Appendix II Histopathology Report

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

65U-08055.001.015.002(F)

ASSESSMENT OF PUBERTAL DEVELOPMENT AND THYROID FUNCTION IN JUVENILE FEMALE CD® (SPRAGUE-DAWLEY) RATS AFTER EXPOSURE TO SELECTED CHEMICALS ADMINISTERED BY GAVAGE ON POSTNATAL DAYS 22 THROUGH 42/43

65U-08055.001.015.0021(F)

EPL PROJECT NO. 237-004

PATHOLOGY REPORT

Submitted to

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Submitted by

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

October 28, 2003



EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

65U-08055.001.015.002(F)

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ASSESSMENT OF PUBERTAL DEVELOPMENT AND
THYROID FUNCTION IN JUVENILE FEMALE CD® (SPRAGUE-DAWLEY)
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ADMINISTERED BY GAVAGE ON
POSTNATAL DAYS 22 THROUGH 42/43

65U-08055.001.015.002(F)

EPL PROJECT NO. 237-004

NARRATIVE SUMMARY

INTRODUCTION

The objective of this study was to examine the sensitivity of pubertal assays to the effects of a wide variety of chemicals that are known to affect the endocrine system through different pathways and/or mechanisms of action. EPA has decided to test several chemicals in multiple-dose studies which may provide greater confidence in the reliability and relevance of the assays.

For this study, the following chemicals were tested: Atrazine, Fenarimol, Methoxychlor, Bisphenol A, Ketoconazole and Propylthiouracil. 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 female weanlings, for each of the two components.

The ovaries, uterus and thyroids were examined microscopically.

SUMMARY

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

 The presence and dose-related increased severity of cytoplasmic vacuolization of the ovarian corpora luteal cells in both the 50 and 100 mg/kg dosed Ketoconazole animals. In addition, the presence of ovarian hypoplasia in the 100 mg/kg dosed animals was observed.

- 2. The presence and dose-related increased severity of thyroid, follicular cell hypertrophy/hyperplasia in both the 2 and 25 mg/kg dosed Propylthiouracil animals.
- 3. The presence of ovarian hypoplasia in several 600 mg/kg dosed Bisphenol A animals.
- 4. The presence of minimal follicular cell hypertrophy in the thyroid glands of several of the 250 mg/kg dosed Fenarimol animals.
- 5. The presence of minimal epithelial hyperplasia within the uterus in several 50 mg/kg/day Methoxychlor animals.

DESIGN OF THE STUDY

Six test chemicals were administered via gavage once daily for 21-22 consecutive days (pnd 22 to pnd 42 or 43) to female CD[®] (Sprague-Dawley) rats under the study conditions outlined in the study protocol (RTI Master Protocol No.: RTI-830).

The study began with 15 weight-matched F1 females/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 Females	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	Corn Oil, Vehicle Control	0	0	5
2	15	Atrazine	75	15	5
3	15	-	150	30	5
. 4	15	Fenarimol	50	10	5
5	15	-	250	50	5
6	15	Methoxychlor	25	5	5
7	15	-	50	10	5

Component #2

Group	No. F1		Dose	Concentration	Dose Volume
No.	Females	Chemical	mg/kg/day	mg/ml	ml/kg
		Corn Oil,			
1	15	Vehicle Control	0	0	5
2	15	Bisphenol A	400	80	5
3	15	-	600	120	5
4	15	Ketoconazole	50	10	5
5	15	-	100	20	5
6	15	Propylthiouracil	2	0.4	5
7	15	-	25	5	5

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

Component 1 Component 2 Group

Table 2 - Treatment Group Designations

According to the study protocol, all F1 females were subjected to a complete necropsy with selected organs dissected and weighed. Protocol tissues were fixed in Bouin's fixative for 24 hours, after which they were rinsed and stored in 70% alcohol. Component #1 thyroids were fixed in Bouin's but this fixation made the later dissection of thyroids from the trachea and subsequent weighing procedures difficult because of the uniform yellow discoloration and tissue hardness. The Component #2 thyroids were fixed in 10% neutral-buffered formalin which facilitated the recognition and dissection of the thyroids from the trachea. 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: ovaries, uterine horns, 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). "Decidual Alteration" of the uterus was designated only as "Present".

RESULTS

The individual animal data are presented by group in the Histopathology Incidence Tables (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 in both control and treated animals. For the most part, these changes were typical of the spontaneous type of microscopic pathology that can be observed at this age and in this strain of rat. During the microscopic examination of ovaries, attempts to quantify the number of corpora lutea were not performed because of the variation that one may observe in any one cross-section of ovary. However, each ovary was examined for the presence of primary, growing and pre-ovulatory follicles.

