

Table 7-2

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

Relative organ weights in females

Group	Body weight (g)	Liver (mg/g)	Kidneys (mg/g)	Adrenal glands (mg/g)	Pituitary gland (mg/g)	Thyroid gland (mg/g)	Uterus (mg/g)	Ovaries (mg/g)
Control	10 267.0 19.9	10 36.429 2.063	10 6.538 0.520	10 0.233 0.022	10 0.052 0.008	10 0.043 0.008	10 1.413 0.211	10 0.316 0.030
3 μ g/kg	10 261.9 15.7	10 37.153 2.028	10 6.712 0.399	10 0.246 0.028	9 0.048 0.005	10 0.046 0.010	10 1.485 0.145	10 0.328 0.048
12 μ g/kg	10 257.2 33.1	10 39.020 3.058	10 6.741 0.475	10 0.283* 0.039	10 0.052 0.005	10 0.051 0.006	10 1.543 0.309	10 0.315 0.054
48 μ g/kg	10 248.0 15.7	10 39.573* 3.060	10 6.876 0.619	10 0.307** 0.060	10 0.054 0.005	10 0.055** 0.009	10 1.515 0.186	10 0.328 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
		10		10		0		9	1
		10		10		0		9	1
		10		10		0		9	1
(Adrenal gland)	[10]	10	[10]	10	[10]	0	[10]	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 9-2
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	10	0	0
Decrease corpus luteum									
Hypertrophy, luteal cell, corpus luteum	10	0	10	0	10	0	10	0	2
Increase atresia follicle	10	0	9	0	8	1	8	1	0
Mineralization, degenerated oocyte	10	0	7	3	10	0	10	0	0
(Uterus, Horn & Cervix)									
Hypertrophy, diffuse, luminal epithelium	10	0	10	0	9	0	8	0	2
Hypertrophy, endometrium & myometrium	10	0	10	0	9	0	5	3	5 #
Mitosis, luminal epithelial cell	1	1	0	4	0	3	0	5	3
Vacuolation, with cell debris, luminal epithelium	0	9	0	8	1	7	2	4	2
Vacuolation, with cell debris, glandular epithelium	0	10	2	8	3	6	1	0	0
Cellular infiltration, eosinophil endometrium & myometrium	0	0	0	2	1	0	6	3	1
(Vagina)									
Cornification, epithelium	7	2	6	3	10	0	10	0	0
Mucification, epithelium	10	0	9	0	9	0	7	1	0
Cellular infiltration, neutrophil epithelium	2	6	1	4	4	3	2	1	0
(Adrenal gland)									
Hypertrophy, cortical cell	10	0	10	0	10	0	10	0	4 #
Ectopic thymic cell	8	1	9	1	9	1	9	1	0
(Mammary gland)									
Hypertrophy, acinar cell (Lung & Bronchus)	10	0	10	0	9	0	10	0	1
Accumulation foam cell	5	3	8	2	4	8	0	0	6
Mineralization artery	10	0	10	0	6	4	0	0	4 #
Hemorrhage focal, cellular infiltration, eosinophils	9	1	9	1	9	1	0	0	1
Metastasis osseous (Liver)	9	1	10	0	9	1	0	0	1
(Kidney)									
Bischoff's tubule, cortex	8	2	9	1	9	1	0	0	1
Fibrosis focal subcapsule	10	0	7	3	4	6	0	0	6
Dilatation renal pelvis	10	0	9	1	10	0	0	0	0
Cellular infiltration, lymphocyte interstitium, cortex	9	1	9	0	10	0	0	0	0
(Spleen)									
Hematomas, extramedullary	0	7	0	3	0	5	0	0	10
Deposit, pigment, brown (Thymus)	0	4	0	5	0	5	0	0	10
Hemorrhage, focal	10	0	10	0	10	0	0	0	0

- Negative, ± Very slight, + Slight, ++ Moderate, +++ Severe Total of positive results
 [] 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.

