

Table 1-1

Twenty-eight-day repeat dose oral toxicity study of tamoxifen 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	10 260.0 5.9	10 288.1 7.4	10 319.5 10.9	10 338.0 12.1	10 361.4 15.4	10 380.4 16.3	10 403.2 19.3	10 416.1 20.3	10 428.3 20.5		
12.5 μ g/kg	10 255.3 9.2	10 286.9 8.0	10 319.6 9.5	10 339.4 12.8	10 364.1 16.0	10 379.1 15.4	10 403.4 18.3	10 414.5 21.0	10 427.6 21.5		
50.0 μ g/kg	10 261.5 4.8	10 284.4 5.8	10 314.3 7.8	10 328.4 9.7	10 349.2 12.9	10 364.6 15.3	10 381.8 * 18.1	10 393.4 * 18.4	10 404.3 * 21.4		
200 μ g/kg	10 260.1 6.8	10 277.3 ** 7.7	10 295.7 ** 9.5	10 307.7 ** 9.5	10 320.4 ** 10.6	10 333.3 ** 13.1	10 344.2 ** 13.6	10 352.8 ** 14.9	10 359.9 ** 17.1		

Parameter, number of animals

mean

S.D.

M.C., multiple comparisons

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

Table 1-2

Twenty-eight-day repeat dose oral toxicity study of tamoxifen 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	191.2 7.5	208.6 6.1	225.6 6.4	234.3 7.0	246.1 8.2	252.0 7.6	261.8 8.8	260.6 10.2	271.7 6.7	10	10
12.5 μ g/kg	192.3 7.1	205.2 8.0	217.6 11.9	225.5 13.5	233.4 * 16.6	241.3 19.4	250.1 22.4	248.8 19.9	254.5 20.8	10	10
50.0 μ g/kg	191.7 5.6	200.5 * 5.2	210.3 ** 8.0	211.9 ** 8.6	218.8 ** 9.9	224.3 ** 10.9	228.7 ** 11.9	227.6 ** 12.4	231.7 ** 14.1	10	10
200 μ g/kg	191.3 5.2	195.5 ** 5.9	197.8 ** 11.4	203.0 ** 6.1	208.2 ** 7.4	212.1 ** 8.1	216.4 ** 8.5	215.2 ** 10.2	219.8 ** 9.1	10	10
Parameter, number of animals											
mean											
S.D.											
M.C., multiple comparisons											
*, 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 tamoxifen in rats

Estrous cycle in females; 0.5 % CMC Na(vehicle control)

Animal no.	Stage														Type	Mean length (days)
	Day of dosing period															
	22	23	24	25	26	27	28	29	30	31	32	33				
41	D	D	D	E	D	D	P	E	D	DS			regular	4		
42	D	D	D	E	D	D	P	E	D	DS			regular	4		
43	E	D	D	P	E	D	D	P	E	D	DS		regular	4		
44	D	D	E	D	D	D	E	D	DS				regular	4		
45	E	D	D	D	E	D	D	DS					regular	4		
46	E	D	D	P	E	D	D	P	E	D	DS		regular	4		
47	D	E	D	D	D	D	E	D	DS				regular	5		
48	D	D	P	E	D	D	P	E	D	DS			regular	4		
49	D	D	D	E	D	D	D	E	D	DS			regular	4		
50	D	D	P	E	D	D	D	E	D	DS			regular	4		
Mean ±S.D.															4.1	

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

Table 2-2

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

Estrous cycle in females; tamoxifen, 12.5 μ g/kg

Animal no.	Stage														Type	Mean length (days)
	22	23	24	25	26	27	28	29	30	31	32	33				
51	D	D	E	D	D	D	E	D	DS						regular	4
52	E	D	D	D	D	D	D	D	DS						uncycler	
53	E	D	D	D	E	D	D	D	E	D	DS				regular	4
54	E	D	D	D	E	D	D	D	P	D	DS				irregular	
55	D	D	D	D	D	P	E	D	DS						irregular	
56	D	D	D	E	D	D	D	E	D	DS					regular	
57	E	D	D	P	E	D	D	P	E	D	DS				regular	4
58	D	D	E	D	D	D	E	D	DS						regular	4
59	D	D	D	E	D	D	D	D	DS						irregular	
60	E	D	D	D	D	D	D	DS							uncycler	
Mean \pm S.D.																4.0

