Table 1-1

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

Body weight changes in males

Group	Body weight(g)								
	Day of dosing period								
	1	4	8	11	15	18	22	25	28
Control	10	10	10	10	10	10	10	10	10
	251.6	277.4	309.7	331.0	358.7	376.3	399.8	413.9	426.7
	9.0	12.4	16.2	24.0	29.0	30.9	36.6	41.4	46.7
3 μg/kg	10	10	10	10	10	10	10	10	10
	254.3	274.7	306.9	325.3	353.1	371.2	395.5	411.7	423.8
	8.3	10.2	14.3	17.6	22.1	24.4	28.3	28.6	31.3
12 μg/kg	10	10	10	10	10	10	10	10	10
	251.7	271.8	297.1	316.0	339.1	355.3	375.1	387.9	398.1
	7.9	9.8	15.3	16.0	19.7	19.4	21.3	23.3	24.9
48 μg/kg	10	10	10	10	10	10	10	10	10
	251.3	271.4	300.6	320.7	344.3	360.6	381.7	392.1	401.1
	6.2	7.2	10.1	11.8	16.2	19.6	21.5	23.4	24.4

Parameter, number of animals
mean
S.D.

Table 1-2

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

Body weight changes in females

Group	Body weight(g)								
	Day of dosing period								
	1	4	8	11	15	18	22	25	28
Control	10	10	10	10	10	10	10	10	10
	189.2	200.4	214.2	221.6	232.3	242.8	252.1	258.4	263.4
	5.6	6.8	9.1	12.3	14.0	14.1	16.3	16.8	18.6
3 μg/kg	10	10	10	10	10	10	10	10	10
	188.4	197.0	208.2	218.2	226.9	233.1	242.0	248.4	254.0
	3.7	6.1	10.3	8.8	9.9	12.8	15.0	14.8	15.4
12 μg/kg	10	10	10	10	10	10	10	10	10
	188.3	195.0	205.0	212.2	221.6	228.9	239.9	245.2	250.9
	7.9	8.6	13.6	15.6	19.4	22.5	26.9	29.0	31.0
48 μg/kg	10	10	10	10	10	10	10	10	10
	185.3**	192.7**	202.9**	210.4**	221.1**	226.1*	233.9**	238.4**	243.9*
	7.0	7.9	8.8	11.6	10.7	11.8	10.4	12.5	13.4

Parameter number of animals
mean
S.D.

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

Table 2-1

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

Estrous cycle in females; CMC Na(vehicle control)

Animal no.	Stage												Mean length (days)
	Day of dosing period												
	22	23	24	25	26	27	28	29	30	31	32	33	
41	D	P	E	D	D	P	E	D	DS				4.0
42	E	E	D	D	P	E	D	DS					4.0
43	E	D	D	P	E	D	D	P	E	D	DS		4.0
44	E	E	D	D	P	E	D	DS					4.0
45	D	D	P	E	D	D	P	E	D	DS			4.0
46	E	E	D	D	D	E	D	DS					4.0
47	E	E	D	D	P	E	D	DS					4.0
48	E	D	D	D	E	D	D	P	E	D	DS		4.0
49	E	E	D	D	P	E	D	DS					4.0
50	E	E	D	D	P	E	D	DS					4.0
Mean													4.0
±S.D.													0.0

D, diestrus; P, proestrus; E, estrus
S, sacrifice

Table 2-2

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

Estrous cycle in females; ethinylestradiol, 3 μg/kg

Animal no.	Stage												Mean length (days)
	Day of dosing period												
	22	23	24	25	26	27	28	29	30	31	32	33	
51	D	D	P	E	D	D	P	E	D	DS			4.0
52	E	D	D	D	E	D	D	P	E	D	DS		4.0
53	E	E	D	D	P	E	D	DS					4.0
54	E	E	D	D	P	E	D	DS					4.0
55	D	D	E	D	D	P	E	D	DS				4.0
56	E	D	D	D	E	D	D	P	E	D	DS		4.0
57	D	E	E	D	D	D	E	E	D	DS			5.0
58	D	D	D	D	E	E	E	D	DS				
59	E	D	D	D	E	D	D	P	D	D	DS		
60	E	D	D	D	E	D	D	E	E	D	DS		4.0
Mean ±S.D.													4.1 0.5