The following chemicals were not associated with any treatment-related histopathologic changes: Component 1 = Atrazine (75 and 150 mg/kg), Fenarimol (50 mg/kg), and Methoxychlor (25 and 50 mg/kg); Component 2 = Bisphenol A (400 mg/kg).

TREATMENT-RELATED FINDINGS BY CHEMICAL

Fenarimol:

Exposure to Fenarimol (250 mg/kg) was associated with follicular cell hypertrophy of the thyroid gland. This lesion was characterized by a subtle increase in cell size, particularly in the height of the follicular lining cells. In addition, the lumen of affected thyroid follicles was slightly reduced in size and the amount and staining intensity of the thyroid colloid was less. The incidence and severity of follicular cell hypertrophy are presented in Table 3.

Table 3 – Incidence and Severity of Follicular Cell Hypertrophy – Fenarimol

Dose (mg/kg)	0	250
THYROID (No. Examined)	(15)	(15)
Hypertrophy, Follicular Cell	0	5
Minimal	0	5

As can be seen in the above Table, 5 out of 15 animals had minimal follicular cell hypertrophy. The toxicological or biological significance of this lesion is not clear since only 1/3 of the animals had hypertrophy and there was no apparent increased thyroid weight changes noted. However in this dose group, the level of thyroxine hormone (4) was decreased and thyroid stimulating hormone (TSH) was increased.



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Bisphenol A:

Exposure to Bisphenol A (600 mg/kg) was associated with the presence of ovarian hypoplasia in 3 out of 14 animals examined. Ovarian hypoplasia was characterized by the complete absence of corpora lutea (CL's) and an apparent reduction or absence of the large pre-ovulatory follicles (Graffian Follicles). Mild hypoplasia seemingly had fewer large follicles and with moderate hypoplasia no large pre-ovulatory follicles were observed. This appearance suggested that some inhibition or delay of follicle development and/or ovulation had occurred. Hypoplasia was used in this context since evidence of complete ovarian maturity and subsequent atrophy was not observed (Davis et al, 1999). According to the organ weight data, animals exposed to 400 and 600 mg/kg of Bisphenol A had lower ovary weights but also had significantly lower body weights.

It has been suggested that significantly reduced body weights, associated with chemical administration, may result in "stress" to the animal decreasing the frequency and amplitude of luteinizing hormone (LH) thus altering the reproductive cycle (Yuan et al, 2002). Although the small incidence of ovarian hypoplasia might have been associated with decreased body weights, it is not clear if other mechanisms might be involved as well.

Ketoconazole:

Exposure to 50 and 100 mg/kg of Ketoconazole was associated with cytoplasmic vacuolization of ovarian corpora luteal cells and ovarian hypoplasia in the 100 mg/kg dosed animals. Cytoplasmic vacuolization was characterized by the presence of clear, variably sized vacuoles within the cytoplasm of corpora luteal cells. Occasionally, small cytoplasmic vacuoles may be noted in some degenerating cells within normal corpora lutea, but the vacuoles in Ketoconazole-exposed animals tended to be larger and more dispersed within the corpora lutea. The severity of cytoplasmic vacuolization was graded according to a subjective evaluation based on the average number and size of the vacuolated cells in a corpora lutea (minimal = 6-25%; mild = 26-50%; moderate = 51-75%; and marked 76-100%). The pathogenesis of the vacuolization could not be determined but was thought to involve the alteration of steroid metabolism at the cellular level.

As previously mentioned, 5 out of 15 high-dosed animals also had mild ovarian hypoplasia which meant there were no corpora lutea present and subsequently, no cytoplasmic vacuolization to evaluate and grade.

The incidence and severity of corpora luteal cytoplasmic vacuolization and ovarian hypoplasia is presented in Table 4.

Table 4 – Incidence and Severity of Corpora Luteal Cytoplasmic Vacuolization and Ovarian Hypoplasia – Ketoconazole

Dose (mg/kg)	0	50	100
Animals (No. Examined)	(14)	(15)	(15)
Vacuolization Cytoplasmic,			
Corpora Luteum	0	12	9
Minimal	0	6	1
Mild	0	4	4
Moderate	0	2	3
Marked	0	0	1
Hypoplasia	0	0	5
Mild	0	0	5

According to the organ weight data, some evidence of decreased ovarian weight was apparent in the 100 mg/kg dosed animals. This may be related to the ovarian hypoplasia seen at this dose level. However, the apparent cytoplasmic vacuolization apparently did not result in any ovarian weight change.

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 pale staining colloid and/or the reduction or absence of colloid within some 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 5.