D, diestrus; P, proestrus; E, estrus

S, sacrifice

Table 2-3

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

Estrous cycle in females; tamoxifen, 50.0 μ g/kg

Animal no.	Stage														Type	Mean length (days)
	22	23	24	25	26	27	28	29	30	31	32	33				
61	D	D	D	D	D	D	D	DS							anestrus	
62	D	D	D	D	D	E	D	D	D	D	DS				irregular	
63	P	D	D	D	D	D	D	D	D	DS					anestrus	
64	D	D	D	D	D	D	D	DS							anestrus	
65	P	D	D	D	D	D	D	DS							anestrus	
66	D	D	D	D	E	D	D	D	D	DS					irregular	5
67	D	E	D	D	D	D	E	D	DS						regular	4
68	D	D	D	E	D	D	D	E	D	DS					regular	
69	D	D	D	D	E	D	D	D	D	D	DS				irregular	
70	D	D	D	E	D	D	D	D	DS						irregular	
Mean \pm S.D.																4.5

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

Table 2-4

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

Estrous cycle in females; tamoxifen, 200 μ g/kg.

Animal no.	Stage														Type	Mean length (days)
	22	23	24	25	26	27	28	29	30	31	32	33				
71	D	D	D	D	D	D	D	DS							anestrus	
72	D	D	D	D	D	D	D	DS							anestrus	
73	D	D	D	D	D	D	D	DS							anestrus	
74	D	D	D	D	D	D	D	DS							anestrus	
75	D	D	D	D	D	D	D	E	E	E	E	ES			irregular	
76	D	D	D	D	D	D	D	DS							anestrus	
77	D	D	D	D	D	D	D	DS							anestrus	
78	D	D	D	D	D	D	D	DS							anestrus	
79	D	D	D	D	D	D	D	DS							anestrus	
80	D	D	D	D	D	D	D	DS							anestrus	
Mean \pm S.D.																

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

Table 3-1

Twenty-eight-day repeat dose oral toxicity study of tamoxifen 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 8.9 1.2	10 236 73	10 41 14	2 8 -	10 2.87 1.25	7 74 85
12.5 μ g/kg	10 9.9 1.5	10 214 49	10 74 16	0 N.D. -	10 2.04 1.13	10 75 67
50.0 μ g/kg	10 11.7 2.2	10 225 38	10 98 37	0 N.D. -	10 1.37 0.88	10 107 112
200 μ g/kg	10 12.1 2.0	10 243 42	10 83 34	0 N.D. -	10 1.38 0.62	10 114 121
Parameter,	number of animals		mean	S.D.		

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

Table 3-2

Twenty-eight-day repeat dose oral toxicity study of tamoxifen 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	8	10
	10.3	162	42	12	117
	2.1	39	14	7	135
12.5 μ g/kg	10	10	10	9	10
	9.9	234	56	21	124
	2.0	87	30	11	148
50.0 μ g/kg	10	10	10	4	10
	9.3	291 **	151	14	133
	0.8	102	246	8	129
200 μ g/kg	10	10	9	3	9
	9.2	248 *	193	9	123
	2.8	63	243	1	177
Parameter,	number of animals				
	mean				
	S.D.				