D, diestrus; P, proestrus; E, estrus
S, sacrifice

Table 2-3

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

Estrous cycle in females; ethinylestradiol, 12 μg/kg

Animal no.	Stage Day of dosing period												Mean length (days)
	22	23	24	25	26	27	28	29	30	31	32	33	
61	E	D	D	D	E	D	D	D	E	D	DS		4.0
62	E	D	D	D	E	D	D	D	E	D	DS		4.0
63	E	D	D	D	D	D	D	D	DS				
64	D	D	P	E	E	D	P	E	D	DS			
65	E	D	D	D	E	D	D	D	E	D	DS		4.0
66	D	D	E	D	D	P	E	D	DS				4.0
67	E	D	D	D	E	D	D	D	E	D	DS		4.0
68	D	D	E	E	D	D	D	E	D	DS			4.0
69	D	D	E	E	D	D	D	E	E	D	DS		5.0
70	E	E	D	D	D	E	D	DS					4.0
Mean ±S.D.													4.1 0.4

D, diestrus; P, proestrus; E, estrus
S, sacrifice

Table 2-4

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

Estrous cycle in females; ethinylestradiol, 48 μg/kg

Animal no.	Stage												Mean length (days)
	Day of dosing period												
	22	23	24	25	26	27	28	29	30	31	32	33	
71	D	P	D	D	D	E	E	D	DS				
72	D	D	D	D	D	D	P	D	P	D	DS		
73	E	D	D	P	E	D	D	D	E	D	DS		4.0
74	E	E	D	D	P	E	D	DS					4.0
75	D	D	D	E	E	D	D	D	E	D	DS		4.0
76	D	E	D	D	P	E	D	DS					4.0
77	D	D	D	D	E	D	D	D	E	D	DS		4.0
78	D	P	E	D	D	D	D	D	DS				
79	D	E	D	D	D	E	E	D	DS				5.0
80	E	D	D	D	E	D	D	D	E	D	DS		4.0
Mean ±S.D.													4.1 0.4

D, diestrus; P, proestrus; E, estrus
S, sacrifice

Table 3-1

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

Serum hormone levels in males

Group	LH (ng/mL)	FSH (ng/mL)	Prolactin (ng/mL)	Oestradiol (pg/mL)	Testosterone (ng/mL)	Corticosterone (ng/mL)
Control	10	10	10	0	10	8
	13.6	313	62	N.D.	2.82	137
	1.7	40	20	-	1.83	119
3 μg/kg	10	10	10	0	10	9
	15.7	305	67	N.D.	3.49	65
	3.2	53	22	-	2.75	66
12 μg/kg	10	10	10	1	10	7
	13.5	282	83	11	4.17	80
	3.9	68	65	-	2.21	97
48 μg/kg	10	10	10	3	10	10
	12.9	310	162 **	13	2.59	49
	2.9	99	72	5	1.34	45

Parameter, *number of animals*
mean
S.D.

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

Table 3-2

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

Serum hormone levels in females

Group	LH (ng/mL)	FSH (ng/mL)	Prolactin (ng/mL)	Oestradiol (pg/mL)	Corticosterone (ng/mL)
Control	10	10	10	6	10
	13.1	210	37	17	413
	2.3	57	41	8	278
3 μg/kg	10	10	10	3	9
	10.9 *	230	34	17	243
	1.6	37	16	5	140
12 μg/kg	10	10	10	4	10
	13.4	251	44	18	235
	1.7	60	21	5	138
48 μg/kg	10	10	10	2	10
	13.0	300	55	15	306
	1.5	139	67	–	221

Parameter, number of animals
mean
S.D.

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

Table 4-1

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

Hematological findings in males

Group	RBC	Hemoglobin	Hematocrit	MCV	MCH	MCHC	WBC	Band neutrophil	Segmented neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte	Platelet	PT
	($x10^4/mm^3$)	(g/dL)	(%)	(μm^3)	(pg)	(%)	($x100/mm^3$)	(%)	(%)	(%)	(%)	(%)	(%)	($x10^4/mm^3$)	(sec)
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Control	705	13.9	40.0	56.9	19.7	34.7	82	0	9	1	0	5	85	90.8	11.4
	28	0.3	1.0	1.8	0.7	0.4	19	0	4	1	0	2	6	5.5	0.4
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
3 μg/kg	698	13.9	39.3	56.4	19.9	35.4 **	87	0	10	0	0	5	85	100.0	11.6
	18	0.4	1.5	1.7	0.6	0.5	20	0	5	1	0	3	7	23.7	0.3
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
12 μg/kg	705	14.0	40.1	57.0	19.8	34.9	85	0	10	1	0	4	86	87.5	11.9 *
	36	0.4	1.3	1.5	0.6	0.4	12	0	4	1	0	3	4	10.1	0.3
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
48 μg/kg	711	13.9	39.8	56.1	19.6	34.9	80	0	10	1	0	5	85	86.9	12.3 **
	17	0.4	1.1	1.8	0.7	0.3	15	0	5	1	0	2	7	9.1	0.6

Parameter, number of animals
mean
S.D.

