	0.165
Levator Ani plus Bulbocavernosus Muscles(g)	0.235	0.259	0.487	0.507	0.278	0.415
%.BODY WEIGHT	0.118	0.143	0.217	0.224	0.120	0.190
Ventral Prostate (g)	0.100	0.053	0.183	0.201	0.097	0.158
% BODY WEIGHT	0.050	0.029	0.081	0.089	0.042	0.072
Adrenals (g)	0.0298	0.0479	0.0333	0.0362	0.0286	0.0359
% BODY WEIGHT	0.0150	0.0264	0.0148	0.0160	0.0124	0.0164
Pituitary (g)	0.0065	0.0019[a]	0.0092	0.0054	0.0057	0.0075
% BODY WEIGHT	0.0033	0.0010[a]	0.0041	0.0024	0.0025	0.0034

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: 7 - 1000 mg/kg/day Dibutylphthalate				STRAIN: SPRAGUE-DAWLEY		
ANIMAL ID:	R15302	R15303	R15304	R15305	R15306	R15307
BODY WEIGHT (g)	263.2	241.8	231.4	237.9	219.6	250.2
Liver (g)	13.707	11.179	9.552	11.114	10.536	11.110
% BODY WEIGHT	5.208	4.623	4.128	4.672	4.798	4.440
Kidneys (Paired) (g)	2.448	1.871	1.808	2.075	2.002	2.091
% BODY WEIGHT	0.930	0.774	0.781	0.872	0.912	0.836
Testes (Paired) (g)	2.469	2.538	2.771	1.991	0.714	2.599
% BODY WEIGHT	0.938	1.050	1.197	0.837	0.325	1.039
Epididymides (Paired) (g)	0.490	0.447	0.514	0.517	0.382	0.495
% BODY WEIGHT	0.186	0.185	0.222	0.217	0.174	0.198
Seminal Vesicle (g)	0.383	0.490	0.277	0.357	0.366	0.350
% BODY WEIGHT	0.146	0.203	0.120	0.150	0.167	0.140
Levator Ani plus Bulbocavernosus Muscle(g)	0.552	0.530	0.293	0.436	0.395	0.556
% BODY WEIGHT	0.210	0.219	0.127	0.183	0.180	0.222
Ventral Prostate (g)	0.363	0.171	0.122	0.199	0.122	0.180
% BODY WEIGHT	0.138	0.071	0.053	0.084	0.056	0.072
Adrenals (g)	0.0347	0.0438	0.0222	0.0567	0.0582	0.0427
% BODY WEIGHT	0.0132	0.0181	0.0096	0.0238	0.0265	0.0171
Pituitary (g)	0.0073	0.0112	0.0078	0.0129	0.0101	0.0093
% BODY WEIGHT	0.0028	0.0046	0.0034	0.0054	0.0046	0.0037

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				STRAIN: LONG-EVANS	
ANIMAL ID:	R15309	R15310	R15311	R15312	R15313
BODY WEIGHT (g)	252.0	203.7	244.7	255.6	200.2
Liver (g)	11.329	8.558	10.940	12.532	9.448
% BODY WEIGHT	4.496	4.201	4.471	4.903	4.719
Kidneys (Paired) (g)	2.356	1.808	1.955	2.331	1.825
% BODY WEIGHT	0.935	0.888	0.799	0.912	0.912
Testes (Paired) (g)	0.673	0.656	0.587	0.777	0.708
% BODY WEIGHT	0.267	0.322	0.240	0.304	0.354
Epididymides(Paired)(g)	0.325	0.307	0.351	0.370	0.344
% BODY WEIGHT	0.129	0.151	0.143	0.145	0.172
Seminal Vesicle (g)	0.104	0.137	0.200	0.150	0.117
% BODY WEIGHT	0.041	0.067	0.082	0.059	0.058
Levator Ani plus Bulbocavernosus Muscle(g)	0.328	0.300	0.290	0.289	0.184
% BODY WEIGHT	0.130	0.147	0.119	0.113	0.092
Ventral Prostate (g)	0.180	0.095	0.042	0.095	0.092
% BODY WEIGHT	0.071	0.047	0.017	0.037	0.046
Adrenals (g)	0.0569	0.0405	0.0410	0.0473	0.0334
% BODY WEIGHT	0.0226	0.0199	0.0168	0.0185	0.0167
Pituitary (g)	0.0081	0.0059	0.0099	0.0068	0.0017[a]
% BODY WEIGHT	0.0032	0.0029	0.0040	0.0027	0.0008[a]

a Weight out of range - excluded from summary data.

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
An Employee-Owned Company

PATHOLOGY REPORT
FOR

ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS

THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

PREPARED FOR
THERIMMUNE RESEARCH CORPORATION

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TABLE OF CONTENTS

I. Pathology Narrative

PATHOLOGY REPORT

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

TherImmune Research Corporation 1143-102

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 (SD) rats and forty-two male Long-Evans (LE) rats were randomly distributed into seven groups as depicted in Text Table 1.

Text Table 1. Group Designation and Dosage Levels

Group	Treatment	Dosage (per kg/day)	Number of males per strain of rat
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 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.

Necropsies were conducted on all moribund animals and on animals not surviving to termination. Moribund animals were weighed and killed by decapitation. 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

Early Deaths and Gross Lesions

There were 3 early deaths. A Group 7 LE rat (R15308) was found dead on post-natal day (PND) 18 and a Group 1 LE rat (R15239) was found dead on PND 19; a Group 5 LE rat (R15288) was sacrificed due to a moribund state on PND 19. The cause of death for these three animals could not be determined. Histopathological evaluation of gross lesions in tissues other than the thyroid, testes and epididymides was not required by the protocol. Text Table 2 shows the number of rats with specific gross lesions by group and strain of rat.

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	0	0	6	6	0	0	0	0	0	0
Thyroid/ gelatinous	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Testes/ small	0	0	1	0	4	6	0	0	0	0	0	0	1	5
Testes/ soft	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Epididymides/ small	0	0	2	1	0	0	0	0	0	0	0	0	0	1
Seminal Vesicle/ small	0	1	5	2	0	0	3	3	1	2*	0	0	0	3
Seminal Vesicle/ enlarged	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Ventral Prostate/ small	0	1	6	1	0	0	2	3	1	0	0	0	0	0
Large Intestine/ discolored	0	1*	0	0	0	0	0	0	0	0	0	0	0	0
Adrenals/ dark area	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Adrenals/ pale &/or enlarged	0	0	0	0	0	0	0	0	4	4*	0	0	0	0
Kidneys/ dilated	0	0	0	1	0	0	0	0	0	0	1	0	0	0
Gastrointestines/ gas	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Pituitary/ small	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Levator Ani/ small	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Lungs/ discolored	0	0	0	0	0	0	0	0	0	0	0	0	0	1*

* Indicates that at least one lesion was in an early death rat, 6SD = Six Sprague-Dawley rats, 6LE = Six Long-Evans rats

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 fewer 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 - All findings in all tissues were considered to be spontaneous changes of no significance to the animal.

Long-Evans - All findings in all tissues were considered to be spontaneous changes of no significance to the animal.

Flutamide (50 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 effects in the testes were hypertrophy/hyperplasia of the interstitial cells and dilation of the seminiferous tubule, both consistent findings as defined above. 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. Dilation of the seminiferous tubules occurred without any detectable decrease in spermatogenesis. This dilation may have been related to the atrophy of the epididymides. Other changes in the epididymides were considered to be spontaneous changes unrelated to the test article.

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. Consistent test article related changes in the testes were hypertrophy/hyperplasia of the interstitial cells and dilation of the seminiferous tubules. Atrophy of the epididymides (consistent finding) was also test article related. Dilation of the seminiferous tubules occurred without any detectable decrease in spermatogenesis. This dilation may have been related to atrophy of the epididymides.

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

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 receiving the test article. Consistent test article related changes in the testes were hypospermatogenesis (decreased sperm production) and interstitial cell atrophy. Consistent test article effects in the epididymides were hypospermia (decreased content of sperm secondary to the decreased production in the testes) and degenerative germ cells (due to the release of degenerating cells from the testes).