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

Table 4-1

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

Hematological findings in males

Group	RBC ($\times 10^6/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	WBC ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	PT (sec)
Control	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	730	14.3	41.1	56.4	19.5	34.7	78	0	10	0	0	2	88	94.7	11.5
	22	0.3	1.0	1.4	0.7	0.6	12	0	4	0	0	2	4	8.6	0.5
12.5 $\mu\text{g}/\text{kg}$	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	712	14.1	40.6	57.1	19.9	34.8	87	0	7	0	0	2	91	86.2	11.8
	27	0.4	1.3	2.2	0.6	0.5	14	0	4	0	0	1	4	11.2	0.6
50.0 $\mu\text{g}/\text{kg}$	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	734	14.2	40.8	55.7	19.4	34.8	87	0	10	0	0	3	87	91.7	11.9
	26	0.3	0.8	1.7	0.6	0.6	26	0	7	0	0	3	9	8.1	0.4
200 $\mu\text{g}/\text{kg}$	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	746	14.5	41.8	56.0	19.4	34.6	75	0	5	0	0	2	93	92.8	12.0
	31	0.5	1.3	1.1	0.4	0.4	15	0	3	1	0	2	4	6.2	0.5

Parameter, number of animals

mean

S.D.

Table 4-2

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

Hematological findings in females

Group	RBC (x10 ⁴ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	MCV (μ m ³)	MCH (pg)	MCHC (%)	WBC (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)	Platelet (x10 ⁴ /mm ³)	PT (sec)
Control	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	694	13.4	39.4	56.9	19.3	34.0	61	0	7	0	0	2	91	91.2	11.4
	28	0.3	1.0	1.5	0.7	0.5	17	0	2	0	0	2	3	9.0	0.7
12.5 μ g/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9
	695	13.4	39.6	56.9	19.3	33.9	65	0	7	1	0	2	91	88.0	11.8
	27	0.6	1.5	1.6	0.5	0.5	33	0	3	1	0	1	5	16.2	0.2
50.0 μ g/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9
	714	13.5	40.3	56.4	18.9	33.5	51	0	8	1	0	2	89	90.4	12.1
	25	0.5	1.6	1.1	0.3	0.5	26	0	6	1	0	2	8	7.5	0.6
200 μ g/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	717	13.7	40.4	56.4	19.1	33.8	57	0	7	1	0	1	91	87.8	12.8 **
	36	0.7	2.0	1.2	0.6	0.5	23	0	4	1	1	2	4	8.7	0.6

Parameter, number of animals

mean

S.D.

M.C., multiple comparisons

**, significantly different from control, p<0.01

Table 5-1

Twenty-eight-day repeat dose oral toxicity study of tamoxifen 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	5.9	3.3	1.28	15	0.6	159	52	153	567	165	35	61	0	6.3	9.4	143.8	4.38	106.5	
	0.3	0.2	0.19	2	0.0	18	7	37	127	89	5	6	0	0.7	0.3	1.9	0.31	1.2	
12.5 μ g/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	5.8	3.2	1.23	16	0.6	170	44 **	207	605	174	37	57	0	6.2	9.4	143.1	4.23	105.4	
	0.3	0.3	0.18	2	0.1	8	4	60	84	76	6	6	0	0.4	0.3	0.9	0.17	1.4	
50.0 μ g/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	5.9	3.2	1.20	17	0.6	164	35 **	199	660	244	34	56	0	6.3	9.4	143.2	4.25	105.3	
	0.1	0.1	0.09	2	0.0	6	6	117	102	221	5	4	0	0.6	0.2	1.3	0.19	1.4	
200 μ g/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	5.8	3.1	1.18	16	0.6	161	30 **	159	575	188	32	51 **	0	6.1	9.4	144.7	4.38	106.7	
	0.3	0.3	0.12	2	0.0	16	3	51	71	142	3	3	0	0.6	0.4	1.7	0.30	1.3	

Parameter, number of animals

mean

S.D.