Table 5 – Incidence and Severity of Thyroid Hypertrophy/Hyperplasia – Propylthiouracil

Dose (mg/kg)	0	2	25
Animals (No. Examined)	(14)	(15)	(15)
Hypertrophy/Hyperplasia	0	15	15
Minimal	0	1	0
Mild	0	13	2
Moderate	0	1	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).

Methoxychlor:

Administration of Methoxychlor was associated with the presence of epithelial hyperplasia of the uterine epithelium.

In control animals, the uterine surface epithelial lining was characterized by having a single layer of columnar cells with a cytoplasmic to nuclear ratio of around 1.5. The height and presence of vacuolar to necrotic changes and the presence of inflammatory cells depended upon the stage of the estrous (reproductive) cycle. In addition, mitotic figures were common in the estrous portion of the cycle (Yuan and Foley, 2002).

In the 50 mg/kg/day dosed group, some animals had changes of the uterine surface epithelium that were diagnosed as epithelial hyperplasia. In these cases, the lining epithelium was generally diffusely affected. This change was characterized by taller columnar cell height and nuclear crowding indicative



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of more cells. In addition, these cells tended to have more cytoplasm (hypertrophy) which appeared lightly basophilic. Mitotic figures were occasionally noted, however, vacuolar to necrotic changes normally associated with the estrous cycle were not observed.

All cases of epithelial hyperplasia were diagnosed as minimal which was a change barely detectable.

The appearance of the lesion suggested a hormonal imbalance as a possible mechanism.

The incidence and severity of uterine epithelial hyperplasia is presented in Table 6.

Table 6 – Incidence and Severity of Uterine Epithelial Hyperplasia – Methoxychlor

	Dose (mg/kg)	0	25	50
Animals (No. Examined)		(15)	(15)	(15)
Hyperplasia, Epithelial		0	0	5
	Minimal	0	0	5

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Senior Pathologist

October 28, 2003

Date



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Yuan Y-D, et al. Female Reproductive System. In. <u>Handbook of Toxicologic Pathology (2nd Ed).</u> Haschek WM, Rousseaux CG, Wallig MA (Eds). Academic Pres, Chapter 43, 2002.

Study Design

Component #1

Group No.	No. F1 Females	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg
1	15	Corn oil, Vehicle Control	0	0	5
2	15	Atrazine	75	15	5
3	15	-	150	30	5
4	15	Fenarimol	50	10	5
5	15	-	250	50	5
6	15	Methoxychlor	25	5	5
7	15	-	50	10	5

SUMMARY INCIDENCE TABLES COMPONENT #1

SUMMARY INCIDENCE TABLE

N/A F1 Sacrifice Female Rat

	GROUP	GROUP	GROUP	GROUP	GROUP	GROUP
	1	2	3	4	5	6
OVARY (NO. EXAMINED)	(15)	(15)	(15)	(15)	(15)	(15)
Cyst, Follicle	1	1		1		
Cyst, Luteal	1	1			2	
Hypoplasia					1	
THYROID (NO. EXAMINED)	(15)	(15)	(15)	(15)	(15)	(15)
Hypertrophy, Follicular Cell					5	
Inflammation, Chronic						
HERRING (NO. BYANTIER)	(15)	(15)	/75\	(15)	(15)	(15)
UTERUS (NO. EXAMINED)	(15)	(15)	(15)	(15) 1	(15)	(15)
Decidual Alteration			1	_		
Hemorrhage, Endometrium						
Hyperplasia, Epithelium		-				
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SUMMARY INCIDENCE TABLE

N/A F1 Sacrifice Female Rat

	GROUP				
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OVARY (NO. EXAMINED)	(15)				
Cyst, Follicle					
Cyst, Luteal					
Hypoplasia					
THYROID (NO. EXAMINED)	(15)	 			
Hypertrophy, Follicular Cell		 			
Inflammation, Chronic	1	 			
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UTERUS (NO. EXAMINED)	(15)				
Decidual Alteration	(±3)				
Hemorrhage, Endometrium	1	 			
Hemorriage, Endometrium	5				
Hyperplasia, Epithelium	, , , , , , , , , , , , , , , , , , ,				
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HISTOPATHOLOGY INCIDENCE TABLES COMPONENT #1

GROUP

1 N/A F1 Sacrifice Female Rat 1 9 9 0 2 6 6 7 1 2 3 4 5 2 3 6 7 0 1 4 5 8 9 8 9 OVARY X Χm X Х X X X Х X X X X X Cyst, Follicle 2 Cyst, Luteal 1 Hypoplasia THYROID X Xm X X Xm X Х X X X X X X Х X Hypertrophy, Follicular Cell Inflammation, Chronic X X Χ Х X X X Х X X X X UTERUS X X X Decidual Alteration Hemorrhage, Endometrium Hyperplasia, Epithelium