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. Consistent test article effects in the testes were hypospermatogenesis and interstitial cell atrophy. Consistent test article effects in the epididymides were hypospermia and degenerative germ cells.

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 – Consistent test article related findings in the thyroid were hypertrophy/ hyperplasia of the follicular cells and colloid depletion within follicles. Both changes were diffuse throughout the gland. Test article related findings in the testes were hypospermatogenesis (sporadic finding) and interstitial cell atrophy (consistent finding). Test article effects in the epididymides were hypospermia and degenerative germ cells, both sporadic findings. 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 – Consistent test article effects in the thyroid were hypertrophy/ hyperplasia of the follicular cells and colloid depletion within follicles. Both changes were diffuse throughout the gland. The only test article related effect in the testes was interstitial cell atrophy, a consistent finding. Test article related findings in the epididymides were hypospermia and degenerative germ cell, both sporadic findings. The epididymal changes were considered to be secondary to changes occurring in the testes.

The thyroid changes were considered to be a direct effect 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. The few changes noted in these tissues were considered to be sporadic in nature and of little or no significance to the animal.

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

Long-Evans – There were no test article related findings in the thyroid glands or testes. A test article effect in the epididymides was hypospermia (sporadic finding). The hypospermia was considered to be secondary to decreased sperm production in the testes (although an effect in the testes was not apparent).

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

Dibutylphthalate (1000 mg/kg/day)

Sprague-Dawley – There were no test article related findings in the thyroid glands; the presence of ultimobranchial cyst(s) in 4 of the 6 rats is considered incidental. Tubular degeneration in the testes was noted in 2 rats (sporadic finding), and hypospermia (2 of 6) and degenerative germ cells (3 of 6) in the epididymides were also sporadic findings in this strain.

Long-Evans – There were no test article related findings in the thyroid glands. Test article effects in the testes were seminiferous tubule degeneration and hypospermatogenesis, both consistent findings. 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 effects in the epididymides were hypospermia (consistent finding) and degenerative germ cells (sporadic 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 observed in both strains were consistent with this action. The difference in the consistency of the testicular and epididymal lesions 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 with either corn oil or one of six test articles for at least 31 days. Text Table 1 summarizes the group designations and dosage levels. Following at least 31 days of dosing, all surviving 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.

There were three early deaths, one each in Groups 1, 5 and 7. The cause of these could not be established; however, they are not thought to be due to receiving a test article. Gross lesions which are considered to be the result of receiving a test article were seen in Group 2 SD's (small seminal vesicles and small ventral prostates), Group 3 SD's and LE's (small testes), Group 4 SD's and LE's (enlarged thyroids, small seminal vesicles and small ventral prostates), Group 5 SD's and LE's (pale and/or enlarged adrenals), and Group 7 LE's (small testes and small seminal vesicles).

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

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:

John M. Pletcher, DVM, DACVP — 6/15/00 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: 1143-102

Reports Code Table	
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: 1143-102

Abbreviations List

# EX	Number Examined
1143102	1143-102
TK	Terminal Kill
FD	Found Dead
MK	Moribund Kill

II. Project Summary Tables

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

PROJECT SUMMARY

STUDY ID : 1143-102
FATE: TK Sprague-Dawley

STUDY NUMBER: 1143102

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
NUMBER OF ANIMALS:		6	6	6	6	6
		#	#	#	#	#
THYROID	# EX	6	6	6	6	6
ULTIMOBRANCHIAL CYST(S)		1	2	1	0	2
CAPSULE- GRANULATION TISSUE		0	1	0	0	0
CAPSULE- ACUTE INFLAMMATION		0	0	0	0	0
FOLLICULAR CELLS- HYPERTROPHY/HYPERPLASIA		0	0	0	6	0
COLLOID DEPLETION		0	1	1	6	0
TESTES	# EX	6	6	6	6	6
TUBULAR DEGENERATION		0	1	0	0	0
HYPOSPERMATOGENESIS		0	0	6	2	0
INTERSTITIAL CELLS- ATROPHY		0	0	6	6	0
INTERSTITIAL CELLS- HYPERTROPHY/HYPERPLASIA		0	6	0	0	0
TUBULES- DILATATION		0	4	0	0	0
EPIDIDYMIDES	# EX	6	6	6	6	6
GRANULOMA(S)		0	1	0	0	0
HYPOSPERMIA		0	0	6	2	0
DEGENERATIVE GERM CELLS		0	0	5	3	0
ATROPHY		0	5	0	0	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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06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

PROJECT SUMMARY

STUDY ID : 1143-102 STUDY NUMBER: 1143102
FATE: TK Sprague-Dawley SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		6 (1)	7 (2)
NUMBER OF ANIMALS:		6	6
		#	#
THYROID	# EX	5	6
ULTIMOBRANCHIAL CYST(S)		1	4
CAPSULE- GRANULATION TISSUE		0	0
CAPSULE- ACUTE INFLAMMATION		1	0
FOLLICULAR CELLS- HYPERTROPHY/HYPERPLASIA		0	0
COLLOID DEPLETION		0	0
TESTES	# EX	6	6
TUBULAR DEGENERATION		0	2
HYPOSPERMATOGENESIS		0	0
INTERSTITIAL CELLS- ATROPHY		1	0
INTERSTITIAL CELLS- HYPERTROPHY/HYPERPLASIA		0	0
TUBULES- DILATATION		1	1
EPIDIDYMIDES	# EX	6	6
GRANULOMA(S)		0	0
HYPOSPERMIA		0	2
DEGENERATIVE GERM CELLS		0	3
ATROPHY		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: 1143-102

PROJECT SUMMARY

STUDY ID : 1143-102 STUDY NUMBER: 1143102
FATE: TK Long-Evans
SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
NUMBER OF ANIMALS:		5	6	6	6	5
		#	#	#	#	#
THYROID	# EX	3	6	6	6	5
ULTIMOBRANCHIAL CYST(S)		1	1	0	0	0
CAPSULE- GRANULATION TISSUE		0	1	0	0	0
INFILTRATING LYMPHOCYTES		0	1	0	0	0
ACUTE INFLAMMATION		0	0	0	0	0
FOLLICULAR CELLS- HYPERTROPHY/HYPERPLASIA		0	0	0	6	1
COLLOID DEPLETION		0	1	0	6	1
TESTES	# EX	5	6	6	6	5
TUBULAR DEGENERATION		0	0	0	0	0
HYPOSPERMATOGENESIS		0	0	6	0	0
INTERSTITIAL CELLS- ATROPHY		0	0	6	6	0
INTERSTITIAL CELLS- HYPERTROPHY/HYPERPLASIA		0	6	0	0	0
TUBULES- DILATATION		0	5	0	0	0
EPIDIDYMIDES	# EX	5	6	6	6	5
SUBACUTE INFLAMMATION		1	0	0	0	0
GRANULOMA(S)		0	1	0	0	0
HYPOSPERMIA		0	0	6	3	0
LYMPHOCYTE INFILTRATION		0	0	0	0	1
DEGENERATIVE GERM CELLS		0	0	6	3	0
ATROPHY		0	6	0	0	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 06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

PROJECT SUMMARY

STUDY ID : 1143-102
FATE: TK Long-Evans

STUDY NUMBER: 1143102

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		6 (1)	7 (2)
NUMBER OF ANIMALS:		6	5
		#	#
THYROID	# EX	5	5
ULTIMOBRANCHIAL CYST(S)		0	0
CAPSULE- GRANULATION TISSUE		0	0
INFILTRATING LYMPHOCYTES		0	0
ACUTE INFLAMMATION		0	1
FOLLICULAR CELLS- HYPERTROPHY/HYPERPLASIA		0	0
COLLOID DEPLETION		0	0
TESTES	# EX	6	5
TUBULAR DEGENERATION		0	5
HYPOSPERMATOGENESIS		0	5
INTERSTITIAL CELLS- ATROPHY		0	0
INTERSTITIAL CELLS- HYPERTROPHY/HYPERPLASIA		0	0
TUBULES- DILATATION		0	0
EPIDIDYMIDES	# EX	6	5
SUBACUTE INFLAMMATION		0	0
GRANULOMA(S)		0	0
HYPOSPERMIA		3	5
LYMPHOCYTE INFILTRATION		0	0
DEGENERATIVE GERM CELLS		0	3
ATROPHY		0	0