M.C., multiple comparisons

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

Table 5-2

Twenty-eight-day repeat dose oral toxicity study of tamoxifen 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)	Triglyceride (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	5.9	3.5	1.49	15	0.6	154	66	139	337	98	31	54	1	6.5	9.6	142.4	4.17	107.6	
	0.4	0.3	0.13	3	0.1	9	14	55	83	21	5	5	1	0.9	0.4	2.0	0.50	2.5	
12.5 μ g/kg	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	5.7	3.4	1.48	17	0.7	162	59	80*	343	86	27	54	0	6.2	9.3	142.1	4.11	110.1	
	0.4	0.3	0.16	3	0.1	20	5	34	76	30	5	5	1	0.7	0.4	1.3	0.33	1.8	
50.0 μ g/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	5.4*	3.2*	1.39	18	0.6	149	52	65**	394	106	26	57	1	6.2	8.9**	142.9	4.01	111.5**	
	0.5	0.3	0.15	4	0.0	18	9	28	90	30	4	9	0	1.0	0.5	1.8	0.15	3.0	
200 μ g/kg	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	5.3**	3.0**	1.31*	18	0.6	151	41**	59**	451**	94**	25	57	1	5.8	8.7**	142.1	4.20	110.6*	
	0.3	0.2	0.15	4	0.1	10	6	23	63	38	4	7	0	0.3	0.3	2.0	0.35	2.3	

Parameter, number of animals

M.C., multiple comparisons

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

mean

S.D.

Table 6-1

Twenty-eight-day repeat dose oral toxicity study of tamoxifen 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)
Control	10 430.0 21.2	10 15938.9 1642.2	10 2915.2 223.8	10 55.0 2.8	10 11.7 1.2	10 18.3 1.8	10 468.5 90.4	10 1311.4 285.0	10 3332.5 250.4	10 1013.0 98.0	10 2348.5 423.8
12.5 μ g/kg	10 429.6 18.5	10 16068.0 1361.7	10 2807.0 231.9	10 55.1 5.1	10 11.3 0.9	10 20.8 1.8	10 431.0 125.1	10 1252.3 180.4	10 3276.8 244.5	10 926.5 83.5	10 2178.4 212.9
50.0 μ g/kg	10 406.7 * 21.8	10 15704.0 1396.9	10 2844.0 190.0	10 58.6 9.0	10 10.5 1.4	10 18.8 4.7	10 437.3 189.0	10 1097.2 281.4	10 3305.3 236.9	10 935.1 68.8	10 1889.5 * 324.8
200 μ g/kg	10 363.8 ** 17.6	10 14539.3 1007.9	10 2852.3 241.6	10 56.1 7.4	10 10.0 ** 0.6	10 19.3 4.8	10 328.1 102.1	10 779.8 ** 268.0	10 3246.1 342.3	10 865.7 ** 79.6	10 1510.6 ** 397.1

Parameter, number of animal

M.C., multiple comparisons

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

mean

S.D.

Table 6-2

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

Absolute organ weights in females

Group	Body weight (g)	Liver (mg)	Kidneys (mg)	Uterus (mg)	Pituitary gland (mg)	Thyroid gland (mg)	Adrenal glands (mg)	Ovaries (mg)
Control	10 278.1 8.4	10 10242.6 572.6	10 1851.2 138.6	10 395.2 67.2	10 14.1 1.6	10 14.4 2.1	10 62.2 9.7	10 84.6 18.9
12.5 μ g/kg	10 259.2 23.3	10 9152.2 1416.4	10 1817.8 181.0	10 390.2 77.8	10 12.4 2.4	10 13.7 3.0	10 66.0 7.6	10 85.9 12.8
50.0 μ g/kg	10 232.5 ** 15.7	10 7914.5 ** 741.4	10 1647.0 ** 131.3	10 266.6 * 49.4	10 11.5 * 1.2	10 14.1 1.5	10 57.5 4.9	10 76.3 8.6
200 μ g/kg	10 219.8 ** 10.4	10 7662.6 ** 604.7	10 1596.9 ** 77.0	10 199.5 ** 28.0	10 10.5 ** 0.7	10 12.9 2.4	10 59.8 8.8	10 44.9 ** 13.4

Parameter number of animals

M.C., multiple comparisons

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

mean

S.D.

