Appendix II

Histopathology Report

- Corrected pages with transmittal letter dated January 22, 2004
- Pathology report (October 22, 2003), Experimental Laboratories, Inc.

EPL®

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.
P.O. BOX 12766, RESEARCH TRIANGLE PARK, NC 27709 (919)998-9407 Fax: (919)998-9607

January 22, 2004

Dr. Julia George
Senior Toxicologist
Research Triangle Institute
P.O. Box 12194
Research Triangle Park, NC 27709-2194

Dear Dr. George:

Please find an original and one punched copy of page 2 and the leader pages for the two components from the final pathology report entitled "Assessment of Pubertal Development and Thyroid Function in Juvenile Male CD® (Sprague-Dawley) Rats After Exposure to Selected Chemicals Administered by Gavage on Postnatal Days 23 Through 52/53" – Client ID 65U-08055.001.015.001(M) – EPL Project No. 237-006.

If there are any questions regarding these pages, please do not hesitate to contact me.

Sincerely,

John Curtis Seely, DVM

JOHN CURTIS SEELY, ~~D.V.~~M.
Diplomate ACVP
Senior Pathologist

JCS:amh

Enclosures

DESIGN OF THE STUDY

Eight test chemicals were administered via gavage once daily for 31-32 consecutive days (pnd 22 to pnd 52 or 53) to male CD® (Sprague-Dawley) rats under the study conditions outlined in the study protocol (RTI Master Protocol No.: RTI-831).

The study began with 15 weight-matched F1 males/group. The study design, test chemicals and target dose levels are presented in Table 1.

Table 1 – Study Design

Component 1

Group No.	No. F1 Males	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	-[a]	0	0.0	5.0
2	15	Methoxychlor	25	5.0	5.0
3	15		50	10.0	5.0
4	15	Atrazine	75	15.0	5.0
5	15		150	30.0	5.0
6	15	p,p-DDE	50	10.0	5.0
7	15		100	20.0	5.0
8	15	Vinclozolin	30	6.0	5.0
9	15		100	20.0	5.0

[a] corn oil, vehicle control

Component 2

Group No.	No. F1 Males	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	-[a]	0	0.0	5.0
2	15	Propylthiouracil	2	0.4	5.0
3	15		25	5.0	5.0
4	15	Linuron	50	10.0	5.0
5	15		100	20.0	5.0
6	15	Ketoconazole	50	10.0	5.0
7	15		100	20.0	5.0
8	15	Phenobarbital	50	10.0	5.0
9	15		100	20.0	5.0

[a] corn oil, vehicle control

Study Design

Component 1

Group No.	No. F1 Males	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	-[a]	0	0.0	5.0
2	15	Methoxychlor	25	5.0	5.0
3	15		50	10.0	5.0
4	15	Atrazine	75	15.0	5.0
5	15		150	30.0	5.0
6	15	p,p-DDE	50	10.0	5.0
7	15		100	20.0	5.0
8	15	Vinclozolinp	30	6.0	5.0
9	15		100	20.0	5.0

[a] corn oil, vehicle control

Study Design

Component 2

Group No.	No. F1 Males	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	-[a]	0	0.0	5.0
2	15	Propylthiouracil	2	0.4	5.0
3	15		25	5.0	5.0
4	15	Linuron	50	10.0	5.0
5	15		100	20.0	5.0
6	15	Ketoconazole	50	10.0	5.0
7	15		100	20.0	5.0
8	15	Phenobarbital	50	10.0	5.0
9	15		100	20.0	5.0

[a] corn oil, vehicle control

ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE CD® (SPRAGUE-DAWLEY) RATS AFTER EXPOSURE TO SELECTED CHEMICALS ADMINISTERED BY GAVAGE ON POSTNATAL DAYS 23 THROUGH 52/53

65U-08055.001.015.001(M)