(1) - Pimozide 30 mg/kg/day

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

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

PROJECT SUMMARY

STUDY ID : 1143-102 STUDY NUMBER: 1143102
FATE: FD Long-Evans,MK Long-Evans SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1 (1)	5 (2)	7 (3)
NUMBER OF ANIMALS:		1	1	1
		#	#	#
THYROID	# EX	0	1	0
TESTES	# EX	1	1	1
TUBULAR DEGENERATION		0	0	1
HYPOSPERMATOGENESIS		0	0	1
EPIDIDYMIDES	# EX	1	1	1
HYPOSPERMIA		0	0	1

(1) - Corn Oil 2.5 ml/kg/day
(2) - Ketoconazole 100 mg/kg/day
(3) - Dibutylphthalate (DBP) 1000 mg/kg/day

LABCAT HP4.33 06-APR-2000

III. Tabulated Animal Data

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Sprague-Dawley

STUDY NUMBER: 1143102
GROUP: 1: Corn Oil 2.5 ml/kg/day
SEX: MALE

ANIMAL ID:	R15230	R15231	R15232	R15233	R15234	R15235
THYROID	N	N	-	N	N	N
ULTIMOBRANCHIAL CYST(S)	-	-	2L	-	-	-
TESTES	N	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N	N

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LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Sprague-Dawley

STUDY NUMBER: 1143102
GROUP: 2: Flutamide 50 mg/kg/day
SEX: MALE

ANIMAL ID:	R15242	R15243	R15244	R15245	R15246	R15247
THYROID	-	-	N	N	-	N
ULTIMOBRANCHIAL CYST(S)	2I	-	-	-	1L	-
CAPSULE- GRANULATION TISSUE	2L	-	-	-	-	-
COLLOID DEPLETION	-	1I	-	-	-	-
TESTES	-	-	-	-	-	-
TUBULAR DEGENERATION	3L	-	-	-	-	-
INTERSTITIAL CELLS- HYPERTROPHY/HYPERPLASIA	2I	2I	2I	2I	2I	2I
TUBULES- DILATATION	-	2I	2I	2L	-	2I
EPIDIDYMIDES	-	-	-	-	-	-
GRANULOMA(S)	(2)L	-	-	-	-	-
ATROPHY	-	2I	2I	3I	2I	2I
Non-Protocol Tissues: SEMINAL VESICLE	*	*	*	*	*	-
Non-Protocol Tissues: VENTRAL PROSTATE	*	*	*	*	*	*

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Sprague-Dawley

STUDY NUMBER: 1143102
GROUP: 3: Methyl testosterone 80 mg/kg/day
SEX: MALE

ANIMAL ID:	R15254	R15255	R15256	R15257	R15258	R15259
THYROID	N	N	-	N	-	N
ULTIMOBRANCHIAL CYST(S)	-	-	2I	-	-	-
COLLOID DEPLETION	-	-	-	-	1I	-
TESTES	-	-	-	-	-	-
HYPOSPERMATOGENESIS	4I	4I	3I	3I	3I	4I
INTERSTITIAL CELLS- ATROPHY	4I	4I	4I	4I	4I	4I
EPIDIDYMIDES	-	-	-	-	-	-
HYPOSPERMIA	4I	4I	3I	3I	3I	3I
DEGENERATIVE GERM CELLS	2I	2I	2I	3I	3I	-
Non-Protocol Tissues: CECUM	-	-	-	-	-	*
Non-Protocol Tissues: STOMACH	-	-	-	-	-	*
Non-Protocol Tissues: INTESTINES	-	-	-	-	-	*

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102 STUDY NUMBER: 1143102
FATE: TK Sprague-Dawley GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day
SEX: MALE

ANIMAL ID:	R15266	R15267	R15268	R15269	R15270	R15271
THYROID	-	-	-	-	-	-
FOLLICULAR CELLS- HYPERTROPHY/HYPERPLASIA	3I	4I	3I	3I	3I	3I
COLLOID DEPLETION	3I	3I	3I	3I	3I	3I
TESTES	-	-	-	-	-	-
HYPOSPERMATOGENESIS	-	3I	-	-	3I	-
INTERSTITIAL CELLS- ATROPHY	2I	3I	1I	3I	3I	2I
EPIDIDYMIDES	N	-	N	-	-	N
HYPOSPERMIA	-	2I	-	-	3I	-
DEGENERATIVE GERM CELLS	-	3I	-	2I	3I	-
Non-Protocol Tissues: SEMINAL VESICLE	-	*	-	*	*	-
Non-Protocol Tissues: VENTRAL PROSTATE	-	*	-	-	*	-
Non-Protocol Tissues: PITUITARY	-	-	-	*	-	-
Non-Protocol Tissues: LEVATOR ANI/BULBOCAVERNO	-	*	-	-	-	-

See Reports Code Table for Symbol Definitions

LABCAT HP4.33 06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Sprague-Dawley

STUDY NUMBER: 1143102
GROUP: 5: Ketoconazole 100 mg/kg/day
SEX: MALE

ANIMAL ID:	R15278	R15279	R15280	R15281	R15282	R15283
THYROID	N	N	-	N	N	-
ULTIMOBRANCHIAL CYST(S)	-	-	1L	-	-	1L
TESTES	N	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N	N
Non-Protocol Tissues: ADRENALS	*	-	*	-	*	*
Non-Protocol Tissues: SEMINAL VESICLE	*	-	-	-	-	-
Non-Protocol Tissues: VENTRAL PROSTATE	*	-	-	-	-	-

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Sprague-Dawley

STUDY NUMBER: 1143102
GROUP: 6: Pimozide 30 mg/kg/day
SEX: MALE

ANIMAL ID:	R15290	R15291	R15292	R15293	R15294	R15295
THYROID	N	-	N	-	U	N
ULTIMOBRANCHIAL CYST(S)	-	-	-	1L	-	-
CAPSULE- ACUTE INFLAMMATION	-	3L	-	-	-	-
TESTES	N	N	-	N	-	N
INTERSTITIAL CELLS- ATROPHY	-	-	2I	-	-	-
TUBULES- DILATATION	-	-	-	-	1I	-
EPIDIDYMIDES	N	N	N	N	N	N
Non-Protocol Tissues:						
KIDNEYS	-	-	-	-	-	*

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Sprague-Dawley

STUDY NUMBER: 1143102
GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day
SEX: MALE

ANIMAL ID:	R15302	R15303	R15304	R15305	R15306	R15307
THYROID	N	-	-	-	N	-
ULTIMOBRANCHIAL CYST(S)	-	2L	1L	2L	-	1I
TESTES	-	N	N	-	-	N
TUBULAR DEGENERATION	-	-	-	2I	4I	-
TUBULES- DILATATION	1I	-	-	-	-	-
EPIDIDYMIDES	-	N	N	-	-	-
HYPOSPERMIA	-	-	-	3I	4I	-
DEGENERATIVE GERM CELLS	1I	-	-	2I	-	1I

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102 STUDY NUMBER: 1143102
FATE: TK Long-Evans GROUP: 1: Corn Oil 2.5 ml/kg/day
SEX: MALE

ANIMAL ID:	R15236	R15237	R15238	R15240	R15241
THYROID	U	N	-	N	U
ULTIMOBRANCHIAL CYST(S)	-	-	2L	-	-
TESTES	N	N	N	N	N
EPIDIDYMIDES	N	N	-	N	N
SUBACUTE INFLAMMATION	-	-	(1)L	-	-