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

Table 4-2

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

Hematological findings in females

Group	RBC	Hemoglobin	Hematocrit	MCV	MCH	MCHC	WBC	Band neutrophil	Segmented neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte	Platelet	PT
	($x10^4/mm^3$)	(g/dL)	(%)	(μm^3)	(pg)	(%)	($x100/mm^3$)	(%)	(%)	(%)	(%)	(%)	(%)	($x10^4/mm^3$)	(sec)
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Control	685	13.2	38.5	56.2	19.3	34.4	58	0	11	1	0	3	86	95.8	11.5
	19	0.5	1.1	1.2	0.6	0.5	17	0	5	1	0	2	6	3.7	0.5
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
3 μg/kg	672	13.2	38.0	56.6	19.6	34.6	56	0	12	0	0	2	85	90.1	11.7
	26	0.6	1.7	1.7	0.7	0.5	16	0	4	1	0	1	5	9.1	0.4
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
12 μg/kg	679	13.2	38.6	56.9	19.5	34.3	72	0	9	0	0	2	89	89.6	12.2 *
	15	0.4	1.2	1.3	0.5	0.6	38	0	4	1	0	2	5	6.3	0.7
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
48 μg/kg	679	12.9	37.8	55.8	19.0	34.1	64	0	9	0 *	0	3	88	90.2	12.5 **
	25	0.4	1.3	2.1	0.7	0.6	33	0	4	0	0	2	4	7.8	0.8

Parameter, number of animals
mean
S.D.

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

Table 5-1

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

Biochemical findings in males

Group	Total protein (g/dL)	Albumin (g/dL)	A/G	BUN (mg/dL)	Creatinine (mg/dL)	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	ALP (U/L)	LDH (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)	Inorg. phos. (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Control	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	5.9	3.3	1.29	18	0.6	166	58	146	582	118	38	60	0	5.9	9.2	143.5	4.11	106.0
	0.2	0.1	0.10	4	0.0	20	6	25	82	30	4	4	0	0.3	0.3	0.8	0.21	1.3
3 μg/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	5.8	3.2	1.26	18	0.6	168	46**	204	556	136	36	58	0	6.3	9.3	143.3	4.13	106.1
	0.2	0.2	0.19	2	0.1	15	5	63	71	65	7	6	0	0.3	0.2	0.7	0.26	1.7
12 μg/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	5.8	3.2	1.28	16	0.6	168	40**	295**	600	151	34	54	0	5.9	9.4	142.7	4.17	107.2
	0.3	0.1	0.18	2	0.1	16	6	76	52	64	5	3	0	0.6	0.2	1.0	0.30	1.4
48 μg/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	6.0	3.2	1.19	16	0.7	169	34**	255**	672*	188	37	57	0	5.7	9.4	143.1	4.00	105.9
	0.2	0.1	0.12	2	0.1	27	6	77	95	106	5	6	0	0.8	0.3	1.5	0.34	1.1

Parameter, number of animals
mean
S.D.

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

Table 5-2

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

Biochemical findings in females

Group	Total protein (g/dL)	Albumin (g/dL)	A/G	BUN (mg/dL)	Creatinine (mg/dL)	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	ALP (U/L)	LDH (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)	Inorg. phos. (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Control	5.9	3.6	1.55	21	0.6	166	68	144	327	99	27	51	0	6.1	9.2	140.6	4.18	108.3
	0.4	0.3	0.10	4	0.0	19	8	82	75	41	5	5	0	0.6	0.3	1.7	0.50	1.9
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
3 μg/kg	5.7	3.4	1.43	24	0.7	170	54**	151	316	116	25	49	0	5.8	9.2	140.3	4.24	109.1
	0.4	0.3	0.12	5	0.1	14	7	92	49	53	6	4	0	0.7	0.4	0.9	0.23	1.6
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
12 μg/kg	5.5*	3.4	1.65	18	0.6	164	39**	149	385	107	24	49	0	5.7	8.9	140.8	3.95	109.4
	0.3	0.3	0.20	3	0.0	16	7	43	86	37	5	5	0	0.5	0.4	2.4	0.33	2.4
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
48 μg/kg	5.6	3.3	1.41	15**	0.6	169	38**	133	383	114	22	46	1**	5.8	8.8	140.4	4.02	109.8
	0.3	0.3	0.19	4	0.1	18	8	69	89	51	5	7	1	0.8	0.4	1.2	0.48	3.1

Parameter, number of animlas
mean
S.D.

