

Table 7-2

Twenty-eight-day repeat dose oral toxicity study of ethinylestradiol in rats

Relative organ weights in females

Group	Body weight	Liver	Kidneys	Adrenal glands	Pituitary gland	Thyroid gland	Uterus	Ovaries
	(g)	(mg/g)	(mg/g)	(mg/g)	(mg/g)	(mg/g)	(mg/g)	(mg/g)
Control	10	10	10	10	10	10	10	10
	267.0	36.429	6.538	0.233	0.052	0.043	1.413	0.316
3 μ g/kg	10	10	10	10	9	10	10	10
	261.9	37.153	6.712	0.246	0.048	0.046	1.485	0.328
12 μ g/kg	10	10	10	10	10	10	10	10
	257.2	39.020	6.741	0.283*	0.052	0.051	1.543	0.315
48 μ g/kg	10	10	10	10	10	10	10	10
	248.0	39.573*	6.876	0.307**	0.054	0.055**	1.515	0.328
	15.7	3.060	0.619	0.060	0.005	0.009	0.186	0.073

Parameter, number of animals

mean

S.D.

*, significantly different from control, $p < 0.05$ **, significantly different from control, $p < 0.01$

Table 8-1
 Twenty-eight-day repeat dose oral toxicity study of ethinylestradiol in rat
 Summary of macroscopic findings in males

Group Grade	Control		3 $\mu\text{g}/\text{kg}$		12 $\mu\text{g}/\text{kg}$		48 $\mu\text{g}/\text{kg}$		
	-	+	-	+	-	+	-	+	
(Testis)	[10]	9	[10]	10	[10]	0	[10]	10	0
(Epididymis)	[10]	9	[10]	10	[10]	0	[10]	10	0
(Prostate)	[10]	10	[10]	10	[10]	0	[10]	10	0
(Lung)	[10]	10	[10]	7	[10]	3	[10]	6	4
(Liver)	[10]	10	[10]	10	[10]	0	[10]	9	1
(Adrenal gland)	[10]	10	[10]	10	[10]	0	[10]	9	1
		10		10		0		9	1
		10		10		0		8	2
		10		10		0		8	2

- , negative; + , positive
 []. Number of animals examined

Table 8-2
 Twenty-eight-day repeat dose oral toxicity study of ethinylestradiol in rat
 Summary of macroscopic findings in females

Group Grade	Control		3 µg/kg		12 µg/kg		48 µg/kg	
	-	+	-	+	-	+	-	+
(Lung)	[10]	9	[10]	10	[10]	10	[10]	10
Spot, dark red	[10]	1	[10]	0	[10]	0	[10]	0
(Kidney)		10		9		10		10
Dilatation, renal pelvis		0		1		0		0

-, Negative; +, Positive
 [], Number of animals examined

Table 9-1
Twenty-eight-day repeat dose oral toxicity study of ethylhexylradical in rats
Summary of histopathological findings in males

Group	Control				3 µg/kg				12 µg/kg				48 µg/kg				Pos		
	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	
(Testis)	[10]	8	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Atrophy seminiferous tubule																			
Multinucleated giant cell in seminiferous tubule		9	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Macrosome Leydig cell, diffuse		8	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1
(Epididymis)	[10]	9	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Decrease sperm in lumen		9	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Cellular debris in lumen (epididymis)		8	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1
(Uterus)	[10]	3	2	3	2	0	0	2	0	4	2	5	2	1	0	0	0	0	4
Myometrial infarction																			
Cellular infiltration, lymphocyte and plasma cell (serpiginous vessels)	[10]	7	3	0	0	0	0	0	0	2	7	3	0	0	0	0	0	0	2
(Spleen)	[10]	9	1	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	0
Atrophy with decreased secretion (adrenal gland)																			
Hypertrophy cortical cell (kidney)	[10]	10	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	8 ##
Eosinophilic body		9	1	0	0	0	0	0	0	1	8	1	1	0	0	0	0	0	1
Basophilic tubule, cortex		4	6	0	0	0	0	0	0	6	4	6	0	0	0	0	0	0	6
Cyst, cortical-medullary junction		9	1	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	0
Dilatation renal pelvis		10	0	0	0	0	0	0	0	1	10	0	0	0	0	0	0	0	0
Fibrosis, with infiltration lymphocyte focal subcapsule (liver)	[10]	10	0	0	0	0	0	0	0	0	9	1	0	0	0	0	0	0	0
Necrosis, focal (spleen)	[10]	10	0	0	0	0	0	0	0	1	9	1	0	0	0	0	0	0	1
Hematomas extramedullary		0	6	4	0	0	0	0	0	10	0	5	5	0	0	0	0	0	10
Deposit pigment, brown (lung & bronchus)	[10]	0	9	1	0	0	0	0	0	10	0	9	1	0	0	0	0	0	10
Accumulation foam cell, cellular infiltration, eosinophil		4	6	0	0	0	0	0	0	4	4	6	0	0	0	0	0	0	7
Mineralization artery		7	3	0	0	0	0	0	0	1	9	1	0	0	0	0	0	0	2
Hemorrhage focal		9	1	0	0	0	0	0	0	1	7	3	0	0	0	0	0	0	1
Mineralize osseous (heart)		8	1	0	0	0	0	0	0	2	7	3	0	0	0	0	0	0	3
Mycocardial degeneration/fibrosis focal (pituitary gland)	[10]	10	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	2
Dilatation, trabeculae cleft (stomach)	[10]	10	0	0	0	0	0	0	0	0	8	1	1	0	0	0	0	0	0
Granulation tissue, bands		9	1	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	0