See Reports Code Table for Symbol Definitions

LABCAT HP4.33 06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Long-Evans

STUDY NUMBER: 1143102
GROUP: 2: Flutamide 50 mg/kg/day
SEX: MALE

ANIMAL ID:	R15248	R15249	R15250	R15251	R15252	R15253
THYROID	-	N	-	-	N	N
ULTIMOBRANCHIAL CYST(S)	-	-	-	1L	-	-
CAPSULE- GRANULATION TISSUE	-	-	-	3L	-	-
INFILTRATING LYMPHOCYTES	(1)L	-	-	-	-	-
COLLOID DEPLETION	-	-	2I	-	-	-
TESTES	-	-	-	-	-	-
INTERSTITIAL CELLS- HYPERTROPHY/HYPERPLASIA	2I	2I	3I	2I	2I	3I
TUBULES- DILATATION	2I	2I	2I	3I	3L	-
EPIDIDYMIDES	-	-	-	-	-	-
GRANULOMA(S)	-	-	-	-	-	(3)L
ATROPHY	3I	3I	2I	3I	3I	2I
Non-Protocol Tissues: ADRENALS	-	*	-	-	-	-
Non-Protocol Tissues: SEMINAL VESICLE	-	-	-	*	-	*
Non-Protocol Tissues: VENTRAL PROSTATE	-	-	-	-	-	*
Non-Protocol Tissues: KIDNEYS	-	*	-	-	-	-

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102 STUDY NUMBER: 1143102
FATE: TK Long-Evans GROUP: 3: Methyl testosterone 80 mg/kg/day
SEX: MALE

ANIMAL ID:	R15260	R15261	R15262	R15263	R15264	R15265
THYROID	N	N	N	N	N	N
TESTES	-	-	-	-	-	-
HYPOSPERMATOGENESIS	4I	4I	4I	4I	4I	4I
INTERSTITIAL CELLS- ATROPHY	4I	4I	4I	4I	4I	4I
EPIDIDYMIDES	-	-	-	-	-	-
HYPOSPERMIA	3I	3I	3I	3I	3I	3I
DEGENERATIVE GERM CELLS	2I	2I	2I	2I	2I	2I
Non-Protocol Tissues:						
SEMINAL VESICLE	-	-	*	-	-	-

See Reports Code Table for Symbol Definitions

LABCAT HP4.33 06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Long-Evans

STUDY NUMBER: 1143102
GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day
SEX: MALE

ANIMAL ID:	R15272	R15273	R15274	R15275	R15276	R15277
THYROID	-	-	-	-	-	-
FOLLICULAR CELLS- HYPERTROPHY/HYPERPLASIA	3I	3I	3I	3I	3I	3I
COLLOID DEPLETION	3I	3I	2I	3I	3I	3I
TESTES	-	-	-	-	-	-
INTERSTITIAL CELLS- ATROPHY	2I	2I	2I	2I	2I	1I
EPIDIDYMIDES	N	-	-	N	-	N
HYPOSPERMIA	-	3I	3I	-	2I	-
DEGENERATIVE GERM CELLS	-	2I	2I	-	2I	-
Non-Protocol Tissues: SEMINAL VESICLE	*	-	-	-	*	*
Non-Protocol Tissues: VENTRAL PROSTATE	*	-	-	-	*	*

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Long-Evans

STUDY NUMBER: 1143102
GROUP: 5: Ketoconazole 100 mg/kg/day
SEX: MALE

ANIMAL ID:	R15284	R15285	R15286	R15287	R15289
THYROID	N	N	N	-	N
FOLLICULAR CELLS- HYPERTROPHY/HYPERPLASIA	-	-	-	3I	-
COLLOID DEPLETION	-	-	-	3I	-
TESTES	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	-
LYMPHOCYTE INFILTRATION	-	-	-	-	<1>L
Non-Protocol Tissues: ADRENALS	-	-	*	*	*
Non-Protocol Tissues: SEMINAL VESICLE	-	-	*	-	-

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Long-Evans

STUDY NUMBER: 1143102
GROUP: 6: Pimozide 30 mg/kg/day
SEX: MALE

ANIMAL ID:	R15296	R15297	R15298	R15299	R15300	R15301
THYROID	N	U	N	N	N	N
TESTES	N	N	N	N	N	N
EPIDIDYMIDES	-	N	-	N	N	-
HYPOSPERMIA	3I	-	2I	-	-	2I

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: TK Long-Evans

STUDY NUMBER: 1143102
GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day
SEX: MALE

ANIMAL ID:	R15309	R15310	R15311	R15312	R15313
THYROID	N	N	N	N	-
ACUTE INFLAMMATION	-	-	-	-	2L
TESTES	-	-	-	-	-
TUBULAR DEGENERATION	3I	4I	4I	3I	3I
HYPOSPERMATOGENESIS	3I	4I	4I	4I	4I
EPIDIDYMIDES	-	-	-	-	-
HYPOSPERMIA	4I	4I	4I	4I	4I
DEGENERATIVE GERM CELLS	2I	-	-	3I	2L
Non-Protocol Tissues:					
SEMINAL VESICLE	*	-	-	*	*

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: FD Long-Evans,MK Long-Evans

STUDY NUMBER: 1143102
GROUP: 1: Corn Oil 2.5 ml/kg/day
SEX: MALE

ANIMAL ID:	R15239
THYROID	U
TESTES	N
EPIDIDYMIDES	N
Non-Protocol Tissues:	
LARGE INTESTINE (LOWER)	*

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: FD Long-Evans,MK Long-Evans

STUDY NUMBER: 1143102
GROUP: 5: Ketoconazole 100 mg/kg/day
SEX: MALE

ANIMAL ID:	R15288
THYROID	N
TESTES	N
EPIDIDYMIDES	N
Non-Protocol Tissues: ADRENALS	*
Non-Protocol Tissues: SEMINAL VESICLE	*

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

TABULATED ANIMAL DATA

STUDY ID : 1143-102
FATE: FD Long-Evans,MK Long-Evans

STUDY NUMBER: 1143102
GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day
SEX: MALE

ANIMAL ID:	R15308
THYROID	A
TESTES	-
TUBULAR DEGENERATION	2I
HYPOSPERMATOGENESIS	3I
EPIDIDYMIDES	-
HYPOSPERMIA	4I
Non-Protocol Tissues:	
LUNGS	*

See Reports Code Table for Symbol Definitions

LABCAT HP4.33

06-APR-2000

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: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102
SEX: MALE

STUDY NUMBER: 1143102
GROUP: 1: Corn Oil 2.5 ml/kg/day

Animal ID: R15239
Animal Fate: MK Long-Evans

Pathologist: JMP

Reference to Necropsy Record:
LARGE INTESTINE (LOWER) - DISCOLORED, DARK BROWN, BLACK

Related Histopathology:
LARGE INTESTINE (LOWER) - Histopathology Not Required

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102
SEX: MALE

STUDY NUMBER: 1143102
GROUP: 2: Flutamide 50 mg/kg/day

Animal ID: R15242
Animal Fate: TK Sprague-Dawley

Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
TESTES - UNEQUALLY SIZED, RIGHT, SMALL	TESTES - TUBULAR DEGENERATION
TESTES - SOFT, RIGHT	TESTES - TUBULAR DEGENERATION
SEMINAL VESICLE - SMALL, BOTH LOBES	SEMINAL VESICLE - Histopathology Not Required
VENTRAL PROSTATE - SMALL	VENTRAL PROSTATE - Histopathology Not Required

Animal ID: R15243
Animal Fate: TK Sprague-Dawley

Pathologist: JMP

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: R15244
Animal Fate: TK Sprague-Dawley

Pathologist: JMP

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

Animal ID: R15245
Animal Fate: TK Sprague-Dawley

Pathologist: JMP

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

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102
STUDY NUMBER: 1143102
SEX: MALE
GROUP: 2: Flutamide 50 mg/kg/day

Animal ID: R15246
Pathologist: JMP
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: R15247
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:	Related Histopathology:
EPIDIDYMIDES - SMALL, BILATERAL	EPIDIDYMIDES - ATROPHY
VENTRAL PROSTATE - SMALL	VENTRAL PROSTATE - Histopathology Not Required