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Cyst, Luteal							1				×4.					-				
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Inflammation, Chronic													100		79 J.1 45 4.2					
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Hyperplasia, Epithelium				900															1	
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Cyst, Luteal																	N. S. S. S.			
Hypoplasia				2.5								F. 3 9					95,8			
									100											
THYROID	X	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х					
Hypertrophy, Follicular Cell						RO									54.39					
Inflammation, Chronic						2.0	130 N 53 / 2													
						73.5														4
UTERUS	X	X	X	X	X	X	X	X	X	X	X	X	X		X					
Decidual Alteration														P						
Hemorrhage, Endometrium		100	Synd		1.2										- 1					
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Cyst, Follicle Cyst, Luteal Hypoplasia	1																	
THYROID Hypertrophy, Follicular Cell	x	X	X	X	Х	X	X	X	X	X	X	X	X	Х	X			
Inflammation, Chronic							1833 S 1838 S									1000		
UTERUS Decidual Alteration	P	X	X	X	X	X	X	X	Х	X	X	Х	Х	X	X			
Hemorrhage, Endometrium Hyperplasia, Epithelium																		
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GROUP 5

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THYROID	X	X	X	Х	Х	Х	Х			X			X	4.1 %	Х					
Hypertrophy, Follicular Cell								1	1		1	1	22.0	1						
Inflammation, Chronic			13.17					To the						Y	5					T
																8-50				
UTERUS	X	Х	X	Х	Х	X	X	Х	X	X	Х	Х	X	Х	Х		200	100 P		
Decidual Alteration	1^		4	A		- - 4 \-	-23	41	# .	** >		-1	4.	41		1 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5			100 m	1
		1 5.32 25.42	11000		3,14			1000						4				1 N N N N N N N N N N N N N N N N N N N	- 88,56 10,633	
Hemorrhage, Endometrium					10 A NO.										2.525					#
Hyperplasia, Epithelium		\$165 () \$465 ()	12-45		50.5	1135									(A. (4.4) S. (4.4)	19,40°5.		3,300	104 TS	
			1											389	4-1				100	
									1.50								1,0	1.53		
												TAMES STATES		4				1		
											# Y.		10.4		Mary 1			100		
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		44					la de la													
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		1												5 50 41		51.2				+
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GROUP 6

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N/A F1 Sacrifice Female Rat A N																				
Å L	6	9	2 0	3	2	4 0	4 3 X	5 4 X	5 7 X	6 8 X	7 1 X	8 2 X	8 5 X	9 6 X	9 9 X					
OVARY	X	X	X	X	X	Х	Λ	Λ	Λ		Λ	Λ	Δ	Λ	Α	10000 10000				
Cyst, Follicle Cyst, Luteal Hypoplasia																				
THYROID	Х	Х	X	Х	Х	Х	X	X	Х	X	X	Х	X	X	X					0.1
Hypertrophy, Follicular Cell								1						100						
Inflammation, Chronic												275	7 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4							
		1.5		•••						4,		4,		1	47					-
UTERUS	X	X	X	X	X	X	X	Х	Х	X	Х	X	Х	X	Х		(1) (4) (4) (4) (4) (4)			-
Decidual Alteration								1,4 ± 5 1,5 ± 5					134. hr 34 km²	APPLE Y	1. 2. \$40 31 - 37		11,41 L			
Hemorrhage, Endometrium Hyperplasia, Epithelium																		45.00		+
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GROUP

시대하다 나는 이 사는 병사 방법이 살아 있다니까?						-, . <u></u>		7		 	<i>i</i>	1 1 1		1				99.6		
N/A																				
F1 Sacrifice Female Rat																				
remale kat																				
경영화 (1985년 - 1985년 - 																				
했다. 경기 내가 가는 사람이 모르는 나를 다 다 없다.															1					
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	7	8	1	2	1	2	5	6		0	3		7	8	5				5	
OVARY	X	X	X	X		X	X	X	X	X	X	Х	Х	X	X					
Cyst, Follicle	1	21	41	43	2011															
Cyst, Luteal																				H
Hypoplasia	1			1. The state of th	75 X										1 1 4					
THYROID	X		Х	Х	Х	Х	X	Х	Х	Х	Х	X	Х	Х	Х			11		
Hypertrophy, Follicular Cell							7.	15.5		177										
Inflammation, Chronic		1				27 (CA) 24 (A)			100											
																17.	715			
UTERUS	X			X			X	X	X	X	X	Х	Х							
Decidual Alteration																				
Hemorrhage, Endometrium			1.00) - 1 (38) 1 - 1 (38)	77.3			1					. 7s	
Hyperplasia, Epithelium		1	1		1	1			1.19	1					1					
										100										
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						100														
														15.75%			1 4			F
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			1000	A 100 100 100 100 100 100 100 100 100 10	100							1 0 15 16	40 (0.00)	47.00	 E. S. C. C. 	Life 1	4100 TO \$	4 00 2 3 00	1878 S. S.	
											N 3.75					7.6				t
																	10.000			