Table 7-1

Twenty-eight-day repeat dose oral toxicity study of tamoxifen 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
	430.0	37.017	6.786	0.128	0.027	0.042	1.092	3.051	7.767	2.362	5.5
	21.2	2.571	0.486	0.005	0.002	0.004	0.218	0.652	0.680	0.267	1.0
12.5 μ g/kg	10	10	10	10	10	10	10	10	10	10	10
	429.6	37.361	6.533	0.128	0.027	0.048	1.006	2.934	7.649	2.162	5.1
	18.5	1.866	0.428	0.010	0.002	0.004	0.299	0.535	0.760	0.237	0.6
50.0 μ g/kg	10	10	10	10	10	10	10	10	10	10	10
	406.7 *	38.593	6.998	0.144	0.026	0.046	1.078	2.698	8.144	2.308	4.7
	21.8	2.500	0.415	0.021	0.003	0.011	0.468	0.681	0.690	0.233	0.8
200 μ g/kg	10	10	10	10	10	10	10	10	10	10	10
	363.8 **	40.003 *	7.838 **	0.154 **	0.027	0.053	0.906	2.139 **	8.934 **	2.386	4.1 **
	17.6	2.855	0.542	0.020	0.002	0.012	0.300	0.727	0.967	0.263	1.1

Parameter, number of animals

mean

S.D.

M.C., multiple comparisons

*, 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 tamoxifen in rats

Relative organ weights in females

Group	Body weight (g)	Liver (mg/g)	Kidneys (mg/g)	Uterus (mg/g)	Pituitary gland (mg/g)	Thyroid gland (mg/g)	Adrenal glands (mg/g)	Ovaries (mg/g)
Control	278.1 8.4	36.848 2.023	6.664 0.548	1.425 0.264	0.051 0.007	0.052 0.007	0.224 0.033	0.304 0.066
12.5 μ g/kg	10 259.2 23.3	10 35.179 2.715	10 7.026 0.508	10 1.515 0.314	10 0.048 0.008	10 0.054 0.015	10 0.255 0.023	10 0.331 0.037
50.0 μ g/kg	10 232.5 ** 15.7	10 34.011 * 1.543	10 7.088 0.379	10 1.148 * 0.210	10 0.049 0.004	10 0.061 0.008	10 0.247 0.016	10 0.329 0.036
200 μ g/kg	10 219.8 ** 10.4	10 34.840 1.717	10 7.285 0.566	10 0.911 ** 0.143	10 0.048 0.002	10 0.058 0.009	10 0.272 ** 0.039	10 0.204 ** 0.060
Parameter number of animals								
mean								
S.D.								

M.C., multiple comparisons

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

Table 8
Twenty-eight-day repeat dose oral toxicity study of tamoxifen in rats

Epididymal 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	96.8 ±1.1	200.4 ±20.6	1037.3 ±59.8	179.9 ±28.0	115.2 ±14.4
12.5 ug/kg	88.8 ±10.2	169.1 ±37.6	929.8 ±138.3	149.7 ±23.9	101.0 ±14.5
50.0 ug/kg	94.0 ±3.7	148.9 * ±24.9	921.8 ±65.1	183.1 ±22.4	120.6 ±14.3
200 ug/kg	92.9 ±3.3	163.1 ±9.5	981.4 ±64.3	169.5 ±35.3	110.6 ±13.3

parameters represented mean ± S.D.
*, significantly different from control, p<0.05.

Table 9-1
 Twenty-eight-day repeat dose oral toxicity study of tamoxifen in rat
 Summary of macroscopic findings in males

Group	Control		12.5 µg/kg		50 µg/kg		200 µg/kg	
	-	+	-	+	-	+	-	+
Grade (Seminal vesicle)	[10]		[10]		[10]		[10]	
Small	9	1	10	0	10	0	6	4
(Prostate)	[10]		[10]		[10]		[10]	
Small	10	0	10	0	10	0	7	3
(Lung)	[10]		[10]		[10]		[10]	
Spot, dark	9	1	10	0	10	0	10	0
(Kidney)	[10]		[10]		[10]		[10]	
Dilatation, renal pelvis, unilateral	10	0	10	0	9	1	10	0
Recessed area	10	0	10	0	10	0	9	1