---

Animal ID: R15249
Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
KIDNEYS - LEFT, DILATED PINPOINT PELVIS	KIDNEYS - Histopathology Not Required
ADRENALS - LEFT, DARK AREA, ONE, BLACK	ADRENALS - Histopathology Not Required

---

Animal ID: R15251
Pathologist: JMP
Animal Fate: TK Long-Evans

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

---

Animal ID: R15252
Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
EPIDIDYMIDES - SMALL	EPIDIDYMIDES - ATROPHY

LABCAT HP4.33
06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102
STUDY NUMBER: 1143102
SEX: MALE
GROUP: 2: Flutamide 50 mg/kg/day

Animal ID: R15253
Pathologist: JMP
Animal Fate: TK Long-Evans

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

LABCAT HP4.33
06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102
STUDY NUMBER: 1143102
SEX: MALE
GROUP: 3: Methyl testosterone 80 mg/kg/day

Animal ID: R15255
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY

Animal ID: R15256
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY

Animal ID: R15257
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY

Animal ID: R15259
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL, MODERATE	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY
CECUM - LUMEN, GAS, MODERATE AMOUNT	CECUM - Histopathology Not Required
STOMACH - LUMEN, GAS, MODERATE AMOUNT	STOMACH - Histopathology Not Required
INTESTINES - LUMEN, GAS, MODERATE AMOUNT	INTESTINES - Histopathology Not Required

Animal ID: R15260
Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY

LABCAT HP4.33
06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102 — STUDY NUMBER: 1143102
SEX: MALE — GROUP: 3: Methyl testosterone 80 mg/kg/day

Animal ID: R15261 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY

Animal ID: R15262 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY
SEMINAL VESICLE - ENLARGED, BILATERAL, MODERATELY	SEMINAL VESICLE - Histopathology Not Required

Animal ID: R15263 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL, SEVERE	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY

Animal ID; R15264 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY

Animal ID: R15265 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL	TESTES - HYPOSPERMATOGENESIS; INTERSTITIAL CELLS- ATROPHY

LABCAT HP4.33 — 06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102
SEX: MALE

STUDY NUMBER: 1143102
GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day

Animal ID: R15266
Animal Fate: TK Sprague-Dawley

Pathologist: JMP

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

Animal ID: R15267
Animal Fate: TK Sprague-Dawley

Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required
LEVATOR ANI/BULBOCAVERNO - SMALL	LEVATOR ANI/BULBOCAVERNO - Histopathology Not Required
VENTRAL PROSTATE - SMALL	VENTRAL PROSTATE - Histopathology Not Required
THYROID - ENLARGED, BILATERAL, SEVERE	THYROID - FOLLICULAR CELLS-HYPERTROPHY/HYPERPLASIA

Animal ID: R15268
Animal Fate: TK Sprague-Dawley

Pathologist: JMP

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

Animal ID: R15269
Animal Fate: TK Sprague-Dawley

Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required
PITUITARY - SMALL	PITUITARY - Histopathology Not Required
THYROID - ENLARGED, BILATERAL, SEVERE	THYROID - FOLLICULAR CELLS-HYPERTROPHY/HYPERPLASIA

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102 — STUDY NUMBER: 1143102
SEX: MALE — GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day

Animal ID: R15270 — Pathologist: JMP
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
THYROID - ENLARGED, SEVERE	THYROID - FOLLICULAR CELLS-HYPERTROPHY/HYPERPLASIA

Animal ID: R15271 — Pathologist: JMP
Animal Fate: TK Sprague-Dawley

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

Animal ID: R15272 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL	SEMINAL VESICLE - Histopathology Not Required
VENTRAL PROSTATE - SMALL	VENTRAL PROSTATE - Histopathology Not Required
THYROID - ENLARGED, SEVERE	THYROID - FOLLICULAR CELLS-HYPERTROPHY/HYPERPLASIA

Animal ID: R15273 — Pathologist: JMP
Animal Fate: TK Long-Evans

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

LABCAT HP4.33 — 06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102
SEX: MALE

STUDY NUMBER: 1143102
GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day

Animal ID: R15274
Animal Fate: TK Long-Evans

Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
THYROID - ENLARGED, SEVERE	THYROID - FOLLICULAR CELLS-HYPERTROPHY/HYPERPLASIA
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology not required
VENTRAL PROSTATE - SMALL	VENTRAL PROSTATE - Histopathology not required

Animal ID: R15275
Animal Fate: TK Long-Evans

Pathologist: JMP

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

Animal ID: R15276
Animal Fate: TK Long-Evans

Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required
VENTRAL PROSTATE - SMALL	VENTRAL PROSTATE - Histopathology Not Required
THYROID - ENLARGED, BILATERAL, SEVERE	THYROID - FOLLICULAR CELLS-HYPERTROPHY/HYPERPLASIA

Animal ID: R15277
Animal Fate: TK Long-Evans

Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required
VENTRAL PROSTATE - SMALL	VENTRAL PROSTATE - Histopathology Not Required
THYROID - ENLARGED, BILATERAL, SEVERE	THYROID - FOLLICULAR CELLS-HYPERTROPHY/HYPERPLASIA

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102 — STUDY NUMBER: 1143102
SEX: MALE — GROUP: 5: Ketoconazole 100 mg/kg/day

Animal ID: R15278 — Pathologist: JMP
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
ADRENALS - ENLARGED, BILATERAL, 4X4X3MM	ADRENALS - Histopathology Not Required
ADRENALS - PALE, BILATERAL, GREY	ADRENALS - Histopathology Not Required

Animal ID: R15280 — Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:	Related Histopathology:
ADRENALS - ENLARGED, BILATERAL, 4X4X4MM	ADRENALS - Histopathology Not Required
ADRENALS - PALE, BILATERAL, GREY	ADRENALS - Histopathology Not Required

Animal ID: R15282 — Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:	Related Histopathology:
ADRENALS - ENLARGED, MODERATE	ADRENALS - Histopathology Not Required

Animal ID: R15283 — Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:	Related Histopathology:
ADRENALS - ENLARGED, BILATERAL, MODERATELY	ADRENALS - Histopathology Not Required

LABCAT HP4.33 — 06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102 — STUDY NUMBER: 1143102
SEX: MALE — GROUP: 5: Ketoconazole 100 mg/kg/day

Animal ID: R15286 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required
ADRENALS - ENLARGED, BILATERAL, 3X3X3MM	ADRENALS - Histopathology Not Required
ADRENALS - PALE, GREY	ADRENALS - Histopathology Not Required

Animal ID: R15287 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
ADRENALS - ENLARGED, BILATERAL, 6X5X4MM	ADRENALS - Histopathology Not Required
ADRENALS - PALE, BILATERAL, GREY	ADRENALS - Histopathology Not Required

Animal ID: R15288 — Pathologist: JMP
Animal Fate: MK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
SEMINAL VESICLE - SMALL, BILATERAL	SEMINAL VESICLE - Histopathology Not Required
ADRENALS - ENLARGED, BILATERAL, 5X5X5MM	ADRENALS - Histopathology Not Required

Animal ID: R15289 — Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
ADRENALS - ENLARGED, BILATERAL, 4X4X3MM	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: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102 STUDY NUMBER: 1143102
SEX: MALE GROUP: 6: Pimozide 30 mg/kg/day

Animal ID: R15291 Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:
THYROID - GELATINOUS

Related Histopathology:
THYROID - CAPSULE- ACUTE INFLAMMATION

Animal ID: R15295 Pathologist: JMP
Animal Fate: TK Sprague-Dawley

Reference to Necropsy Record:
KIDNEYS - DILATED, RIGHT PELVIS, MODERATELY

Related Histopathology:
KIDNEYS - 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: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102
SEX: MALE

STUDY NUMBER: 1143102
GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day

Animal ID: R15306
Animal Fate: TK Sprague-Dawley
Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL, BILATERAL	TESTES - TUBULAR DEGENERATION