EPL PROJECT NO. 237-006

PATHOLOGY REPORT

Submitted to

Research Triangle Institute
P.O. Box 12194
Research Triangle Park, NC 27709

Submitted by

Experimental Pathology Laboratories, Inc.
P.O. Box 12766
Research Triangle Park, NC 27709

October 22, 2003

TABLE OF CONTENTS

ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE MALE CD® (SPRAGUE-DAWLEY) RATS AFTER EXPOSURE TO SELECTED CHEMICALS ADMINISTERED BY GAVAGE ON POSTNATAL DAYS 23 THROUGH 52/53

65U-08055.001.015.001(M)

EPL PROJECT NO. 237-006

NARRATIVE SUMMARY

INTRODUCTION

The objective of this study was to quantify the effects of environmental compounds on pubertal development and thyroid function in the intact juvenile/peripubertal male rat. This assay detects compounds that display antithyroid, estrogenic, androgenic, antiandrogenic [androgen receptor (AR) or steroid enzyme mediated] activity, or alter follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, growth hormone (GH), or hypothalamic function.

For this study, the following chemicals were tested: Methoxychlor, Atrazine, p-p-DDE, Vinclozolin, Propylthiouracil, Linuron, Ketoconazole, and Phenobarbital. The study was conducted in two components. Each component consisted of two dose groups per test material and one vehicle control group, each group comprised of 15 weight-matched F1 male weanlings, for each of the two components.

The testes, epididymides and thyroids were examined microscopically.

SUMMARY

Administration of the test chemicals by gavage to male, CD® (Sprague-Dawley) rats, under the conditions of this study, was associated with the following histopathologic changes:

1. The presence and dose-related increased severity of thyroid, follicular cell hypertrophy/hyperplasia in both the 2 and 25 mg/kg dosed Propylthiouracil animals.

DESIGN OF THE STUDY

Eight test chemicals were administered via gavage once daily for 31-32 consecutive days (pnd 22 to pnd 52 or 53) to male CD® (Sprague-Dawley) rats under the study conditions outlined in the study protocol (RTI Master Protocol No.: RTI-831).

The study began with 15 weight-matched F1 males/group. The study design, test chemicals and target dose levels are presented in Table 1.

Table 1 – Study Design

Component 1

Group No.	No. F1 Males	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	-[a]	0	0.0	5.0
2	15	Methoxychlor	25	5.0	5.0
3	15		50	10.0	5.0
4	15	Atrazine	75	15.0	5.0
5	15		150	30.0	5.0
6	15	p,p-DDE	50	10.0	5.0
7	15		100	20.0	5.0
8	15	Vinclozolin	30	6.0	5.0
9	15		100	20.0	5.0

[a] stripped corn oil, vehicle control

Component 2

Group No.	No. F1 Males	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	-[a]	0	0.0	5.0
2	15	Propylthiouracil	2	0.4	5.0
3	15		25	5.0	5.0
4	15	Linuron	50	10.0	5.0
5	15		100	20.0	5.0
6	15	Ketoconazole	50	10.0	5.0
7	15		100	20.0	5.0
8	15	Phenobarbital	50	10.0	5.0
9	15		100	20.0	5.0

[a] stripped corn oil, vehicle control

Individual treatment groups within each component of the study were given unique five digit codes that are presented in Table 2.

Table 2 – Treatment Group Designations

Group	Component 1	Component 2
1	78967	82703
2	96509	04691
3	68843	65437
4	84156	46916
5	39239	59969
6	29505	27489
7	48266	16317
8	15492	34563
9	07983	95962

According to the study protocol, all F1 males were subjected to a complete necropsy with selected organs dissected and weighed. The testes and epididymides were fixed in Bouin's fixative for 24 hours, after which they were rinsed and stored in 70% alcohol. The thyroid with attached portion of trachea was fixed in 10% buffered neutral formalin. All tissues were trimmed, embedded in paraffin, sectioned and stained with Hematoxylin and Eosin (H&E).