Key:X=Not Remarkable N=No Section I=Incomplete A=Autolysis I=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 #1

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

		Do	Do	Do	Do	D.	p.e.	p.c.	D.C.	D	DG.	D 5	PS.	Do.	Dig.	P.C.
	n mpled															
nled																
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illed ide hv	? }			The second secon												
Fluid filled	Right s															
E4	<u>&</u>															
	RUS VEY															
	UTERUS															
Number	63 90															

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat	t.	Sex. Females Group!	Group Identification: 2
Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
103	UTERUS	Fluid filled - clear	No Correlating Lesion

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

1											
Microscopic Observations	No Comment Required	Decidual Alteration	Intentionally Not Sampled								
Client Gross Observations	Pulled apart above cervix (2 sections)	Right horn, cyst 5mm in diameter	Right, hydronephrosis								
Client Topography / Site	UTERUS	UTERUS	KIDNEY								
Animal Number	51	63	102								

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat	.	Sex. Females Groupl	Group Identification: 4
Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
,	UTERUS	Uterine horn, right, cysts, two (solid), 3mm in diameter	Cyst, Follicle (OVARY)
25	UTERUS	Fluid filled	No Correlating Lesion
4.5	UTERUS	Fluid filled - clear	No Correlating Lesion
52	KIDNEY	Bilateral, hydronephrosis	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

Microscopic Observations	No Correlating Lesion	Intentionally Not Sampled	d No Correlating Lesion	No Correlating Lesion	No Correlating Lesion	No Correlating Lesion							
Client Gross Observations	Fluid filled	Bilateral, hydronephrosis	Right horn, 1/2 of length, reduced in size	Left side, fluid filled	Fluid filled	Fluid filled							
Client Topography / Site	UTERUS	KIDNEY	UTERUS	UTERUS	UTERUS	UTERUS							
Animal Number	33	29	72		8.6	56							

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations	
	UTERUS	Uterine horns, fluid filled	No Correlating Lesion	
	LUNG	Congested oil present - probable aspiration of dosing suspension	Intentionally Not Sampled	
	UTERUS	Fluid filled	No Correlating Lesion	
	KIDNEY	Left, hydronephrosis	Intentionally Not Sampled	

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

Animal Number	Client Topography/Site	Client Gross Observations	Microscopic Observations
8	UTERUS	Fluid filled	No Correlating Lesion
21	UTERUS	Fluid filled	No Correlating Lesion
22	UTERUS	Fluid filled	No Correlating Lesion
41	UTERUS	Fluid filled - clear	No Correlating Lesion
69	KIDNEY	Bilateral, hydronephrosis	Intentionally Not Sampled
70	UTERUS	Fluid filled	No Correlating Lesion
1.05	UTERUS	Fluid filled - clear	No Correlating Lesion

Study Design

Component #2

Group No.	No. F1 Females	Chemical	Dose mg/kg/day	Concentration mg/ml	Dose Volume ml/kg	
1	15	Corn oil, Vehicle Control	0	0	5	
2	15	Bisphenol A	400	80	5	
3	15		600	120	5	
4	15	Ketoconazole	50	10	5	
5	15		100	20	. 5	
6	15	Propylthiouracil	2	0.4	5	
7	15	·	25	5	5	