Animal ID: R15308
Animal Fate: FD Long-Evans
Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
LUNGS - RIGHT, DISCOLORED, RED, PINK	LUNGS - Histopathology Not Required

Animal ID: R15309
Animal Fate: TK Long-Evans
Pathologist: JMP

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

Animal ID: R15310
Animal Fate: TK Long-Evans
Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL	TESTES - TUBULAR DEGENERATION

Animal ID: R15311
Animal Fate: TK Long-Evans
Pathologist: JMP

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL	TESTES - TUBULAR DEGENERATION

LABCAT HP4.33

06-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

CORRELATION OF GROSS & MICRO

STUDY ID: 1143-102 STUDY NUMBER: 1143102
SEX: MALE GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day

Animal ID: R15312 Pathologist: JMP
Animal Fate: TK Long-Evans

Reference to Necropsy Record:	Related Histopathology:
TESTES - SMALL	TESTES - TUBULAR DEGENERATION
EPIDIDYMIDES - SMALL	EPIDIDYMIDES - HYPOSPERMIA
SEMINAL VESICLE - SMALL	SEMINAL VESICLE - Histopathology Not Required

Animal ID: R15313 Pathologist: JMP
Animal Fate: TK Long-Evans

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

LABCAT HP4.33 06-APR-2000

V. Comment Report

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

COMMENT REPORT

STUDY ID: 1143-102 STUDY NUMBER: 1143102
SEX: MALE GROUP: 1: Corn Oil 2.5 ml/kg/day

No Comments for any animal in this group

LABCAT HP4.33 07-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

COMMENT REPORT

STUDY ID: 1143-102
STUDY NUMBER: 1143102
SEX: MALE
GROUP: 2: Flutamide 50 mg/kg/day

Animal ID: R15244
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - DAMAGE TO WALL OF ESOPHAGUS NOTED

Animal ID: R15245
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - ACUTE INFLAMMATION NOTED IN WALL OF ESOPHAGUS AND CONNECTIVE TISSUE SURROUNDING THE THYROID

Animal ID: R15251
Pathologist: JMP
Animal Fate: TK Long-Evans

TISSUE COMMENTS:
THYROID - AN ABSCESS WITH A WALL COMPOSED OF GRANULATION TISSUE IS NOTED BETWEEN THE ESOPHAGUS AND ONE LOBE OF THE THYROID GLAND

Animal ID: R15253
Pathologist: JMP
Animal Fate: TK Long-Evans

TISSUE COMMENTS:
THYROID - ONE LOBE OF THYROID GLAND AVAILABLE FOR EVALUATION

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07-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

COMMENT REPORT

STUDY ID: 1143-102 STUDY NUMBER: 1143102
SEX: MALE GROUP: 3: Methyl testosterone 80 mg/kg/day

Animal ID: R15255 Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - SUBACUTE INFLAMMATION AND EARLY GRANULATION TISSUE ADJACENT TO THYROID

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PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

COMMENT REPORT

STUDY ID: 1143-102
STUDY NUMBER: 1143102
SEX: MALE
GROUP: 4: Propylthiouracil (PTU) 240 mg/kg/day

No Comments for any animal in this group

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

COMMENT REPORT

STUDY ID: 1143-102 STUDY NUMBER: 1143102
SEX: MALE GROUP: 5: Ketoconazole 100 mg/kg/day

Animal ID: R15279 Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - MODERATE INFLAMMATION IN CONNECTIVE TISSUE SURROUNDING ESOPHAGUS NOTED

Animal ID: R15282 Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - INFLAMMATION NOTED IN CONNECTIVE TISSUE ADJACENT TO ESOPHAGUS

Animal ID: R15284 Pathologist: JMP
Animal Fate: TK Long-Evans

TISSUE COMMENTS:
THYROID - SCANT SECTION OF THYROID GLAND AVAILABLE FOR EVALUATION

Animal ID: R15285 Pathologist: JMP
Animal Fate: TK Long-Evans

TISSUE COMMENTS:
THYROID - ONE LOBE OF THYROID GLAND AVAILABLE FOR EVALUATION

Animal ID: R15288 Pathologist: JMP
Animal Fate: MK Long-Evans

TISSUE COMMENTS:
THYROID - INFLAMMATION AND GRANULATION TISSUE NOTED ADJACENT TO ESOPHAGUS

LABCAT HP4.33 07-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

COMMENT REPORT

STUDY ID: 1143-102
STUDY NUMBER: 1143102
SEX: MALE
GROUP: 6: Pimozide 30 mg/kg/day

Animal ID: R15291
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - MODERATE ACUTE INFLAMMATION NOTED ADJACENT TO ESOPHAGUS AND INVOLVING THE CAPSULE OF ONE LOBE OF THE THYROID GLAND

Animal ID: R15292
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - ONE LOBE OF THYROID GLAND AVAILABLE FOR EVALUATION

Animal ID: R15295
Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - ONE LOBE OF THYROID GLAND AVAILABLE FOR EVALUATION

Animal ID: R15297
Pathologist: JMP
Animal Fate: TK Long-Evans

Animal Comments:
INFLAMMATION NOTED IN WALL OF ESOPHAGUS AND SURROUNDING CONNECTIVE TISSUE

Animal ID: R15298
Pathologist: JMP
Animal Fate: TK Long-Evans

TISSUE COMMENTS:
THYROID - SCANT SECTION OF ONE LOBE OF THYROID GLAND AVAILABLE FOR EVALUATION

LABCAT HP4.33
07-APR-2000

PATHOLOGY ASSOCIATES INTERNATIONAL
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION
IN JUVENILE MALE RATS
THERIMMUNE RESEARCH CORPORATION STUDY NUMBER: 1143-102

COMMENT REPORT

STUDY ID: 1143-102 STUDY NUMBER: 1143102
SEX: MALE GROUP: 7: Dibutylphthalate (DBP) 1000 mg/kg/day

Animal ID: R15303 Pathologist: JMP
Animal Fate: TK Sprague-Dawley

TISSUE COMMENTS:
THYROID - MILD ACUTE INFLAMMATION NOTED IN PERIESOPHAGEAL CONNECTIVE TISSUE

Animal ID: R15313 Pathologist: JMP
Animal Fate: TK Long-Evans

TISSUE COMMENTS:
THYROID - LARGE ABSCESS NOTED ADJACENT TO ESOPHAGUS AND AFFECTED LOBE OF THYROID

LABCAT HP4.33 (END OF REPORT) 07-APR-2000

VI. Quality Assurance Statement

Pathology Associates International
A Company of Science Applications International Corporation
An Employee-Owned Company

Pathology Report

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

TherImmune Research Corporation Study Number: 1143-102

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.

Date of Inspection	Phase Inspected	Date Findings Reported to PAI Management/Study Pathologist
03/03/00	Tissue Trimming	03/03/00
04/05,06/00	Individual Animal Data	04/06/00
04/05,06/00	Draft Pathology Report	04/06/00
06/15/00	Final Pathology Report	06/15/00

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)
	GROUP: 1 - 2.5 ML/KG/DAY CORN OIL	
R15230	5.58	2.76
R15231	4.36	2.58
R15232	5.26	1.51
R15233	4.96	3.42
R15234	5.28	3.28
R15235	3.36	2.74
	GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE	
R15242	2.50	1.21
R15243	4.87	1.17
R15244	4.28	1.74
R15245	1.43	2.77
R15246	3.39	3.72
R15247	4.95	1.82
	GROUP: 3 - 80 MG/KG/Dimethyl TESTOSTERONE	
R15254	5.28	2.30
R15255	4.00	1.03
R15256	3.22	3.22
R15257	4.03	3.49
R15258	3.93	1.25
R15259	1.29	1.56
	GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL	
R15266	0.07	28.75
R15267	0.00	23.67
R15268	0.00	34.00
R15269	0.00	26.31
R15270	0.00	23.67
R15271	0.00	23.40
	GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE	
R15278	6.07	6.27
R15279	5.33	2.46
R15280	4.13	1.50
R15281	5.21	1.47
R15282	4.43	2.18
R15283	3.15	3.13
	GROUP: 6 - 30 MG/KG/DAY PIMOZIDE	
R15290	5.54	1.64
R15291	3.28	0.45
R15292	3.55	1.85
R15293	3.48	1.70
R15294	6.25	3.59
R15295	4.00	2.51
	GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE	
R15302	3.60	1.15
R15303	5.27	3.61
R15304	1.82	2.69
R15305	2.71	1.69
R15306	3.65	2.24
R15307	2.97	2.86