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

Table 6-1

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

Absolute organ weights in males

Group	Body weight (g)	Liver (mg)	Kidneys (mg)	Adrenal glands (mg)	Pituitary gland (mg)	Thyroid gland (mg)	Prostate (mg)	Seminal vesicles (mg)	Testes (mg)	Epididymides (mg)	Accessory reproductive gland (mg)
	10	10	10	9	10	10	10	10	10	10	10
Control	432.8	16304.8	2807.2	49.8	11.0	17.1	537.0	1318.7	3027.9	915.5	2334.6
	48.8	2341.4	330.6	4.9	1.4	3.2	82.4	171.2	593.8	148.4	263.2
	10	10	10	10	10	10	10	10	10	10	10
3 μg/kg	433.1	17454.8	2777.8	56.4	11.9	17.5	521.2	1367.8	3260.2	909.5	2382.8
	33.5	2415.1	281.8	7.2	1.2	3.7	60.6	215.7	413.1	123.2	290.2
	10	10	10	10	10	10	10	10	10	10	10
12 μg/kg	405.7	16569.9	2776.5	52.5	11.2	17.1	471.0	1388.4	3248.3	958.2	2394.3
	26.7	1429.1	266.0	8.7	1.4	3.5	147.0	172.1	238.4	58.7	326.7
	10	10	10	10	10	10	10	10	10	10	10
48 μg/kg	407.1	17450.3	2704.1	78.5**	13.0**	16.3	472.9	1318.8	3126.0	952.9	2249.4
	23.8	2150.6	346.6	20.7	1.5	2.6	82.8	164.3	231.3	101.9	223.5

Parameter, number of animals
mean
S.D.

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

Table 6-2

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

Absolute organ weights in females

Group	Body weight (g)	Liver (mg)	Kidneys (mg)	Adrenal glands (mg)	Pituitary gland (mg)	Thyroid gland (mg)	Uterus (mg)	Ovaries (mg)
Control	10	10	10	10	10	10	10	10
	267.0	9735.6	1742.8	62.1	13.8	11.4	375.4	84.1
	19.9	1018.2	159.0	7.4	1.8	2.2	51.9	7.4
3 μg/kg	10	10	10	10	9	10	10	10
	261.9	9744.9	1755.1	64.2	12.6	11.9	388.4	86.0
	15.7	959.0	102.8	6.6	1.5	2.3	37.6	13.2
12 μg/kg	10	10	10	10	10	10	10	10
	257.2	10103.6	1730.6	72.7	13.3	13.1	389.9	81.7
	33.1	1872.0	236.1	12.8	1.5	2.0	51.0	19.5
48 μg/kg	10	10	10	10	10	10	10	10
	248.0	9835.5	1702.4	75.6*	13.4	13.7	374.0	80.7
	15.7	1167.2	154.1	13.7	1.3	2.1	34.8	16.6

Parameter, number of animlas
mean
S.D.

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

Table 7-1

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

Relative organ weights in males

Group	Body weight (g)	Liver (mg/g)	Kidneys (mg/g)	Adrenal glands (mg/g)	Pituitary gland (mg/g)	Thyroid gland (mg/g)	Prostate (mg/g)	Seminal vesicles (mg/g)	Testes (mg/g)	Epididymides (mg/g)	Accessory reproductive gland (mg/g)
Control	10	10	10	10	10	10	10	10	10	10	10
	432.8	37.587	6.497	0.115	0.025	0.040	1.251	3.072	7.000	2.122	5.436
	48.8	1.944	0.432	0.007	0.003	0.007	0.213	0.471	1.245	0.336	0.724
3 μg/kg	10	10	10	10	10	10	10	10	10	10	10
	433.1	40.156	6.420	0.131	0.028	0.041	1.210	3.175	7.560	2.111	5.534
	33.5	2.656	0.499	0.020	0.004	0.009	0.160	0.553	1.079	0.325	0.809
12 μg/kg	10	10	10	10	10	10	10	10	10	10	10
	405.7	40.829*	6.860	0.130	0.028	0.042	1.168	3.449	8.055	2.374	5.942
	26.7	1.952	0.695	0.023	0.003	0.008	0.380	0.572	0.950	0.248	1.004
48 μg/kg	10	10	10	10	10	10	10	10	10	10	10
	407.1	42.743**	6.628	0.192**	0.032**	0.040	1.164	3.241	7.712	2.353	5.526
	23.8	3.144	0.625	0.045	0.003	0.007	0.198	0.358	0.812	0.317	0.425

Parameter, number of animals
mean
S.D.