SUMMARY INCIDENCE TABLES COMPONENT #2

SUMMARY INCIDENCE TABLE

N/A F1 Sacrifice Female Rat

	GROUP	GROUP	GROUP	GROUP	GROUP	GROUP
	1	2	3	4	5	6
VARY (NO. EXAMINED)	(14)	(11)	(14)	(15)	(15)	(15)
Cyst, Luteal				1		
Hypoplasia			3		5	
Vacuolization Cytoplasmic,				10	9	
Corpus Luteum				12	.	
THYROID (NO. EXAMINED)	(13)	(11)	(14)	(15)	(15)	(15)
Hypertrophy/Hyperplasia	(13)	3++/	(+97)	(12)		15
Inflammation, Chronic	1 1	1 2 2				
IIII Fannac LVII, VIII VIII						
JTERUS (NO. EXAMINED)	(14)	(11)	(14)	(15)	(15)	(15)
Dilatation, Lumen, Unilateral	1					
Hemorrhage, Endometrium						1
Hyperplasia, Epithelium				1		
Hypoplasia			1			
						1
		4				
	41 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	7. [15. 15. 15. 15 15 15 15 15 15 15 15 15 15 15 15 15	기 : 11			
		(4) 12 14 14 15 15 16 16 16 16 16 16 16 16 16 16 16 16 16				
들어 이번 경험에 가장 그렇게 되었다. 이 경험에 가장 보고 있는 것이 되었다. 그런 것이 되었다. 						
		1. 15 15 15 15 15 15 15				
		1 1 1 1 1 1 1 1 1 1				
는 사용적으로 현실 전 경기를 가려면 보고 있습니다. 그는 사람들은 사용적으로 함께 되었습니다. [2] 전 10 전 1				1		
					<u> </u>	<u> </u>

SUMMARY INCIDENCE TABLE

N/A F1 Sacrifice Female Rat

	GROUP 7				
OVARY (NO. EXAMINED)	(15)				
Cyst, Luteal					
Hypoplasia					
Vacuolization Cytoplasmic,					
Corpus Luteum	· 원기 및 기계설				
THYROID (NO. EXAMINED)	(15)				
Hypertrophy/Hyperplasia	15				
Inflammation, Chronic					
TERUS (NO. EXAMINED)	(15)				
Dilatation, Lumen, Unilateral	1				
Hemorrhage, Endometrium					
Hyperplasia, Epithelium	1		h i 15. st. 50 128 15. s Taran katangan		
Hypoplasia				1.6.15 1.151(1);1.564 2.161(1) 1710 2.161(1)	
	1 12 13 14 15 15 15 15 15 15 15				
경우 현실 교육 시간 경우는 경우 전환 경우 전환 전환 등 기계 등 경우 전환 경우 전환 경우 기계 등 기계 등 경우 기계 등 기계	14 (14 원) 는 12 (14 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2				
경기 전환 경기 및 경기 전로 전시 경기 전 시간 시간 경기 보다 하는데 있다. 그 것은 다시 경기 전략 경기 전략 기업 경기 전기 기업 전략 기업 기업 전략 기업		21, 5, 2000 10 44 44 45 10 50 17 4 4 17 4 17 4 17 17 17 17 17 17 17 17 17 17 17 17 17			
등 경기 등 하는 것으로 하고 있는 것이 되었다. 					
등 등 사용하다 경우 등 경우 등 사용하는 것이 되었다. 그는 사용하는 것이 되었다. 그는 것이 되었다. 그는 것이 되었다. 그는 것이 되었다. 	일 <mark>. 라마마하다 하시다 : 함께</mark> 제 대원 : 한 기 리 교육 스타트				
경기 사용을 받았다. 이 경기 등을 보는 것이 되었다. 그런 경기 가장 등을 받는 것이 되었다. 기계 기계 기					
선생이 12 항상 경우는 전 경우에 남편하는 것이 있는 항상 수 있습니다. 그런 것은 것이 되었습니다. 12 강기 기본 경우를 살아왔다는 것이 되었습니다.					
					C.