Histopathological examination of selected organs was conducted on the protocol-required tissues. The protocol-required tissues were: testis, epididymis and thyroid glands.

The gross and histopathologic data were entered in the Experimental Pathology Laboratories, Inc. Computerized Pathology Reporting System. Each lesion was graded according to a four-grade severity scale (1-4). "Aspermia" of the epididymis was designated only as "Present".

RESULTS

The individual animal data are presented by group in the Histopathology Incidence Table (HIT) and the group summary data in the Summary Incidence Tables (SIT). Gross necropsy findings were correlated to the microscopic findings, whenever possible. These findings are presented in the section "Correlation of Gross and Microscopic Findings Tables".

A limited number of histopathologic changes were observed during the study. No lesions were noted in any control animals from either Component 1 or Component 2. A few degenerative lesions of the testicular seminiferous tubules associated, in some cases, with the presence of exfoliated germ cells in epididymal tubule lumens were occasionally observed. None of these changes appeared to be treatment-related because of their overall low incidence and lack of any dose response.

In addition, because of the young age of the animals, the epididymal tubules appeared to be slightly immature and fewer sperm compared to older animals were present. This was particularly noted in the epididymal cauda of all animals examined.

The following chemicals were not associated with any treatment-related histopathologic changes: Component 1 = Methoxychlor (25 and 50 mg/kg); Atrazine (75 and 150 mg/kg), p,p-DDE (50 and 100 mg/kg), and Vinclozolin (30 and 100 mg/kg); Component 2 = Linuron (50 and 100 mg/kg), Ketoconazole (50 and 100 mg/kg), and Phenobarbital (50 and 100 mg/kg).

Although some relative and/or adjusted organ weight changes were statistically different (either increased or decreased) for the testes, epididymides or thyroid glands for several of the above chemicals, no related histopathology by routine H&E examination was detected in these tissues to account for the weight changes.

TREATMENT-RELATED FINDINGS BY CHEMICAL

Propylthiouracil

Administration of both 2 and 25 mg/kg Propylthiouracil was associated with the presence and dose-related increased severity of thyroid follicular cell hypertrophy/hyperplasia which was clearly related to increased thyroid weights and levels of TSH and decreased levels of T4.

Follicular cell hypertrophy/hyperplasia was characterized by a spectrum of histologic changes including the increased size and apparent number of follicular cells, the reduction in follicular lumen size, the presence of thyroid follicles. The severity of hypertrophy/hyperplasia was subjectively based on a

number of criteria: minimal = multifocal follicles affected, size and number of follicular cells slightly enlarged and increased; mild = diffuse change with further increased cell size and hyperplasia; moderate = enhanced severity with the presence of notable numbers of follicular cell mitoses; marked = increased mitotic rate, some degenerative cells (deeply eosinophilic cytoplasm and pyknotic nuclei) within the follicular epithelium, and obvious thyroid gland size and shape enlargement. No alteration of the thyroid vasculature was noted.

The incidence and severity of thyroid hypertrophy/hyperplasia is presented in Table 3.

Table 3 – Incidence and Severity of Thyroid Hypertrophy/Hyperplasia
Propylthiouracil

Dose (mg/kg)	0	2	25
THYROID (No. Examined)	(14)	(15)	(14)
Hypertrophy/Hyperplasia	0	15	14
Mild	0	10	1
Moderate	0	5	9
Marked	0	0	4

Results of the microscopic examination of the thyroid gland are compatible with previous reports on the direct action of Propylthiouracil on the thyroid gland (Thomas and Williams, 1999).