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)
	GROUP: 1 - 2.5 ML/KG/DAY CORN OIL	
R15236	7.63	2.87
R15237	7.44	1.38
R15238	6.46	2.41
R15240	6.46	2.43
R15241	5.25	2.03
	GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE	
R15248	8.32	9.90
R15249	5.78	2.21
R15250	8.27	1.89
R15251	0.40	0.83
R15252	6.54	2.06
R15253	4.20	1.88
	GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE	
R15260	6.04	1.39
R15261	5.27	1.09
R15262	4.28	2.20
R15263	6.77	2.14
R15264	6.66	2.49
R15265	4.81	1.44
	GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL	
R15272	0.02	26.03
R15273	0.10	39.06
R15274	0.00	22.86
R15275	4.06	7.66
R15276	2.96	14.70
R15277	0.00	29.62
	GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE	
R15284	7.73	2.83
R15285	7.52	5.12
R15286	5.69	2.44
R15287	4.92	2.49
R15289	4.92	1.95
	GROUP: 6 - 30 MG/KG/DAY PIMOZIDE	
R15296	6.32	1.98
R15297	2.79	1.77
R15298	6.18	1.54
R15299	5.67	1.98
R15300	5.51	1.52
R15301	4.65	1.07
	GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE	
R15309	3.91	1.75
R15310	0.69	1.87
R15311	4.17	3.06
R15312	5.61	2.55
R15313	1.28	1.23

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

ANIMAL ID	DAY OF DEATH
	GROUP: 1 - 2.5 ML/KG/DAY CORN OIL
R15230	53
R15231	53
R15232	53
R15233	54
R15234	54
R15235	54
	GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE
R15242	53
R15243	53
R15244	53
R15245	54
R15246	54
R15247	54
	GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE
R15254	53
R15255	53
R15256	53
R15257	54
R15258	54
R15259	54
	GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL
R15266	53
R15267	53
R15268	53
R15269	54
R15270	54
R15271	54
	GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE
R15278	53
R15279	53
R15280	53
R15281	54
R15282	54
R15283	54
	GROUP: 6 - 30 MG/KG/DAY PIMOZIDE
R15290	53
R15291	53
R15292	53
R15293	54
R15294	54
R15295	54
	GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE
R15302	53
R15303	53
R15304	53
R15305	54
R15306	54
R15307	54

Appendix Continued

APPENDIX 9 (CONTINUED)
INDIVIDUAL DAY OF DEATH
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG-EVANS)

ANIMAL ID	DAY OF DEATH
GROUP: 1 - 2.5 ML/KG/DAY CORN OIL	
R15236	53
R15237	53
R15238	53
R15239	50
R15240	54
R15241	54
GROUP: 2 - 50 MG/KG/DAY FLUTAMIDE	
R15248	53
R15249	53
R15250	53
R15251	54
R15252	54
R15253	54
GROUP: 3 - 80 MG/KG/DAY METHYL TESTOSTERONE	
R15260	53
R15261	53
R15262	53
R15263	54
R15264	54
R15265	54
GROUP: 4 - 240 MG/KG/DAY PROPYLTHIOURACIL	
R15272	53
R15273	53
R15274	53
R15275	54
R15276	54
R15277	54
GROUP: 5 - 100 MG/KG/DAY KETOCONAZOLE	
R15284	53
R15285	53
R15286	53
R15287	54
R15288	50
R15289	54
GROUP: 6 - 30 MG/KG/DAY PIMOZIDE	
R15296	53
R15297	53
R15298	53
R15299	54
R15300	54
R15301	54
GROUP: 7 - 1000 MG/KG/DAY DIBUTYLPHTHALATE	
R15308	49
R15309	53
R15310	53
R15311	54
R15312	54
R15313	54

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

Experiment R1143-102 - 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	0.5237
liver	0.4932
kidney	0.7577
testes	0.1620
epid	0.8033
seminal	0.5298
levwt	0.0638
prost	0.4480
prep	0.0736
adren	0.3418
pit	0.0531
t4	0.2332
tsh	0.4419

Experiment R1143-102 - Sprague Dawley Juvenile Male Rats
Body and Organ Weights
Table 2
Analysis of Covariance: Test for PND22 x Dose Interaction

Dependent	ProbF
term	0.8482
liver	0.5224
kidney	0.7700
testes	0.3407
epid	0.6517
seminal	0.6190
levwt	0.8301
prost	0.5849
prep	0.3211
adren	0.6501
pit	0.7021
t4	0.1772
tsh	0.8790

Experiment R1143-102 - 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	0.0427
Control_vs_Dose6	<.0001
Control_vs_Dose7	0.0891

Experiment R1143-102 - 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	0.9165
kidney	0.3588
testes	0.1839
epid	0.2537
seminal	0.0690
levwt	0.0699
prost	0.2537
adren	0.3790
pit	0.1062

Experiment R1143-102 - Sprague Dawley Juvenile Male Rats
Ratio Data
Table 5
Analysis of Covariance: Test for Weaning Body Weight x Dose Inter

Dependent	ProbF
liver	0.4021
kidney	0.6428
testes	0.2613
epid	0.0872
seminal	0.8744
levwt	0.9960
prost	0.3734
adren	0.6461
pit	0.7118

Experiment R1143-102 - Sprague Dawley Juvenile Male Rats
Ratio Data
Table 6
Ratios: Results of MANCOVA

Hypothesis	ProbF
Control_vs_Dose2	0.0034
Control_vs_Dose3	<.0001
Control_vs_Dose4	<.0001
Control_vs_Dose5	0.0751
Control_vs_Dose6	0.2391
Control_vs_Dose7	0.1072

TABLE (1143-102)
ADJUSTED MEANS FROM CONVARIANCE ANALYSIS
ASSESSMENT OF PUBERTYL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (SPRAGUE-DAWLEY)

	DOSE GROUP						
	CORN OIL	FLUTAMIDE	METHYL TESTOSTERONE	PROPYLTHIOURACIL	KETOCONAZOLE	PIMOZIDE	DIBUTYLPHTHALATE
ADRENAL	0.057	0.048	0.049	0.041	*0.220	0.033	0.029
EPIDIDYMIDES	0.495	**0.334	*0.411	**0.273	0.452	**0.382	0.466
KIDNEY	2.065	*1.840	2.192	**0.896	1.877	**1.500	2.036
LEVATOR MUSCLES WT	0.580	**0.265	0.676	**0.108	0.410	**0.334	0.445
LIVER	10.711	11.038	9.825	**4.962	10.523	*8.903	11.195
PITUITARY	0.009	0.007	*0.007	**0.006	0.007	**0.006	0.010
PREPUCE SEPARATION	43.059	**54.468	**37.323	**54.063	**45.889	**50.115	43.416
VENTRAL PROSTATE	0.217	**0.041	**0.395	**0.042	*0.136	**0.126	0.196
SEMINAL	0.395	**0.063	**0.727	**0.042	*0.242	**0.230	0.375
T4, TOTAL	4.724	3.611	3.638	**-0.069	4.648	4.416	3.444
TERM	259.257	239.935	*229.593	**120.777	*233.375	**204.222	238.891
TESTES	3.117	3.273	**0.929	**1.843	2.975	2.474	1.976
TSH	2.686	1.873	1.924	**26.984	2.529	1.630	2.158