-, negative; +, positive

[.]. Number of animals examined

Table 9-2
 Twenty-eight-day repeat dose oral toxicity study of tamoxifen in rat
 Summary of macroscopic findings in females

Group	Control		12.5 µg/kg		50 µg/kg		200 µg/kg	
	-	+	-	+	-	+	-	+
Grade (Ovary)	[10]		[10]		[10]		[10]	
Small	10	0	10	0	10	0	4	6
(Uterus)	[10]		[10]		[10]		[10]	
Small	10	0	10	0	10	0	9	1

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

Table 10-1
Twenty-eight-day lowest dose oral toxicity study of lamoxifen in rats
Summary of histological findings in males

Group	Control			125 µg/kg			50 µg/kg			200 µg/kg		
	Pos	**	***	Pos	**	***	Pos	**	***	Pos	**	***
(Lung & Bronchus)												
Hemorrhage, focal	9	1	0	10	0	0	0	0	0	2	0	0
(Spleen)												
Hemolysis, extramedullary	3	7	0	10	3	7	0	0	0	8	0	0
Deposit, pigment, brown	0	10	0	10	0	0	0	0	0	10	0	0
(Kidney)												
Eosinophilic body	10	0	0	10	9	1	0	0	0	1	0	0
Basophilic tubule, cortex	4	6	0	6	4	0	0	0	0	6	0	0
Cellular infiltration, lymphocyte	5	5	0	6	4	0	0	0	0	3	0	0
(Thyroid gland)												
Cellular infiltration, lymphocyte	10	0	0	10	9	1	0	0	0	0	0	0
(Ovary, Ventrals & Dorsolateral lobes)												
Cellular infiltration, lymphocyte	5	5	0	5	3	2	0	0	0	5	0	0
Cellular infiltration, plasma cell	10	0	0	8	2	0	0	0	0	2	0	0

- Negative, ± Very slight, + Slight, ** Moderate, *** Severe, Pos. Total of positive areas
[] Number of animals examined

Table 10-2
Twenty-eight day repeat dose oral toxicity study of tamoxifen in rats
Summary of histopathological findings in females

Group	Control		12.5 µg/kg		50 µg/kg		200 µg/kg		Pos
	±	+	±	+	±	+	±	+	
(Lung & Bronchus)	[10]		[10]		[10]		[10]		
Accumulation, foam cell, focal	0	2	7	3	0	0	0	0	0
Cellular infiltration, eosinophili	9	1	10	0	0	0	0	0	1
(Spleen)	[10]		[10]		[10]		[10]		
Hemopoiesis, extramedullary	5	5	7	3	0	0	0	0	3
Deposit, pigment, brown	1	9	0	10	0	0	0	0	10
(Kidney)	[10]		[10]		[10]		[10]		
Cellular infiltration, lymphocyte	9	1	7	3	0	0	0	0	0
Basophilic tubule, cortex	8	2	7	3	0	0	0	0	2
(Thyroid gland)	[10]		[10]		[10]		[10]		
Ectopic thymus	10	0	9	1	0	0	0	0	0
(Ovary)	[10]		[10]		[10]		[10]		
Decrease corpus luteum	9	1	9	0	1	0	0	0	10
Increase stroma follicle	10	0	9	1	0	0	0	0	10
Increase interstitial gland	10	0	9	1	0	0	0	0	10
Follicular cyst	10	0	9	0	1	0	0	0	10
Ovarian follicle	10	0	10	0	0	0	0	0	2
(Uterus, Horn & Cervix)	[10]		[10]		[10]		[10]		
Hypertrophy, luminal epithelial cell	9	1	6	3	1	0	0	0	10
Atrophy, endometrium	10	0	10	0	0	0	0	0	7
Cellular infiltration, eosinophili	0	3	0	0	0	0	0	0	7
Decrease, endometrium & myometrium	10	0	0	0	2	5	3	0	9
Vacuolation, with cell debris, glandular epithelium	10	0	10	0	0	0	0	0	6
Dilatation, cystic, gland	10	0	9	1	0	0	0	0	0
Vacuolation, with cell debris, luminal epithelium	9	1	9	1	0	0	0	0	0
Mitosis, luminal epithelial cell	0	10	0	9	1	0	0	0	10
Increase, capillary, endometrium	1	8	6	2	2	0	0	0	3
Hemorrhage, focal, endometrium	10	0	10	0	0	0	0	0	6
(Vagina)	[10]		[10]		[10]		[10]		
Mucification, epithelium	8	2	10	0	0	0	0	0	0
Corrification, epithelium	6	1	2	3	5	0	0	0	9
Cellular infiltration, neutrophili	9	0	9	1	0	0	0	0	7
Increase, thickness, epithelial layer	2	5	1	8	1	0	0	0	7
Mitosis, epithelial cell	9	0	9	0	0	1	0	0	8
Cell debris, acicloballs, lumen	4	5	9	1	0	0	0	0	0
	10	0	2	6	2	0	0	0	10