John Curtis Seely, DVM

JOHN CURTIS SEELY, D.V.M.
Diplomate, ACVP
Senior Pathologist

October 22, 2003
Date

REFERENCES

Thomas GA and Williams ED. Thyroid Stimulating Hormone (TSH) – Associated Follicular Hypertrophy and Hyperplasia as a Mechanism of Thyroid Carcinogenesis in Mice and Rats. In. Species Differences in Thyroid, Kidney, and Urinary Bladder Carcinogenesis. Capen CC, Dybing E, Rice JM, and Wilbourn (Eds) IARC Scientific Publications No. 147, pp 45-59, 1999.

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Assessment of Pubertal Development and Thyroid Function in Juvenile Male CD® (Sprague-Dawley) Rats After Exposure to Selected Chemicals Administered by Gavage on Postnatal Days 23 Through 52/53

Client Study: RTI Contract 65U-08055.001.015.001(M) EPL Project Coordinator: Dr. John Curtis Seely

EPL Project Number: 237-006 EPL Pathologist: Dr. John Curtis Seely

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the EPL Project Coordinator and Management are indicated below.

	Dates	
Area Inspected	Inspection	Reporting
EPL Project Sheets	October 8, 2002; December 13, 2002; March 10, 2003	October 8, 2002; December 13, 2002; March 10, 2003
Project Setup	November 26&27, 2002; March 11, 2003	November 27, 2002; March 11, 2003
Histology Setup	November 27, 2002; March 12, 2003	November 27, 2002; March 12, 2003
Data Review	January 17, 2003; April 11, 2003	January 17, 2003; April 11, 2003
Draft Report	July 2&3, 2003	July 3, 2003
Final Report	October 22, 2003	October 22, 2003

Date Reported to Study Director/Management: October 22, 2003

Date of last quarterly facility inspection: August 2003

Jane J. Hollingsworth
EPL Quality Assurance Unit

October 22, 2003
Date

Form No. 6-2 (09/10/99)

Study Design

Component 1

Group No.	No. F1 Males	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	-[a]	0	0.0	5.0
2	15	Methoxychlor	25	5.0	5.0
3	15		50	10.0	5.0
4	15	Atrazine	75	15.0	5.0
5	15		150	30.0	5.0
6	15	p,p-DDE	50	10.0	5.0
7	15		100	20.0	5.0
8	15	Vinclozolin	30	6.0	5.0
9	15		100	20.0	5.0

[a] stripped corn oil, vehicle control

SUMMARY INCIDENCE TABLES

COMPONENT #1

SUMMARY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 6
EPIDIDYMIS (NO. EXAMINED)	(12)	(15)	(13)	(12)	(12)	(13)
Aspermia				1		
Exfoliated Germ Cells, Lumen				1		
TESTIS (NO. EXAMINED)	(12)	(15)	(13)	(12)	(12)	(13)
Degeneration, Seminiferous						
Tubule				1		
THYROID (NO. EXAMINED)	(12)	(15)	(13)	(12)	(12)	(13)

SUMMARY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

	GROUP 7	GROUP 8	GROUP 9			
EPIDIDYMIS (NO. EXAMINED)	(15)	(13)	(12)			
Aspermia						
Exfoliated Germ Cells, Lumen						
TESTIS (NO. EXAMINED)	(15)	(13)	(12)			
Degeneration, Seminiferous						
Tubule		1				
THYROID (NO. EXAMINED)	(15)	(13)	(12)			

HISTOPATHOLOGY INCIDENCE TABLES

COMPONENT #1

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

GROUP 1

ANIMAL	1	15	32	33	50	51	68	87	104	105	122	123								
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X								
Aspermia																				
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X								
Degeneration, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X								

EPL
Experimental Pathology Laboratories, Inc.