EPL								
	Ex	nerir	nent	al Pat	tholog	v Lab	oratori	es. Inc

HISTOPATHOLOGY INCIDENCE TABLES COMPONENT #2

GROUP 1

[불명보고] 한 마음 사람들이 되었다. 그 집에 없는 이번 없는			2.33	11.24.112	<u> </u>	<u> </u>	1	10.00						5.75						
N/A															3-4					
F1 Sacrifice												12, 8								
Female Rat A																				
	1	1	2	3		4	5	5	7	7	8	8	9	9						
경우 경우 경우 전환	4	5	8	0	3	4	7	8	1	2	5	6	б	7		A and	4,2			
OVARY	X	X	X	X	Xm	X	X	X	X	X	Х	X	Х	X						
Cyst, Luteal				100																
Hypoplasia																				
Vacuolization Cytoplasmic,																				
Corpus Luteum						W45						e great								
										-757										
THYROID	X	X	Х	Х	Х	Х	Х		Х	Х	Х	Х	X	N						
Hypertrophy/Hyperplasia											No.	. T. Y.								K
Inflammation, Chronic		Fix						1												
										7										
UTERUS	Х	Х	Х	Х	Х	X	Х	Х	Х	Х	X	Х	Х		2					T
Dilatation, Lumen, Unilateral		1 3 3									100			2						
Hemorrhage, Endometrium																				Ĭ.
Hyperplasia, Epithelium													1000		5349			120 03		1
Hypoplasia					7 178 71 (1.15)								1.3		13.50 mg/					
			13.5			100	A	All IA II Friday II												
		1		1947		10 (10 kg) 10 (10 kg)				7.5		70.11		200 (A)				1,00		1.00
성 전경 (1) 전 경영 (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)		/ 1995 199 / 1915 1915	13971 15972	1877 S.									110.1	2 W 1 W 92			2.2	100	43.0	+
는 생물하는 경험을 되었다. 경우 사람들은 마이트를 모르는 데이터를 모르는 것이 되었다. 그렇게 되었다. 그렇게 되었다. 												1916.3				7.58			2014	
는 사람들이 살아 있다. 그리고 말이 되었습니다. 그 사람들은 그리고 있다면 되었습니다. 그 사람들은 그리고 있는데 그리고 있다는 것이다. 그리고 있다는 것이다. 그리고 있다는 것이다. 그리고 있다 그리고 있는데 그리고 있다면 보다는 것이 되었습니다. 그리고 있는데 그리고 있는데 그리고 있다면 보다는 것이다. 그리고 있다는데 그리고 있다면 그리고 있다. 그리고 있다는데 그리고 있다. 그리고 있							, legita M Banayan			150.45	1 - 3 Geo.		14 - 61 1 5 - 61 1 1						111.00°	
			4.32							96 (A) 1872 - 1					1898	1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2			1.43	+
		36 (A)	100	1466 E.S.	7572 Y 11 23 X X	A A	6			1000 A	1.753 1.154	7-1.30		8,530-5 3,530-5		Mark.	(2.05%) (3.74%)		350	╁
						100	100 m					27.E				100			Market Right A	+
					10.7%	4.4						14 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	13438 10038		1284A					1
				Service of						1	1000									
																[2/26]				1
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		ļ														100				
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		423											1.50							L
					<i>V</i> . 3													4.5		1
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[2017] [2017] [2017] [2017] [2017] [2017] [2017] [2017] [2017] [2017] [2017] [2017] [2017] [2017] [2017]	A 10 10 10 10 10 10 10 10 10 10 10 10 10	4 7 7 7 7	1000									10.00	13.0					3710		3 75
			1.5	1	130.61	100	142 45 5	4.3550	1.000	100000	G2 164	130-11	1000	100		2000	1 50000	12,5200	100	100
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GROUP

[일일: 12] [12] [12] [12] [12] [12] [12] [12]	4 <u>4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 </u>				in the part of the	2								# 74						
N/A														BA.						
F1 Sacrifice								1 \$140.00 10 141613												
Female Rat A								14 4 7 14 4 7							- X.,					
[유명] : [1] :												1 J. N. 18			105					
: 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1																15.00			1443	
: [1] - [1] - [1] - [2]																				
		1	3	4	4	5	7	7	8	9	9						4.4%			
	2	3	1	2	5		0	3	4	5	8									
OVARY	X	X	X			X	X	X	X		Х									14-94
Cyst, Luteal		1			- 21	- 43	23								1,000					
Hypoplasia		-				1000											and sign		3., 4.7	1
Vacuolization Cytoplasmic,							74.5		1 4 2 3 2 4 2 3											
	18 (4.36) Vale (1.56)							La gela Ta						3, 8, 7 7 (2)	Alvata Elstini,			<u>), 21%.</u> 기하자	253	
Corpus Luteum					19-24-5 18-34-5			200									881212 1889 94	10 3/11 7 19 3.		
			ļ.,-	1 8 Y S	4,	47	17	17	w	70	*0"					1.837	3000	25.55	4.96	+
THYROID	X	X	X	1600	Х	X	X	X	X	X	X			JANES						
Hypertrophy/Hyperplasia				150%	538.									1350) 1383)						13
Inflammation, Chronic				1							15.0					1900AC				1
							1000							7 V (A)						
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Hypertrophy/Hyperplasia																		73.5		
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Inflammation, Chronic															10559					
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Hemorrhage, Endometrium															19-19					
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Cyst, Luteal																			
Hypoplasia																			
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Corpus Luteum					y 1.11														
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THYROID													4						
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EPL Experimental Pathology Laboratories, Inc.