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

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	10	10	10	10	10	10	10
	267.0	36.429	6.538	0.233	0.052	0.043	1.413	0.316
	19.9	2.063	0.520	0.022	0.008	0.008	0.211	0.030
3 μg/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
	15.7	2.028	0.399	0.028	0.005	0.010	0.145	0.048
12 μg/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
	33.1	3.058	0.475	0.039	0.005	0.006	0.309	0.054
48 μg/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		Control			3 μg/kg			12 μg/kg			48 μg/kg		
Grade			−	+		−	+		−	+		−	+
(Testis)		[10]			[10]			[10]			[10]		
	Small		9	1		10	0		10	0		10	0
(Epididymis)		[10]			[10]			[10]			[10]		
	Small		9	1		10	0		10	0		10	0
(Prostate)		[10]			[10]			[10]			[10]		
	Small		10	0		10	0		9	1		10	0
(Lung)		[10]			[10]			[10]			[10]		
	Spot, dark red		10	0		7	3		7	3		6	4
(Liver)		[10]			[10]			[10]			[10]		
	Enlargement		10	0		10	0		10	0		9	1
	Accentuated lobular pattern		10	0		10	0		10	0		9	1
	Yellowish		10	0		10	0		10	0		9	1
(Adrenal gland)		[10]			[10]			[10]			[10]		
	Enlargement		10	0		10	0		10	0		8	2
	Dark		10	0		10	0		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		Control			3 μg/kg			12 μg/kg			48 μg/kg		
Grade			−	+		−	+		−	+		−	+
(Lung)		[10]			[10]			[10]			[10]		
	Spot, dark red		9	1		10	0		10	0		10	0
(Kidney)		[10]			[10]			[10]			[10]		
	Dilatation, renal pelvis		10	0		9	1		10	0		10	0

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

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

Group / Grade	Control						3 μg/kg						12 μg/kg						48 μg/kg						
	-	±	+	++	+++	Pos	-	±	+	++	+++	Pos	-	±	+	++	+++	Pos	-	±	+	++	+++	Pos	
(Testis)	[10]						[10]						[10]						[10]						
Atrophy, seminiferous tubule	8	0	1	1	0	2	8	1	1	0	0	2	7	1	2	0	0	3	8	1	1	0	0	2	
Multinucleated giant cell, in seminiferous tubule	9	0	0	1	0	1	10	0	0	0	0	0	10	0	0	0	0	0	8	2	0	0	0	2	
Hyperplasia, Leydig cell, diffuse	8	1	0	1	0	2	9	1	0	0	0	1	9	1	0	0	0	1	9	1	0	0	0	1	
(Epididymis)	[10]						[10]						[10]						[10]						
Decrease, sperm in lumen	9	0	0	1	0	1	9	1	0	0	0	1	10	0	0	0	0	0	10	0	0	0	0	0	
Cell debris, in lumen	8	0	1	1	0	2	9	0	1	0	0	1	7	3	0	0	0	3	9	0	1	0	0	1	
(Prostate Ventral & Dorsolateral lobe)	[10]						[10]						[10]						[10]						
Cellular infiltration, lymphocyte, interstitium	3	2	3	2	0	7	6	2	0	2	0	4	2	5	2	1	0	8	6	1	1	2	0	4	
Cellular infiltration, lymphocyte and plasma cell, epithelial layer	7	3	0	0	0	3	8	2	0	0	0	2	7	3	0	0	0	3	8	2	0	0	0	2	
(Seminal vesicle)	[10]						[10]						[10]						[10]						
Atrophy, with decreased secretion	9	1	0	0	0	1	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	
(Adrenal gland)	[10]						[10]						[10]						[10]						
Hypertrophy, cortical cell	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	2	6	2	0	0	8	##
(Kidney)	[10]						[10]						[10]						[10]						
Eosinophilic body	9	1	0	0	0	1	9	1	0	0	0	1	8	1	1	0	0	2	9	1	0	0	0	1	
Basophilic tubule, cortex	4	6	0	0	0	6	4	6	0	0	0	6	4	6	0	0	0	6	4	6	0	0	0	6	
Cyst, cortico-medullaly junction	9	1	0	0	0	1	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	
Dilatation, renal pelvis	10	0	0	0	0	0	9	0	1	0	0	1	10	0	0	0	0	0	10	0	0	0	0	0	
Fibrosis, with infiltration lymphocyte, focal, subcapsule	10	0	0	0	0	0	10	0	0	0	0	0	9	1	0	0	0	1	10	0	0	0	0	0	
(Liver)	[10]						[10]						[10]						[10]						
Necrosis, focal	10	0	0	0	0	0	9	1	0	0	0	1	9	1	0	0	0	1	9	1	0	0	0	1	
(Spleen)	[10]						[10]						[10]						[10]						
Hematopoiesis, extramedullary	0	6	4	0	0	10	0	3	7	0	0	10	0	5	5	0	0	10	0	5	5	0	0	10	
Deposit, pigment, brown	0	9	1	0	0	10	0	9	1	0	0	10	0	9	1	0	0	10	0	10	0	0	0	10	
(Lung & Bronchus)	[10]						[10]						[10]						[10]						
Accumulation, foam cell, Cellular infiltration, eosinophil	4	6	0	0	0	6	6	4	0	0	0	4	4	6	0	0	0	6	3	7	0	0	0	7	
Mineralization, artery	7	3	0	0	0	3	9	1	0	0	0	1	9	1	0	0	0	1	8	2	0	0	0	2	
Hemorrhage, focal	9	1	0	0	0	1	9	1	0	0	0	1	7	3	0	0	0	3	9	1	0	0	0	1	
Metaplasia, osseous	9	1	0	0	0	1	8	2	0	0	0	2	7	3	0	0	0	3	7	2	1	0	0	3	
(Heart)	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	8	2	0	0	0	2	
Myocardial degeneration/fibrosis, focal	[10]						[10]						[10]						[10]						
(Pituitary gland)	10	0	0	0	0	0	10	0	0	0	0	0	9	1	0	0	0	1	10	0	0	0	0	0	
Dilatation, Rathke's cleft	[10]						[10]						[10]						[10]						
(Stomach)	10	0	0	0	0	0	10	0	0	0	0	0	8	1	1	0	0	2	10	0	0	0	0	0	
Granulation tissue, serosa	[10]						[10]						[10]						[10]						
	9	1	0	0	0	1	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	