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

	GROUP 2																			
ANIMAL	2	16	31	34	49	52	67	70	85	88	103	106	121	124	134					
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Aspermia																				
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Degeneration, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

	GROUP 3												
ANIMAL	3	14	35	48	53	66	71	84	89	102	107	120	125
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X
Aspermia													
Exfoliated Germ Cells, Lumen													
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X
Degeneration, Seminiferous Tubule													
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X

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HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

GROUP 4

ANIMAL	4	29	36	47	65	72	83	90	101	108	126	133
EPIDIDYMIS	X	X	X	X	X	X	X	X		X	X	X
Aspermia									P			
Exfoliated Germ Cells, Lumen									3			
TESTIS	X	X	X	X	X	X	X	X		X	X	X
Degeneration, Seminiferous Tubule									3			
THYROID	X	X	X	X	X	X	X	X	X	X	X	X

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

GROUP
5

ANIMAL	5	13	19	28	37	46	64	73	82	91	100	109								
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X								
Aspermia																				
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X								
Degeneration, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X								

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Experimental Pathology Laboratories, Inc.

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HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

	GROUP 6																			
ANIMAL	6	12	27	38	45	56	63	81	92	99	110	117	128							
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X							
Aspermia																				
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X							
Degeneration, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X							

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HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

GROUP 7

ANIMAL	7	21	26	39	44	57	62	75	80	93	98	111	116	129	132					
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Aspermia																				
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Degeneration, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

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HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

GROUP 8

ANIMAL	8	11	22	25	40	43	58	61	76	94	97	112	130
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X
Aspermia													
Exfoliated Germ Cells, Lumen													
TESTIS	X	X	X		X	X	X	X	X	X	X	X	X
Degeneration, Seminiferous Tubule				1									
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X

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Experimental Pathology Laboratories, Inc.

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HISTOPATHOLOGY INCIDENCE TABLE

08055.001
F1 Sacrifice
Male Rat

GROUP 9

ANIMAL	9	10	23	41	42	59	60	77	78	95	96	113								
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X								
Aspermia																				
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X								
Degeneration, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X								

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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P=Present B=Benign M=Malignant
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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

COMPONENT #1

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 1

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
15	KIDNEY	Right side, hydronephrosis	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 3

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
89	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 4

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
101	TESTIS	Left, not descended	No Comment Required
	TESTIS	Left, smaller in size	Degeneration, Seminiferous Tubule
	EPIDIDYMIS	Left, smaller in size	Exfoliated Germ Cells, Lumen; Aspermia
133	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 5

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
13	KIDNEY	Right, hydronephrosis, mild	Intentionally Not Sampled
91	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 6

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
12	KIDNEY	Right side, hydronephrosis, slight	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 7

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
7	NOSE	Chromodacryorrhea (not saved)	Intentionally Not Sampled
26	INTESTINES	Distended with air	Intentionally Not Sampled
39	KIDNEY	Bilateral, hydronephrosis	Intentionally Not Sampled
44	KIDNEY	Right side, hydronephrosis, slight	Intentionally Not Sampled
98	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
116	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 8

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
8	KIDNEY	Right side, hydronephrosis	Intentionally Not Sampled
11	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
22	KIDNEY	Right side, hydronephrosis	Intentionally Not Sampled
61	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 9

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
10	KIDNEY	Right side, hydronephrosis	Intentionally Not Sampled
42	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
59	KIDNEY	Right side, hydronephrosis	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled

Study Design

Component 2

Group No.	No. F1 Males	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	-[a]	0	0.0	5.0
2	15	Propylthiouracil	2	0.4	5.0
3	15		25	5.0	5.0
4	15	Linuron	50	10.0	5.0
5	15		100	20.0	5.0
6	15	Ketoconazole	50	10.0	5.0
7	15		100	20.0	5.0
8	15	Phenobarbital	50	10.0	5.0
9	15		100	20.0	5.0

[a] stripped corn oil, vehicle control

SUMMARY INCIDENCE TABLES

COMPONENT #2

SUMMARY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 6
EPIDIDYMIS (NO. EXAMINED)	(14)	(15)	(14)	(15)	(15)	(15)
Exfoliated Germ Cells, Lumen						1
TESTIS (NO. EXAMINED)	(14)	(15)	(14)	(15)	(15)	(15)
Degeneration, Seminiferous Tubule			1			1
THYROID (NO. EXAMINED)	(14)	(15)	(14)	(15)	(15)	(15)
Congestion		1				
Hemorrhage, Follicle						
Hypertrophy/Hyperplasia, Follicular Cell		15	14			