- Necrosis, 2 Very slight, 3 Slight, 4 Moderate, 5+ Severe, Pos., Total of positive animals
 [] Number of animals examined
 ** Significantly different from control p<0.01 (Two-tailed Mann-Whitney U test)
 ## Significantly different from control p<0.01 (One-tailed Fisher exact test)

Table 9-2
Twenty-eight day repeat dose oral toxicity study of ethinylloestradiol in rats
Summary of histopathological findings in females

Group	Control		3 µg/kg		12 µg/kg		48 µg/kg		Pos							
	n	Pos	n	Pos	n	Pos	n	Pos								
(Ovary)	10	0	10	0	10	0	8	1	0	0	0	0	0	0	0	2
Decrease corpus luteum																
Hypertrophy, luteal cell, corpus luteum	10	0	10	0	10	0	9	0	1	0	0	8	1	1	0	0
Increase atresia follicle	10	0	9	0	9	0	8	1	1	0	0	8	1	1	0	0
Mineralization, degenerated oocyte	10	0	7	3	7	0	10	0	0	0	0	10	0	0	0	0
(Uterus: Horn & Cervix)																
Hypertrophy, diffuse, luminal epithelium	10	0	10	0	10	0	9	0	1	0	0	8	0	2	0	0
Hypertrophy, endometrium & myometrium	10	0	10	0	10	0	9	0	1	0	0	5	3	2	0	0
Mitosis, luminal epithelial cell	1	1	0	4	5	1	0	3	3	4	0	0	5	3	2	0
Vacuolation, with cell debris, luminal epithelium	0	9	0	8	2	0	1	7	2	0	0	1	4	3	2	0
Vacuolation, with cell debris, glandular epithelium	0	10	0	8	0	0	3	6	1	0	0	2	6	2	0	0
Cellular infiltration, eosinophil endometrium & myometrium	0	0	0	2	6	2	1	0	6	3	0	2	1	3	3	1
(Vagina)																
Cornification, epithelium	7	2	6	3	1	0	10	0	0	0	0	10	0	0	0	0
Mucification, epithelium	10	0	9	0	1	0	9	0	0	1	0	7	1	1	0	0
Cellular infiltration, neutrophil epithelium	2	6	2	4	3	2	4	3	2	1	0	6	1	5	2	2
(Adrenal gland)																
Hypertrophy, cortical cell	10	0	10	0	10	0	6	3	1	0	0	4	1	5	4	0
(Thyroid gland)																
Ectopic thymic cell	8	1	9	1	0	0	9	1	0	0	0	1	0	0	0	0
(Mammary gland)																
Hypertrophy, acinar cell (Lung & Bronchus)	10	0	10	0	0	0	9	0	1	0	0	1	0	0	0	2
Accumulation foam cell	5	3	8	2	0	0	4	8	0	0	0	6	5	0	0	0
Mineralization artery	10	0	10	0	0	0	6	4	0	0	0	8	2	0	0	2
Hemorrhage focal	9	1	9	1	0	0	9	1	0	0	0	10	0	0	0	0
Cellular infiltration, eosinophils	9	1	10	0	0	0	9	1	0	0	0	10	0	0	0	0
(Liver)																
Metaplasia, eosinophil (Liver)	9	1	9	1	0	0	10	0	0	0	0	10	0	0	0	0
(Kidney)																
Microgranuloma	8	2	9	1	0	0	9	1	0	0	0	9	1	0	0	1
(Spleen)																
Basophilic tubule, cortex	8	2	7	3	0	0	4	6	0	0	0	8	2	0	0	2
Fibrosis focal subcapsule	10	0	9	1	0	0	10	0	0	0	0	10	0	0	0	0
Dilatation renal pelvis	10	0	9	0	0	1	10	0	0	0	0	10	0	0	0	0
Cellular infiltration, lymphocyte interstitium, cortex	9	1	10	0	0	0	10	0	0	0	0	10	0	0	0	0
(Salivary)																
Hematoxylin, extramedullary	0	7	0	3	7	0	0	5	5	0	0	0	6	4	0	0
Deposit, pigment, brown (Thymus)	0	4	0	5	5	0	0	5	5	0	0	0	6	4	0	10
Hemorrhage, focal	10	0	10	0	0	0	10	0	0	0	0	8	1	0	0	0