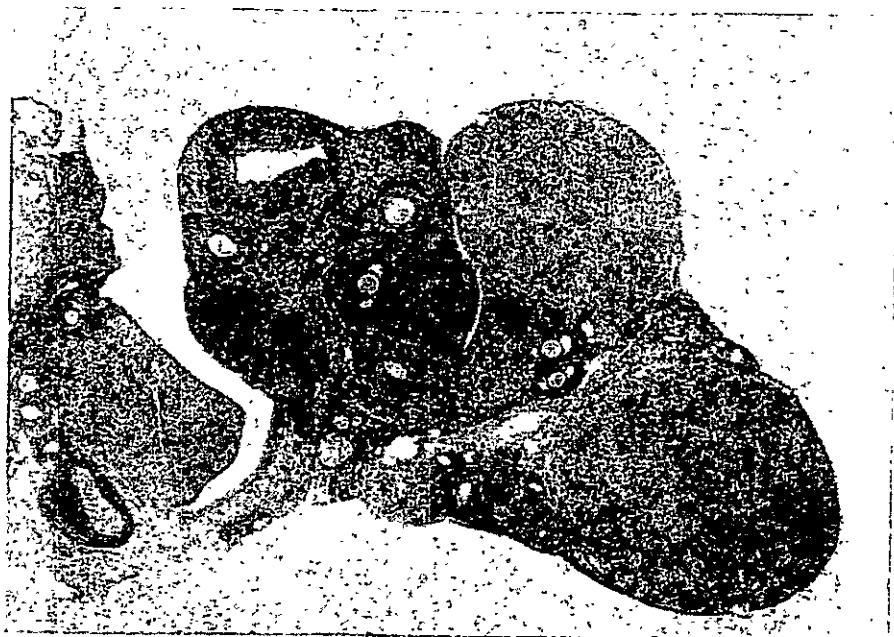


Photo 1 A microphotography of the ovary from the female animal of ethinylestradiol, 48 $\mu\text{g}/\text{kg}$ group (Animal No. 80) showing corpus luteum with hypertrophic lutein cell. x 35, Hematoxylin-eosin stain.

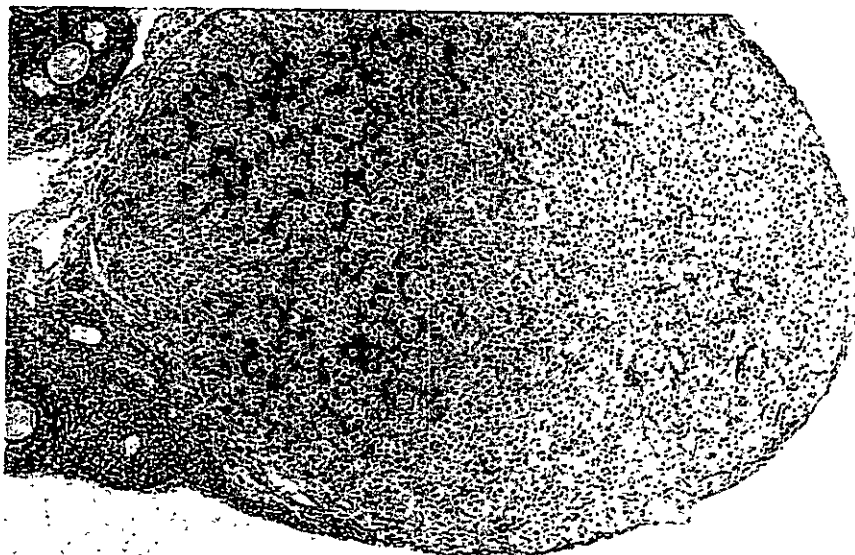


Photo 2 A microphotography of the ovary from the female animal of ethinylestradiol, 48 $\mu\text{g}/\text{kg}$ group (Animal No. 80) showing hypertrophy of lutein cell in corpus luteum. x 85, Hematoxylin-eosin-stain.



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.