SUMMARY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

	GROUP 7	GROUP 8	GROUP 9			
EPIDIDYMIS (NO. EXAMINED)	(14)	(15)	(15)			
Exfoliated Germ Cells, Lumen			1			
TESTIS (NO. EXAMINED)	(14)	(15)	(15)			
Degeneration, Seminiferous Tubule						
THYROID (NO. EXAMINED)	(14)	(15)	(15)			
Congestion						
Hemorrhage, Follicle			1			
Hypertrophy/Hyperplasia, Follicular Cell						

HISTOPATHOLOGY INCIDENCE TABLES

COMPONENT #2

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

GROUP 1

	ANIMAL	136	153	154	171	172	182	199	200	218	235	236	253	254	270						
EPIDIDYMIS		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Exfoliated Germ Cells, Lumen																					
TESTIS		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Degeneration, Seminiferous Tubule																					
THYROID		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Congestion																					
Hemorrhage, Follicle																					
Hypertrophy/Hyperplasia, Follicular Cell																					

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

	GROUP 2																			
ANIMAL	137	152	155	170	173	183	198	201	216	219	234	237	252	255	269					
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Degeneration, Seminiferous Tubule																				
THYROID																				
Congestion			2																	
Hemorrhage, Follicle																				
Hypertrophy/Hyperplasia, Follicular Cell	2	3	2	3	3	2	3	2	3	2	2	2	2	2	2					

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

GROUP 3

ANIMAL	138	151	156	169	174	184	197	202	215	220	233	238	251	256						
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X		X	X	X						
Degeneration, Seminiferous																				
Tubule											1									
THYROID																				
Congestion																				
Hemorrhage, Follicle																				
Hypertrophy/Hyperplasia,																				
Follicular Cell	4	2	3	4	3	4	3	3	3	3	4	3	3	3						

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1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

	GROUP 4														
ANIMAL	139	150	157	168	175	185	196	203	214	221	232	239	250	257	267
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exfoliated Germ Cells, Lumen															
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Degeneration, Seminiferous Tubule															
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Congestion															
Hemorrhage, Follicle															
Hypertrophy/Hyperplasia, Follicular Cell															

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

GROUP
5

ANIMAL	140	149	158	167	176	186	195	204	213	222	231	240	249	258	266					
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Exfoliated Germ Cells, Lumen																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Degeneration, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Congestion																				
Hemorrhage, Follicle																				
Hypertrophy/Hyperplasia, Follicular Cell																				

EPL
Experimental Pathology Laboratories, Inc.

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

GROUP 6

ANIMAL	141	148	159	166	177	187	194	205	212	223	230	241	248	259	265					
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Exfoliated Germ Cells, Lumen															2					
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Degeneration, Seminiferous Tubule															1					
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Congestion																				
Hemorrhage, Follicle																				
Hypertrophy/Hyperplasia, Follicular Cell																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

GROUP
7

ANIMAL	142	147	160	165	178	188	193	206	211	224	229	247	260	264
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exfoliated Germ Cells, Lumen														
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Degeneration, Seminiferous Tubule														
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Congestion														
Hemorrhage, Follicle														
Hypertrophy/Hyperplasia, Follicular Cell														

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

	GROUP 8																		
ANIMAL	143	146	161	164	179	189	192	207	210	225	228	243	246	261	263				
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Exfoliated Germ Cells, Lumen																			
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Degeneration, Seminiferous Tubule																			
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Congestion																			
Hemorrhage, Follicle																			
Hypertrophy/Hyperplasia, Follicular Cell																			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