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

GROUP 7 N/A F1 Sacrifice Female Rat N M A 1 1 9 0 0 6 7 2 3 1 2 6 7 0 1 4 5 8 9 2 2 3 8 X X X Х Xm X X X OVARY X X Xm X X X Cyst, Luteal Hypoplasia Vacuolization Cytoplasmic, Corpus Luteum THYROID 3 2 Hypertrophy/Hyperplasia 2 3 3 3 3 3 4 3 4 4 3 4 3 Inflammation, Chronic X X X X X X X X X Х UTERUS X X X Dilatation, Lumen, Unilateral 1 Hemorrhage, Endometrium Hyperplasia, Epithelium 1 Hypoplasia

EPL							
	Exp	erime	ntal P	athol	ogy La	borato	ries, Inc.

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES COMPONENT #2

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

Group Identification:

Microscopic Observations Intentionally Not Sampled Intentionally Not Sampled Intentionally Not Sampled Client Gross Observations Right, hydronephrosis Right, hydronephrosis Right, hydronephrosis Client Topography / Site KIDNEY KIDNEY KIDNEY Animal Number 85 86 57

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
12	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
77	KIDNEY	Left, hydronephrosis	Intentionally Not Sampled
74	KIDNEY	Bilateral, hydronephrosis	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Scx: Females

															コンドーラング 一番を記す
Microscopic Observations	Intentionally Not Sampled														
Client Gross Observations	Pale in color	Pale in color	Bilateral, hydronephrosis	Pale in color	Both, hydronephrosis	Bilateral, enlarged	Enlarged	Pale	Enlarged and pale	Enlarged					量の きょう しょうき ちゅうきき カラ・シャス ワーハー・ハンド すってい タイル マジギ 好きのなる 気を吹き 海の後 好ない あた ないのかな
Client Topography / Site	ADRENAL	ADRENAL	KIDNEY	ADRENAL	KIDNEY	ADRENAL	ADRENAL	ADRENAL	ADRENAL	ADRENAL					多年的一次通常的经验 医克洛氏病 计记录 人名 化二氯化物 医多种神经 医多种 医二甲酚二甲酚 经非常的经济的 医乳腺学院
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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females Group Identification: 5

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
3.9	ADRENAL	Bilateral, increased in size	Intentionally Not Sampled
87	ADRENAL	Bilateral, increased in size	Intentionally Not Sampled
53	ADRENAL	Enlarged	Intentionally Not Sampled
62	ADRENAL		Intentionally Not Sampled
105	ADRENAL	Both, pale and gray in color	Intentionally Not Sampled
N.			

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

	Client Gross Observations	Microscopic Observations
	Right, hydronephrosis	Intentionally Not Sampled
100	Right, hydronephrosis	Intentionally Not Sampled
	Bilateral, hydronephrosis	Intentionally Not Sampled
Company of		

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat

Sex: Females

Microscopic Observations	Hypertrophy/Hyperplasia	Hypertrophy/Hyperplasia	Dilatation, Lumen, Unilateral	Intentionally Not Sampled	Intentionally Not Sampled							
Client Gross Observations	Reddened and enlarged	Bilateral, increased in size	Fluid filled	Bilateral, hydronephrosis	Right, pale and mishaped - polycystic							
Client Topography / Site	THYROID	THYROID	UTERUS	KIDNEY	KIDNEY							
Animal Number	37	50	92	79	102							

EXPERIMENTAL PATHOLOGY LABORATORIES, INC. QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Assessment of Pubertal Development and Thyroid Function in Juvenile Female CD[®] (Sprague-Dawley) Rats After Exposure to Selected Chemicals Administered by Gavage on Postnatal Days 22 Through 42/43

Client Study: RTI Contract 65U-08055.001.015.002(F) EPL Project Coordinator: Dr. John Curtis Seely

EPL Project Number: 237-004 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.

중에게 함께 되는데 하는데 모르다 그래?	BALINAN, AND THE CONTROL OF THE BALINAN AND THE SECOND SEC	
Area Inspected	Inspection	Reporting
EPL Project Sheets	October 7, 2002;	October 7, 2002;
	January 13, 2003;	January 13, 2003;
	May 30, 2003	May 30, 2003 ∴
Project Setup	October 28, 2002;	October 28, 2002;
	January 8, 2003	January 8, 2003
Histology Setup	October 28, 2002;	October 28, 2002;
	January 14, 2003	January 14, 2003
Data Review	December 17, 2002;	December 17, 2002;
	February 18, 2003	February 18, 2003
Phase/Data Review	November 25, 2003;	November 25, 2003;
	December 11, 2002;	December 11, 2002;
	January 14, 2003;	January 14, 2003;
	January 20, 2003;	January 20, 2003;
	February 18, 2003	February 18, 2003
Draft Report	June 12&13, 2003	June 13, 2003
Final Report	October 24, 2003	October 24, 2003

EPI Quality Assurance Unit

October 28, 2003