-, Negative, ±, Very slight, +, Slight, ++, Moderate, +++, Severe, Pos, Total of positive grade
[ ] 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 ethinylestradiol in rats
Summary of histopathological findings in females

Group	Control						3 μg/kg						12 μg/kg						48 μg/kg						
Grade	-	±	+	++	+++	Pos	-	±	+	++	+++	Pos	-	±	+	++	+++	Pos	-	±	+	++	+++	Pos	
(Ovary)	[10]						[10]						[10]						[10]						
Decrease, corpus luteum	10	0	0	0	0	0	10	0	0	0	0	0	8	1	1	0	0	2	8	2	0	0	0	2	
Hypertrophy, lutein cell, corpus luteum	10	0	0	0	0	0	10	0	0	0	0	0	9	0	1	0	0	1	8	1	1	0	0	2	
Increase, atresia, follicle	10	0	0	0	0	0	9	0	1	0	0	1	8	1	1	0	0	2	8	1	1	0	0	2	
Mineralization, degenerated oocyte	10	0	0	0	0	0	7	3	0	0	0	3	10	0	0	0	0	0	10	0	0	0	0	0	
(Uterus Horn & Cervix)	[10]						[10]						[10]						[10]						
Hyperplasia, diffuse, luminal epithelium	10	0	0	0	0	0	10	0	0	0	0	0	9	0	1	0	0	1	8	0	2	0	0	2	
Hypertrophy, endmetrium & myometrium	10	0	0	0	0	0	10	0	0	0	0	0	9	0	1	0	0	1	5	3	2	0	0	5	#
Mitosis, luminal epithelial cell	1	1	8	0	0	9	0	4	5	1	0	10	0	3	3	4	0	10	0	5	3	2	0	10	
Vacuolation, with cell debris, luminal epithelium	0	9	1	0	0	10	0	8	2	0	0	10	1	7	2	0	0	9	1	4	3	2	0	9	
Vacuolation, with cell debris, glandular epithelium	0	10	0	0	0	10	2	8	0	0	0	8	3	6	1	0	0	7	2	6	2	0	0	8	
Cellular infiltration, eosinophil, endometrium & myometrium	0	0	5	5	0	10	0	2	6	2	0	10	1	0	6	3	0	9	2	1	3	3	1	8	
(Vagina)	[10]						[10]						[10]						[10]						
Cornification, epithelium	7	2	1	0	0	3	6	3	1	0	0	4	10	0	0	0	0	0	9	1	0	0	0	1	
Mucification, epithelium	10	0	0	0	0	0	9	0	1	0	0	1	9	0	0	1	0	1	7	1	1	1	0	3	
Cellular infiltration, neutrophil, epithelium	2	6	2	0	0	8	1	4	3	2	0	9	4	3	2	1	0	6	1	5	2	2	0	9	
(Adrenal gland)	[10]						[10]						[10]						[10]						
Hypertrophy, cortical cell	10	0	0	0	0	0	10	0	0	0	0	0	6	3	1	0	0	4 #	1	5	4	0	0	** 9	##
(Thyroid gland)	[10]						[10]						[10]						[10]						
Ectopic thymic cell	8	1	1	0	0	2	9	1	0	0	0	1	9	1	0	0	0	1	9	1	0	0	0	1	
(Memmary gland)	[10]						[10]						[10]						[10]						
Hyperplasia, acinar cell	10	0	0	0	0	0	10	0	0	0	0	0	9	0	1	0	0	1	8	1	1	0	0	2	
(Lung & Bronchus)	[10]						[10]						[10]						[10]						
Accumulation, foam cell	5	3	2	0	0	5	8	2	0	0	0	2	4	6	0	0	0	6	5	5	0	0	0	5	
Mineralization, artery	10	0	0	0	0	0	10	0	0	0	0	0	6	4	0	0	0	4 #	8	2	0	0	0	2	
Hemorrhage, focal	9	1	0	0	0	1	9	1	0	0	0	1	9	1	0	0	0	1	10	0	0	0	0	0	
Cellular infiltration, eosinophil	9	1	0	0	0	1	10	0	0	0	0	0	9	1	0	0	0	1	10	0	0	0	0	0	
Meteplasia, osseous	9	1	0	0	0	1	9	1	0	0	0	1	10	0	0	0	0	0	10	0	0	0	0	0	
(Liver)	[10]						[10]						[10]						[10]						
Microgranuloma	8	2	0	0	0	2	9	1	0	0	0	1	9	1	0	0	0	1	9	1	0	0	0	1	
(Kidney)	[10]						[10]						[10]						[10]						
Basophilic tubule, cortex	8	2	0	0	0	2	7	3	0	0	0	3	4	6	0	0	0	6	8	2	0	0	0	2	
Fibrosis, focal, subcapsule	10	0	0	0	0	0	9	1	0	0	0	1	10	0	0	0	0	0	10	0	0	0	0	0	
Dilatation, renal perbis	10	0	0	0	0	0	9	0	0	1	0	1	10	0	0	0	0	0	10	0	0	0	0	0	
Cellular infiltration, lymphocyte, interstitium, cortex	9	1	0	0	0	1	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	
(Spleen)	[10]						[10]						[10]						[10]						
Hematopoiesis, extramedullary	0	7	3	0	0	10	0	3	7	0	0	10	0	5	5	0	0	10	0	6	4	0	0	10	
Deposit, pigment, brown	0	4	6	0	0	10	0	5	5	0	0	10	0	5	5	0	0	10	0	6	4	0	0	10	
(Thymus)	[10]						[10]						[10]						[10]						
Hemorrhage, focal	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	9	1	0	0	0	1	