08055.001
Terminal Sacrifice
Male Rat

	GROUP 9																		
ANIMAL	144	145	162	163	180	181	190	191	208	209	226	227	244	245	262				
EPIDIDYMIS	X	X	X	X	X	X		X	X	X	X	X	X	X	X				
Exfoliated Germ Cells, Lumen							1												
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Degeneration, Seminiferous Tubule																			
THYROID	X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Congestion																			
Hemorrhage, Follicle		1																	
Hypertrophy/Hyperplasia, Follicular Cell																			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

COMPONENT #2

08055.001
Terminal Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 1

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
199	URINARY BLADDER	Multiple 1-3mm calculi	Intentionally Not Sampled
	URINARY BLADDER	Wall, thickened	Intentionally Not Sampled

08055.001
Terminal Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 2

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
152	THYROID	Left side, enlarged and darkened	Hypertrophy/Hyperplasia, Follicular Cell
170	THYROID	Slightly enlarged and darkened	Hypertrophy/Hyperplasia, Follicular Cell
173	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
	THYROID	Right side, slightly enlarged	Hypertrophy/Hyperplasia, Follicular Cell
	THYROID	Darkened	Hypertrophy/Hyperplasia, Follicular Cell
183	THYROID	Increased in size	Hypertrophy/Hyperplasia, Follicular Cell
198	THYROID	Enlarged, bilateral	Hypertrophy/Hyperplasia, Follicular Cell
201	THYROID	Increased in size	Hypertrophy/Hyperplasia, Follicular Cell
219	PROSTATE	Ventral and dorsolateral, reduced in size	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size, bilateral	Intentionally Not Sampled
	THYROID	Enlarged and reddened, bilateral	Hypertrophy/Hyperplasia, Follicular Cell
237	THYROID	Enlarged and reddened	Hypertrophy/Hyperplasia, Follicular Cell
252	THYROID	Enlarged	Hypertrophy/Hyperplasia, Follicular Cell
269	LUNG	Multiple foci	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 3

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
138	THYROID	Increased in size	Hypertrophy/Hyperplasia, Follicular Cell
151	THYROID	Enlarged, bilaterally	Hypertrophy/Hyperplasia, Follicular Cell
156	THYROID	Enlarged and red, bilaterally	Hypertrophy/Hyperplasia, Follicular Cell
169	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
	THYROID	Enlarged/reddened, bilateral	Hypertrophy/Hyperplasia, Follicular Cell
174	LIVER	Reduced in size	Intentionally Not Sampled
	THYROID	Enlarged and reddened, bilateral	Hypertrophy/Hyperplasia, Follicular Cell
184	THYROID	Enlarged and reddened, bilateral	Hypertrophy/Hyperplasia, Follicular Cell
197	LIVER	Appears mottled	Intentionally Not Sampled
	THYROID	Enlarged	Hypertrophy/Hyperplasia, Follicular Cell
202	THYROID	Enlarged and reddened, bilateral	Hypertrophy/Hyperplasia, Follicular Cell
	PITUITARY	Reduced in size	Intentionally Not Sampled
215	ADRENAL	Reduced in size, bilateral	Intentionally Not Sampled
	THYROID	Increased in size	Hypertrophy/Hyperplasia, Follicular Cell
220	ADRENAL	Reduced in size, bilateral	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 3

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
220 (cont)	THYROID	Increased in size, bilateral	Hypertrophy/Hyperplasia, Follicular Cell
233	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
	LIVER	Mottled	Intentionally Not Sampled
	THYROID	Enlarged	Hypertrophy/Hyperplasia, Follicular Cell
238	LIVER	Reduced in size	Intentionally Not Sampled
	ADRENAL	Reduced in size, bilateral	Intentionally Not Sampled
	KIDNEY	Reduced in size, bilateral	Intentionally Not Sampled
	THYROID	Enlarged and reddened	Hypertrophy/Hyperplasia, Follicular Cell
251	LIVER	Ventral, reduced in size	Intentionally Not Sampled
	PROSTATE	Dorsolateral, reduced in size	Intentionally Not Sampled
	THYROID	Enlarged and reddened	Hypertrophy/Hyperplasia, Follicular Cell
256	LIVER	Reduced in size	Intentionally Not Sampled
	ADRENAL	Reduced in size, bilateral	Intentionally Not Sampled
	THYROID	Enlarged and reddened	Hypertrophy/Hyperplasia, Follicular Cell