- Negative, ± Very slight, + Slight, ++ Moderate, +++ Severe. Total of positive areas.
 [] Number of animals examined
 ** Significantly different from control p<0.01 (Two-tailed Mann-Whitney U test)
 # Significantly different from control p<0.05 (One-tailed Fisher exact test)
 ## Significantly different from control p<0.01 (One-tailed Fisher exact test)

Table 10
Twenty-eight-day repeat dose oral toxicity study of ethinylestradiol in rats

Sperm findings

Group	Sperm motility(%)	Caudal epididymal sperm counts (million)	Caudal epididymal sperm counts /caudal weight (million/g)	Testicular sperm head counts (million)	Testicular sperm head counts /testis weight (million/g)
Control	5	5	5	5	5
	87.8 12.7	166.3 56.2	868.5 152.5	171.5 20.8	119.9 22.5
3 μ g/kg	5	5	5	5	5
	93.1 6.1	168.2 28.9	944.7 166.5	168.3 21.9	117.4 9.3
12 μ g/kg	5	5	5	5	5
	93.5 3.7	156.7 26.6	829.3 94.2	164.2 25.9	115.3 23.6
48 μ g/kg	5	5	5	5	5
	91.6 3.5	169.0 41.7	901.6 137.0	166.4 17.9	125.1 14.8

Parameter, number of animals
mean
S.D.

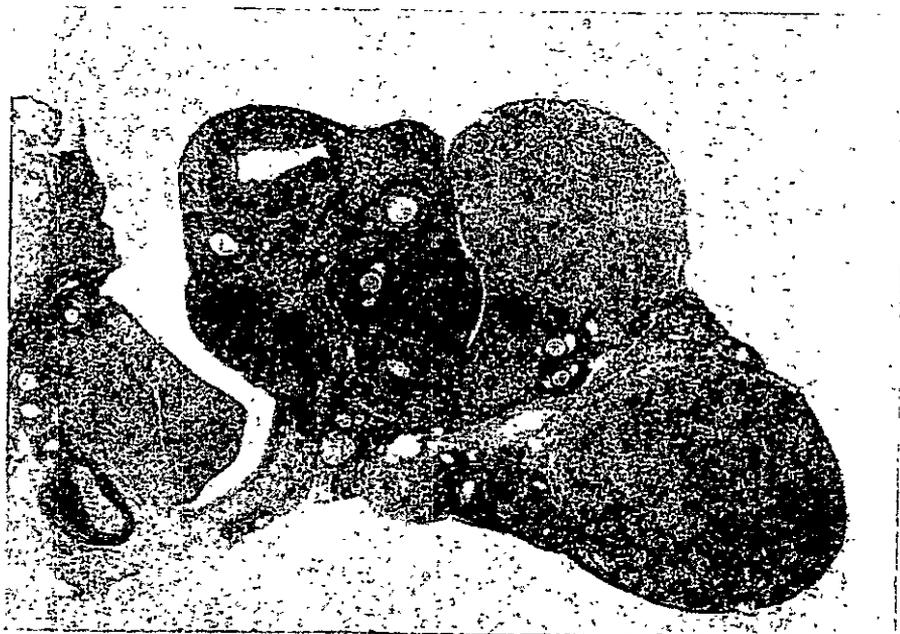


Photo 1 A microphotography of the ovary from the female animal of ethinylestradiol, 48 $\mu\text{g}/\text{kg}$ group (Animal No. 80) showing corpus luteum with hypertrophic lutein cell. x 35, Hematoxylin-eosin stain.