TABLE (1143-102)
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	PROPYLTHIOURACIL	KETOCONAZOLE	PINOZIDE	DIBUTYLPHTHALATE
ADRENAL	0.023	0.021	0.022	0.031	0.100	0.016	0.012
EPIDIDYMIDES	0.192	**0.139	0.180	0.225	0.195	0.187	0.194
KIDNEY	0.797	0.770	**0.955	*0.742	0.804	0.738	0.851
LEVATOR MUSCLES WT	0.225	0.111	0.293	**0.075	0.175	0.156	0.181
LIVER	4.114	**4.622	4.267	4.128	4.500	4.347	4.682
PITUITARY	0.003	0.003	0.003	**0.005	0.003	0.003	0.004
VENTRAL PROSTATE	0.084	**0.018	**0.174	**0.036	0.057	0.061	0.081
SEMINAL	0.154	**0.029	**0.327	**0.037	0.104	0.116	0.160
TESTES	1.204	1.379	**0.406	1.537	1.276	1.217	0.829

TABLE (1143-102)
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	KETOCONAZOLE	PIMOZIDE	DIBUTYLPHTHALATE
BODY WT ON DAY OF SEP	187.70 ± 4.37 (6)	**231.57 ± 8.70 (6)	**147.62 ± 6.79 (6)	**120.32 ± 3.45 (6)	190.00 ± 1.30 (6)	193.68 ± 7.03 (6)	187.20 ± 2.87 (6)

Experiment R1143-102 - 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	0.6944
liver	0.6320
kidney	0.2857
testes	0.0922
epid	0.6685
seminal	0.1647
levwt	0.4876
prost	0.7299
adren	0.9925
pit	0.8016
t4	0.5355
tsh	0.7451
prep	0.1834

Experiment R1143-102 - Long Evans Juvenile Male Rats
Body and Organ Weights
Table 2
Analysis of Covariance: Test for PND22 x Dose Interaction

Dependent	ProbF
term	0.3286
liver	0.6829
kidney	0.3900
testes	0.7210
epid	0.1540
seminal	0.2190
levwt	0.5888
prost	0.5203
adren	0.0546
pit	0.0516
t4	0.0665
tsh	0.1925
prep	0.5684

Experiment R1143-102 - 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	0.0436
Control_vs_Dose6	0.0006
Control_vs_Dose7	<.0001

Experiment R1143-102 - 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	0.9580
kidney	0.8557
testes	0.1153
epid	0.5325
seminal	0.6855
levwt	0.5380
prost	0.0679
adren	0.8072
pit	0.7428

Experiment R1143-102 - Long Evans Juvenile Male Rats
Ratio Data
Table 5
Analysis of Covariance: Test for Weaning Body Weight x Dose Inter

Dependent	ProbF
liver	0.9910
kidney	0.1207
testes	0.8704
epid	0.1167
seminal	0.2276
levwt	0.9303
prost	0.6781
adren	0.0302
pit	0.1335

Experiment R1143-102 - 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	0.0004
Control_vs_Dose6	0.8171
Control_vs_Dose7	<.0001

TABLE (1143-102)
ADJUSTED MEANS FROM ANALYSIS OF COVARIANCE
ASSESSMENT OF PUBERYL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG EVANS)

	DOSE GROUP						
	CORN OIL	FLUTAMIDE	METHYL TESTOSTERONE	PROPYLTHIOURACIL	KETOCONAZOLE	PIMOZIDE	DIBUTYLPHTHALATE
ADRENAL	0.045	0.047	**0.032	**0.024	**0.100	*0.034	0.043
EPIDIDYMIDES	0.464	**0.224	0.451	**0.234	**0.384	**0.347	**0.341
KIDNEY	2.362	**2.033	2.278	**0.852	2.260	**1.676	**2.069
LEVATOR MUSCLES WT	0.490	**0.268	**0.710	**0.187	0.409	*0.351	**0.283
LIVER	12.024	12.317	**9.759	**4.437	12.167	**9.300	10.614
PITUITARY	0.007	0.008	0.006	0.005	0.006	0.006	0.007
PREPUCE SEPARATION	50.703	**54.567	**33.506	**54.451	49.596	49.753	*53.369
VENTRAL PROSTATE	0.174	**0.036	**0.356	**0.037	0.118	0.117	*0.092
SEMINAL	0.322	**0.064	**0.724	**0.073	*0.186	0.241	**0.142
T4, TOTAL	6.524	5.671	5.646	**1.127	6.150	5.297	**3.093
TERMINAL BODY WT	278.247	**247.101	**248.412	**106.601	256.321	**211.063	**232.100
TESTES	2.616	*2.922	**0.638	**1.729	2.564	**2.157	**0.684
TSH	2.119	2.290	1.719	**20.445	2.796	1.638	1.980

TABLE (1143-102)
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	PIMOZIDE	DIBUTYLPHTHALATE
ADRENAL	0.017	0.019	0.013	*0.023	**0.042	0.016	0.019
EPIDIDYMIDES	0.165	**0.089	0.180	**0.219	0.149	0.163	0.147
KIDNEY	0.847	0.825	0.917	0.793	0.882	0.800	0.892
LEVATOR MUSCLES WT	0.180	0.107	*0.285	0.175	0.160	0.164	0.122
LIVER	4.322	**4.999	3.915	4.131	4.747	4.400	4.566
PITUITARY	0.002	0.003	0.002	**0.005	0.002	0.003	0.003
VENTRAL PROSTATE	0.066	**0.015	**0.147	*0.038	0.047	0.060	0.044
SEMINAL	0.113	**0.026	**0.285	*0.063	0.069	0.109	*0.060
TESTES	0.944	**1.182	**0.259	**1.645	1.001	1.024	**0.295

TABLE (1143-102)
SUMMARY OF BODY WEIGHT AND PREPUCE SEPARATION
ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE RATS (LONG EVANS)

	DOSE GROUP						
	CORN OIL	FLUTAMIDE	METHYL TESTOSTERONE	PROPYLTHIOURACIL	KETOCONAZOLE	PIMOZIDE	DIBUTYLPHTHALATE
BODY WT ON DAY OF SEP	258.30 ± 13.59 (6)	248.97 ± 8.98 (6)	**120.77 ± 3.80 (6)	**105.23 ± 2.76 (6)	*228.98 ± 8.75 (5)	**197.70 ± 7.47 (6)	*231.98 ± 7.96 (6)

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

TherImmune No. 1143-102

THERIMMUNE
Research Corporation

STUDY PROTOCOL

Assessment of Pubertal Development and Thyroid Function in Juvenile Male Rats

APPROVED:

TherImmune Research Corporation:

Meredith S. Rocca 12.14.99
Meredith S. Rocca, Ph.D. Date
Study Director

EPA:

12/9/99
Kenneth H. Elstein Date
Project Officer

REVIEWED:

12/7/99
Cecilia Matos-Rosa Date
Quality Assurance Auditor

EPA Requisition No. AC5001 – TherImmune No. 1143-102
EPA Reference No. QT-RT-99-002276

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 (1143-100) 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. Pletcher, D.V.M., M.P.H., 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.

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 15, 2000
Last Terminal Sacrifice:	February 15, 2000
Progress Report:	December 31, 1999
Draft Report	March 24, 2000
Final Report:	May 26, 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.

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.

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 1143-102 and 1143-103. 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 1143-103.

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 morbundity 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 runted pups and unthrifty litters; pups will not be individually identified.)

c. Culling

On PND 3 or 4, litters will be culled to 8 to 10 pups (approximately equal numbers of male and females 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 runted pups will not be selected.

Procedures for selected males are described in Section XII.

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 1143-103.

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

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 morbundity 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.

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 µl/animal will be aliquoted into 1.7 ml siliconized microcentrifuge tubes, stored at -20° 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 µl/animal will be aliquoted into 1 ml microcentrifuge tubes, stored at -20° C, and shipped 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

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

4. **Tissue Preservation**
The thyroid, epididymes 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, epididymes 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.

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.

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.: 1143-102	
AMENDMENT NUMBER: 1	amd by MSR 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/M. James 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 1.11.00

Meredith S. Rocca, Ph.D. Date