- Negative, ±, Very slight, * Slight, **, Moderate, ***, Severe, Pos., Total of positive graph
 [] Number of animals examined
 *, Significantly different from control p<0.05 (Two-tailed Mann-Whitney U test)
 **, 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)



Photo 1 A microphotograph of the ovary from the animal of tamoxifen, 200 $\mu\text{g}/\text{kg}$ group (Animal No. 72) showing decrease corpus luteum and increase atretic follicle, H-E, x 70.



Photo 2 A microphotograph of the uterus from the animal of tamoxifen, 200 $\mu\text{g}/\text{kg}$ group (Animal No. 80) showing atrophy of endometrium, H-E, x70.

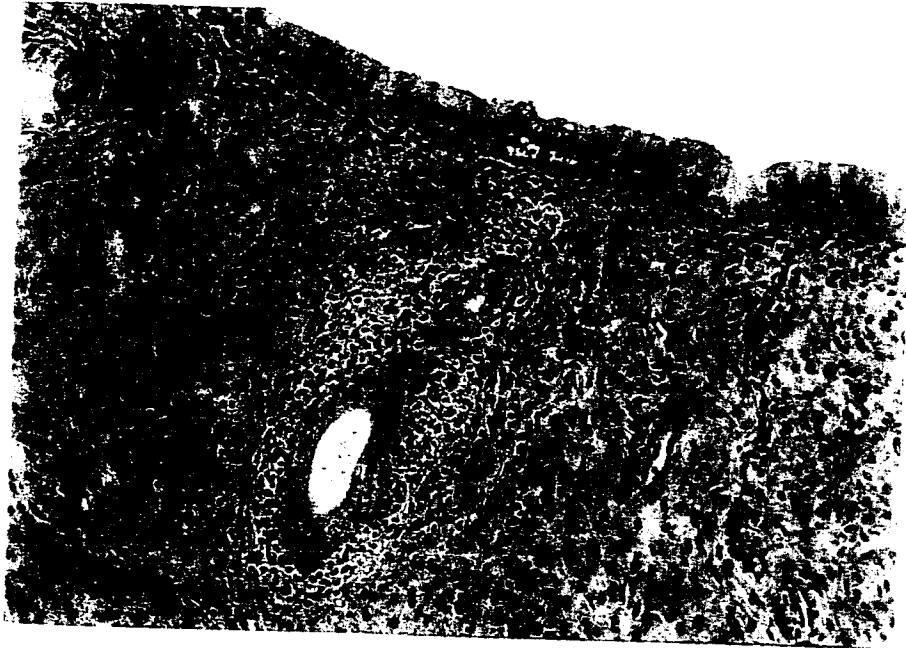


Photo 3 A microphotograph of the uterus from the animal of tamoxifen, 12.5 $\mu\text{g}/\text{kg}$ group (Animal No. 55) showing cellular infiltration in the endometrium, H-E, x180.



Photo 4 A microphotograph of the vagina from the animal of tamoxifen, 200 $\mu\text{g}/\text{kg}$ group (Animal No. 71) showing mucification of epithelial cells, H-E, x70.