-, Negative, ±, Very slight, +, Slight, ++, Moderate, +++, Severe, Pos, Total of positive grade
[ ], 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	166.3	868.5	171.5	119.9
	12.7	56.2	152.5	20.8	22.5
3 μg/kg	5	5	5	5	5
	93.1	168.2	944.7	168.3	117.4
	6.1	28.9	166.5	21.9	9.3
12 μg/kg	5	5	5	5	5
	93.5	156.7	829.3	164.2	115.3
	3.7	26.6	94.2	25.9	23.6
48 μg/kg	5	5	5	5	5
	91.6	169.0	901.6	166.4	125.1
	3.5	41.7	137.0	17.9	14.8

Parameter, number of animals
mean
S.D.

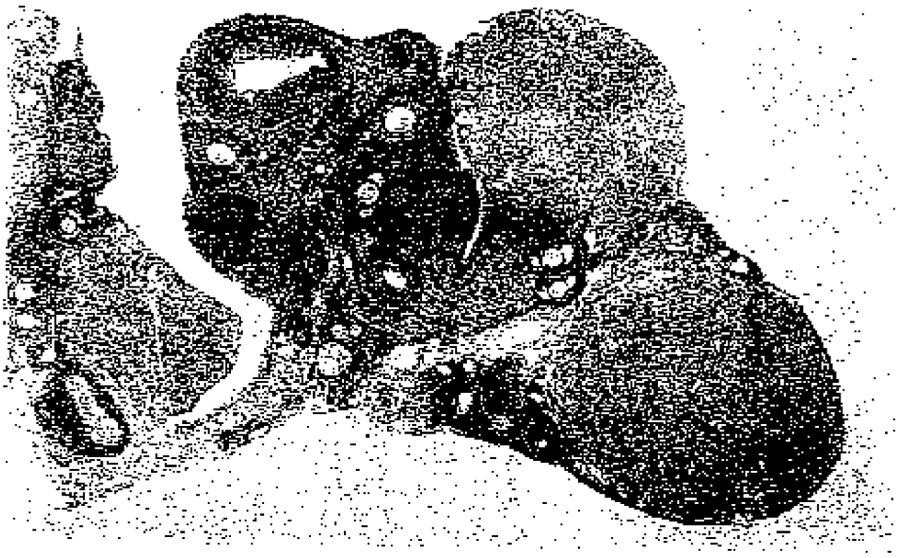

Photo 1 A microphotography of the ovary from the female animal of ethinylestradiol, 48 μg/kg group (Animal No. 80) showing corpus luteum with hypertropic lutein cell. x 35, Hematoxylin-eosin stain.