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Terminal Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 4

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
139	SEMINAL VESICLE	Reduced in size, bilateral	Intentionally Not Sampled
	PROSTATE	Ventral, reduced in size	Intentionally Not Sampled
196	SEMINAL VESICLE	Right, reduced in size	Intentionally Not Sampled
214	PROSTATE	Ventral and dorsolateral, reduced in size	Intentionally Not Sampled
232	SEMINAL VESICLE	Reduced in size, bilateral	Intentionally Not Sampled
	PROSTATE	Dorsal, reduced in size	Intentionally Not Sampled

08055.001
Terminal Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 5

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
149	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
158	SEMINAL VESICLE	Reduced in size, bilaterally	Intentionally Not Sampled
	PROSTATE	Ventral and dorsolateral, reduced in size	Intentionally Not Sampled
195	SEMINAL VESICLE	Reduced in size, bilateral	Intentionally Not Sampled
	PROSTATE	Ventral and dorsolateral, reduced in size	Intentionally Not Sampled
	PITUITARY	Reduced in size	Intentionally Not Sampled
204	SEMINAL VESICLE	Ventral/dorsolateral, with coagulating glands, reduced in size	Intentionally Not Sampled
231	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
240	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
249	PROSTATE	Ventral, reduced in size	Intentionally Not Sampled
258	SPLEEN	Enlarged white foci	Intentionally Not Sampled
	LUNG	Multiple reddened areas	Intentionally Not Sampled
	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

08055.001
Terminal Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 6

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
177	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
	PROSTATE	Dorsal, reduced in size	Intentionally Not Sampled
194	ADRENAL	Dark tan to brown in color	Intentionally Not Sampled
205	ADRENAL	Pale in color, both	Intentionally Not Sampled
212	ADRENAL	Slightly enlarged	Intentionally Not Sampled
223	KIDNEY	Right side, hydronephrosis	Intentionally Not Sampled
230	ADRENAL	Pale in color	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 7

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
160	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
178	ADRENAL	Enlarged	Intentionally Not Sampled
188	ADRENAL	Increased in size, bilateral	Intentionally Not Sampled
193	ADRENAL	Increased in size, bilateral	Intentionally Not Sampled
206	PROSTATE	Ventral and dorsolateral, reduced in size	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size, bilateral	Intentionally Not Sampled
	ADRENAL	Enlarged, bilateral	Intentionally Not Sampled
211	PROSTATE	Ventral, reduced in size	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
	ADRENAL	Increased in size, bilateral	Intentionally Not Sampled
224	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
229	SEMINAL VESICLE	Reduced in size, bilateral	Intentionally Not Sampled
	PROSTATE	Ventral, reduced in size	Intentionally Not Sampled
247	LUNG	Right, pinpoint foci	Intentionally Not Sampled
264	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
	ADRENAL	Left, increased in size	Intentionally Not Sampled

08055.001
Terminal Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 8

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
164	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
210	PROSTATE	Ventral and dorsolateral, reduced in size	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size, bilateral	Intentionally Not Sampled
246	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

08055.001
Terminal Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 9

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
163	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
181	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
	PROSTATE	Dorsal, reduced in size	Intentionally Not Sampled
208	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
226	PROSTATE	Ventral and dorsolateral, reduced in size	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size, bilateral	Intentionally Not Sampled
245	PROSTATE	Ventral, reduced in size	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled