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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					
12.5 µg/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					
50.0 µg/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					
200 µg/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					

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)
	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	4
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	
67	D	E	D	D	D	D	E	D	DS						regular	5
68	D	D	D	E	D	D	D	E	D	DS					regular	4
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	10	10	2	10	7
	8.9	236	41	8	2.87	74
	1.2	73	14	-	1.25	85
12.5 μ g/kg	10	10	10	0	10	10
	9.9	214	74 *	N.D.	2.04	75
	1.5	49	16	-	1.13	67
50.0 μ g/kg	10	10	10	0	10	10
	11.7 **	225	98 **	N.D.	1.37 **	107
	2.2	38	37	-	0.88	112
200 μ g/kg	10	10	10	0	10	10
	12.1 **	243	83 **	N.D.	1.38 **	114
	2.0	42	34	-	0.62	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 10.3 2.1	10 162 39	10 42 14	8 12 7	10 117 135
12.5 µg/kg	10 9.9 2.0	10 234 87	10 56 30	9 21 11	10 124 148
50.0 µg/kg	10 9.3 0.8	10 291 102	10 151 246	4 14 8	10 133 129
200 µg/kg	10 9.2 2.8	10 248 63	9 193 243	3 9 1	9 123 177
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 ($\times 10^6/\text{mm}^3$)	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
12.5 $\mu\text{g}/\text{kg}$	22	0.3	1.0	1.4	0.7	0.6	12	0	4	0	0	2	4	8.6	0.5
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
50.0 $\mu\text{g}/\text{kg}$	712	14.1	40.6	57.1	19.9	34.8	87	0	7	0	0	2	91	88.2	11.8
	27	0.4	1.3	2.2	0.6	0.5	14	0	4	0	0	1	4	11.2	0.6
200 $\mu\text{g}/\text{kg}$	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
200 $\mu\text{g}/\text{kg}$	26	0.3	0.8	1.7	0.6	0.6	26	0	7	0	0	3	9	8.1	0.4
	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
200 $\mu\text{g}/\text{kg}$	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

TableS-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)	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 0.3	3.3 0.2	1.28 0.19	15 2	0.6 0.0	159 18	52 7	153 37	567 127	165 89	35 5	61 6	0 0	6.3 0.7	9.4 0.3	143.8 1.9	4.38 0.31	106.6 1.2
12.5 μ g/kg	5.8 0.3	3.2 0.3	1.23 0.18	16 2	0.6 0.1	170 8	44 ** 4	207 60	605 84	174 76	37 6	57 6	0 0	6.2 0.4	9.4 0.3	143.1 0.9	4.23 0.17	105.4 1.4
50.0 μ g/kg	5.9 0.1	3.2 0.1	1.20 0.09	17 2	0.6 0.0	164 6	35 ** 6	199 117	660 102	244 221	34 5	56 4	0 0	6.3 0.6	9.4 0.2	143.2 1.3	4.25 0.19	105.3 1.4
200 μ g/kg	5.8 0.3	3.1 0.3	1.18 0.12	16 2	0.5 0.0	161 16	30 ** 3	159 51	575 71	188 142	32 3	51 ** 3	0 0	6.1 0.6	9.4 0.4	144.7 1.7	4.38 0.30	106.7 1.3

Parameter, number of animals

M.C., multiple comparisons

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

mean

S.D.

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 0.4	3.5 0.3	1.48 0.13	15 3	0.6 0.1	154 9	66 14	139 55	337 83	88 21	31 5	54 5	1 1	6.5 0.9	9.6 0.4	142.4 2.0	4.17 0.50	107.6 2.5
12.5 μ g/kg	5.7 0.4	3.4 0.3	1.48 0.16	17 3	0.7 0.1	162 20	59 5	90* 34	343 76	86 30	27 5	54 5	0 1	6.2 0.7	9.3 0.4	142.1 1.3	4.11 0.33	110.1 1.8
50.0 μ g/kg	5.4* 0.5	3.2* 0.3	1.39 0.15	18 4	0.6 0.0	149 18	52 9	65** 28	394 90	106 30	26 4	57 9	1 0	6.2 1.0	8.9** 0.5	142.9 1.8	4.01 0.15	111.5** 3.0
200 μ g/kg	5.3** 0.3	3.0** 0.2	1.31* 0.15	18 4	0.6 0.1	151 10	41** 6	59** 23	451** 63	94 38	25 4	57 4	1 0	5.8 0.3	8.7** 0.3	142.1 2.0	4.20 0.35	110.6* 2.3