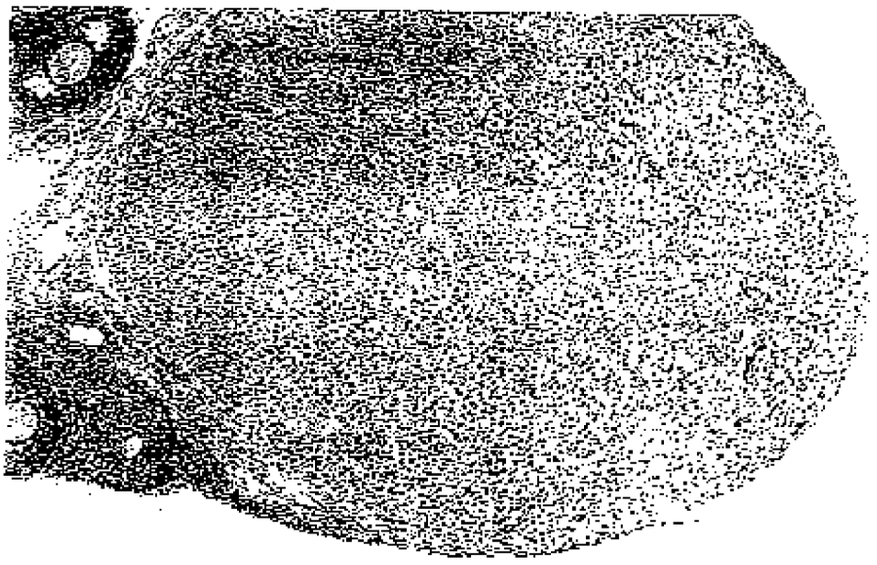

Photo 2 A microphotography of the ovary from the female animal of ethinylestradiol, 48 μg/kg group (Animal No. 80) showing hypertropy of lutein cell in corpus luteum. x 85, Hematoxylin-eosin-stain.

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

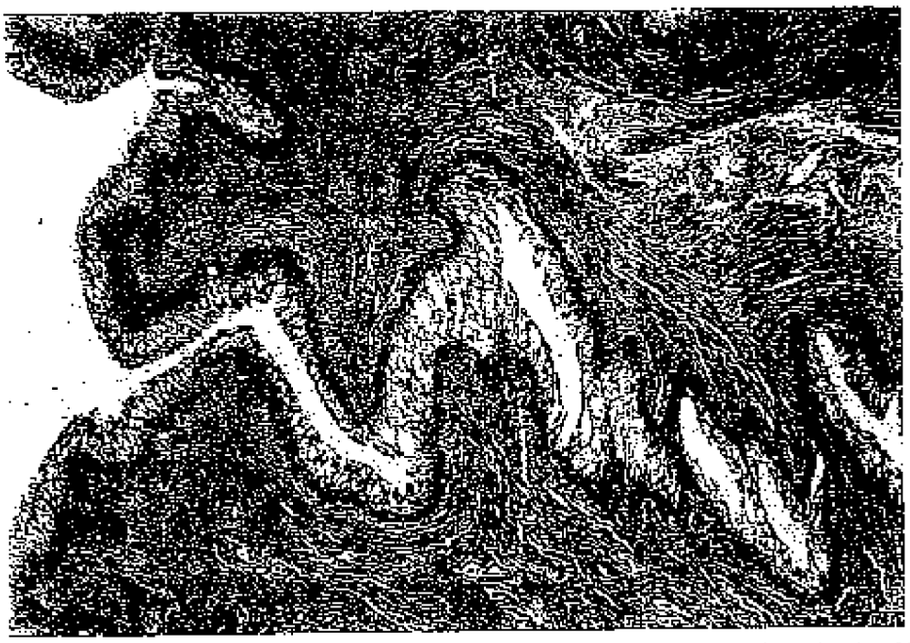

Photo 4 A microphotography of the vagina from the female animal of ethinylestradiol, 48 micro-g/kg group (Animal No. 80) showing mucification of epithelium. x 85, Hematoxylin-eosin stain.