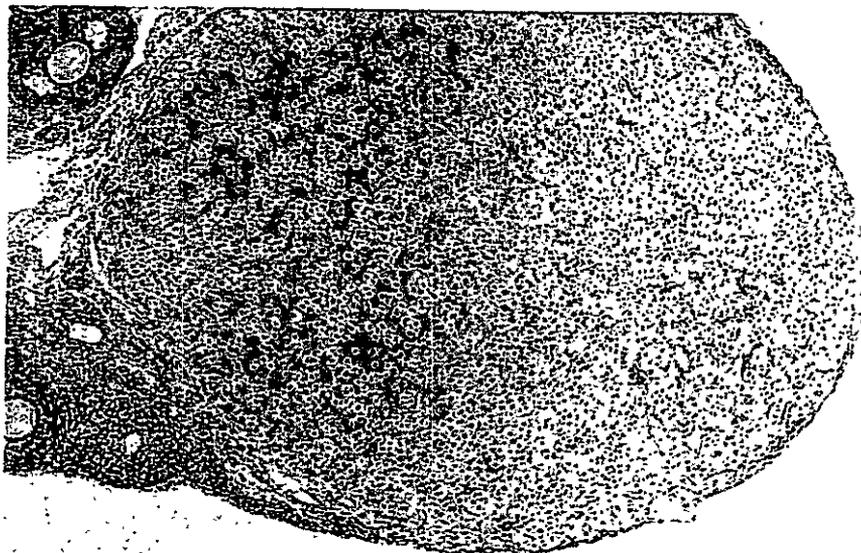


Photo 2 A microphotography of the ovary from the female animal of ethinylestradiol, 48 $\mu\text{g}/\text{kg}$ group (Animal No. 80) showing hypertrophy of lutein cell in corpus luteum. x 85, Hematoxylin-eosin-stain.



Photo 3 A microphotography of the uterus from the female animal of ethinylestradiol, 48 μ g/kg group (Animal No. 80) showing diffuse hyperplasia of luminal epithelium. x 85, Hematoxylin-eosin stain.

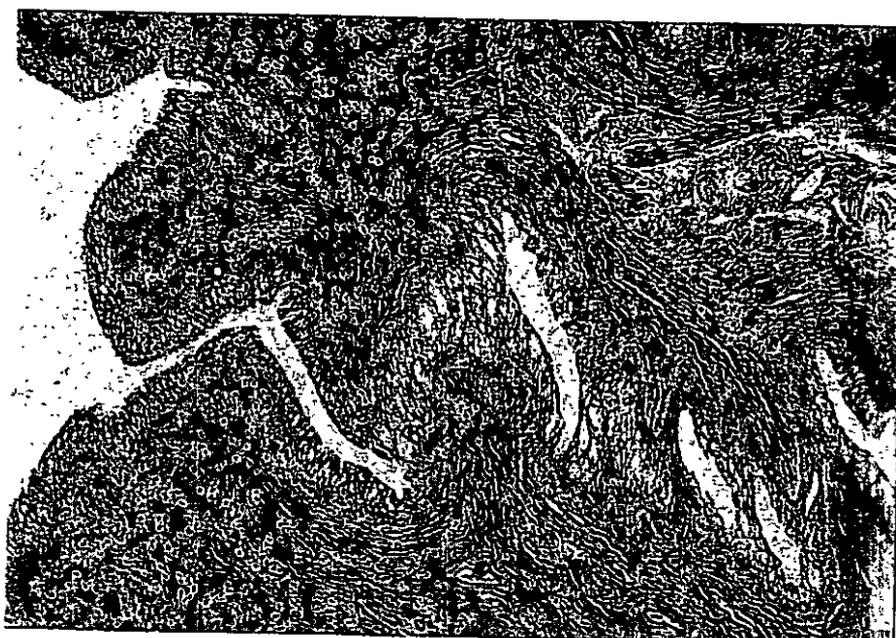


Photo 4 A microphotography of the vagina from the female animal of ethinylestradiol, 48 micro-g/kg group (Animal No. 80) showing mucification of epithelium. x 85, Hematoxylin-eosin stain.