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 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	10	10	10	10	10	10	10	10	10	10
	430.0	15938.9	2915.2	55.0	11.7	18.3	468.5	1311.4	3332.5	1013.0	2348.5
	21.2	1642.2	223.8	2.8	1.2	1.8	90.4	285.0	250.4	98.0	423.8
12.5 μ g/kg	10	10	10	10	10	10	10	10	10	10	10
	429.6	16088.0	2807.0	55.1	11.3	20.8	431.0	1252.3	3276.8	926.5	2178.4
	18.5	1361.7	231.9	5.1	0.9	1.8	125.1	180.4	244.5	83.5	212.9
50.0 μ g/kg	10	10	10	10	10	10	10	10	10	10	10
	406.7 *	15704.0	2844.0	58.6	10.5	18.8	437.3	1097.2	3305.3	935.1	1889.5 *
	21.8	1396.9	190.0	9.0	1.4	4.7	189.0	281.4	236.9	68.8	324.8
200 μ g/kg	10	10	10	10	10	10	10	10	10	10	10
	363.8 **	14539.3	2852.3	56.1	10.0 **	19.3	328.1	779.8 **	3246.1	865.7 **	1510.6 **
	17.6	1007.9	241.6	7.4	0.6	4.8	102.1	268.0	342.3	79.6	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

mean

S.D.

M.C., multiple comparisons

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

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	430.0	37.017	6.786	0.128	0.027	0.042	1.092	3.051	7.767	2.362	5.5
12.5 μ g/kg	429.6	37.361	6.533	0.128	0.027	0.048	1.006	2.934	7.649	2.162	5.1
50.0 μ g/kg	406.7 *	38.593	6.998	0.144	0.026	0.046	1.078	2.698	8.144	2.308	4.7
200 μ g/kg	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

M.C., multiple comparisons

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

mean

S.D.

Table 7-2

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

Relative organ weights in females

Group	Body weight		Liver (mg/g)	Kidneys (mg/g)	Uterus (mg/g)	Pituitary gland (mg/g)	Thyroid gland (mg/g)	Adrenal glands (mg/g)	Ovaries (mg/g)
	(g)								
Control	10		10	10	10	10	10	10	10
	278.1		36.848	6.664	1.425	0.051	0.052	0.224	0.304
12.5 μ g/kg	8.4		2.023	0.548	0.264	0.007	0.007	0.033	0.066
	10		10	10	10	10	10	10	10
259.2			35.179	7.026	1.515	0.048	0.054	0.255	0.331
	23.3		2.715	0.508	0.314	0.008	0.015	0.023	0.037
50.0 μ g/kg	10		10	10	10	10	10	10	10
	232.5 **		34.011 *	7.088	1.148 *	0.049	0.061	0.247	0.329
15.7			1.543	0.379	0.210	0.004	0.008	0.016	0.036
	10		10	10	10	10	10	10	10
219.8 **			34.840	7.285	0.911 **	0.048	0.058	0.272 **	0.204 **
	10.4		1.717	0.566	0.143	0.002	0.009	0.039	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 Grade	Control		12.5 µg/kg		50 µg/kg		200 µg/kg					
	-	+	-	+	-	+	-	+				
(Seminal vesicle)	[10]	9	[10]	1	[10]	0	[10]	0	[10]	6	4	
Small												
(Prostate)	[10]	10	[10]	0	[10]	0	[10]	0	[10]	7	3	
Small												
(Lung)	[10]	9	[10]	1	[10]	0	[10]	0	[10]	10	0	
Spot, dark												
(Kidney)	[10]	10	[10]	0	[10]	0	[10]	1	[10]	10	0	
Dilatation, renal pelvis, unilateral												
Recessed area												
		10		0		0		9			10	0
		10		0		0		10			9	1

-, negative; +, positive

[.], Number of animals examined

