

(IET 06-0070)

Table 15 Ophthalmology - Incidence of findings in male rats

	Dose (mg/kg/day)			
	0	1	8	40
Site & Lesion	0 <sup>a</sup>	0 <sup>a</sup>	0 <sup>a</sup>	0 <sup>a</sup>
Week	4	0 <sup>a</sup>	0 <sup>a</sup>	4
Number of animals examined	10	10	10	10
No abnormalities detected	10	10	10	10
				4

<sup>a</sup>: Week before initiation of treatment.

Table 16 Ophthalmology - Incidence of findings in female rats

Site & Lesion	Dose (mg/kg/day)				40
	0 <sup>a</sup>	4	0 <sup>a</sup>	8	
Week	0 <sup>a</sup>	4	0 <sup>a</sup>	0 <sup>a</sup>	4
Number of animals examined	10	10	10	10	5
No abnormalities detected	10	10	10	10	5

<sup>a</sup>: Week before initiation of treatment.

Key to Tables 17 and 18  
Standard key to urinalysis data

Grades for glucose, bilirubin, ketones, occult blood, protein:

-	Negative
±	Trace
+	Slight
++	Moderate
+++	Severe
++++	Extreme

Appearance:

C	Colorless
PY	Pale yellow
Y	Yellow
YB	Yellow brown
B	Brown

Urinary sediments:

Abnormal crystals	Crystals of cholesterol, tyrosine, leucine, cystine or test substance, etc.
-	Nil
+	A few in some fields
++	A few in any field
+++	Many in any field



Urinalysis - Summary data in male rats

Table 17 - 2

At 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	Appearance				Urine volume (mL/day) Mean $\pm$ S.D.	Urinary sediments						
		C	PY	Y	YB		B	Red blood cells	White blood cells	Abnormal crystals			
0	10			10		10.1 $\pm$ 1.7	-	+	++	+++	8	2	
1	10			9	1	11.8 $\pm$ 2.5					9	1	1
8	10			10		12.2 $\pm$ 6.5					9	1	
40	4			4		10.9 $\pm$ 1.5					4		

  

	Urinary sediments														
	White blood cells			Epithelial cells			Casts			Abnormal crystals					
-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++
10					10										10
10					10										10
10					10										10
4					4										4

S.D.: Standard deviation.

Urinalysis - Summary data in female rats

Table 18 - 1

At 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	Specific gravity Mean $\pm$ S.D.	Glucose					Bilirubin			Ketones		
			-	$\pm$	+	++	+++	++++	-	+	++	+++	++++
0	10	1.020 $\pm$ 0.013	10					10				8	2
1	10	1.026 $\pm$ 0.014	10					9	1			7	1 2
8	10	1.027 $\pm$ 0.021	10					10				8	2
40	7	1.038 $\pm$ 0.036	7					6	1			5	1 1

  

Occult blood	pH	Protein	Urobilinogen (Ehrlich unit/dL)							
			-	$\pm$	+	++	+++	++++		
9	1		7	3					7	3
10			3	2	3	2			6	4
5	4	1	4	3	1	2			6	4
6	1		4	1	1	1	1	1	4	2 1

S.D.: Standard deviation.

Table 18 - 2 Urinalysis - Summary data in female rats

At 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	Appearance				Urine volume (mL/day) Mean $\pm$ S.D.	Urinary sediments							
		C	PY	Y	YB		B	Red blood cells	White blood cells	Abnormal crystals				
0	10			10		10.5 $\pm$ 3.9	-	+	+++	10	-	+	++	+++
1	10			10		9.6 $\pm$ 3.1				10				
8	10			10		9.5 $\pm$ 3.2				9				1
40	7			6	1	9.8 $\pm$ 7.8				7				

  

Urinary sediments															
White blood cells				Epithelial cells				Casts				Abnormal crystals			
-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++
10				10				10				10			
10				10				10				10			
10				10				10				10			
7				7				7				7			

S.D.: Standard deviation.

Key to Tables 19 and 20  
Standard key to hematology data

Hematology:

Ht	Hematocrit
Hb	Hemoglobin concentration
RBC	Erythrocyte count
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
PLT	Platelet count
Retics	Reticulocyte count
PT	Prothrombin time
APTT	Activated partial thromboplastin time
WBC	Total leukocyte count

Differential leukocyte count

L	Lymphocyte
N	Neutrophil
M	Monocyte
E	Eosinophil
B	Basophil
LUC	Large unstained cell

Table 19 - 1  
Hematology - Group mean values in male rats  
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	Ht (%)	Hb (g/dL)	RBC ( $10^6/\mu\text{L}$ )	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ( $10^3/\mu\text{L}$ )	Retics ( $10^9/\text{L}$ )	PT (sec)	APTT (sec)
0	10	Mean	16.0	8.75	52.4	18.3	34.9	1046	175.3	18.5	23.9
		S.D.	0.4	0.34	1.8	0.6	0.2	116	19.7	2.3	2.0
1	10	Mean	15.9	8.74	51.8	18.2	35.1	1083	198.6	19.4	24.3
		S.D.	0.4	0.21	1.0	0.4	0.5	119	56.2	2.3	2.0
8	10	Mean	15.8	8.72	51.6	18.2	35.3	1114	177.7	18.7	25.2
		S.D.	0.3	0.33	1.5	0.5	0.4	178	17.4	1.5	1.9
40	4	Mean	16.0	8.53	53.7	18.7	34.9	1106	195.4	19.6	24.8
		S.D.	0.3	0.32	1.2	0.4	0.5	107	24.9	1.8	1.6

S.D. : Standard deviation.

Table 19 - 2 Hematology - Group mean values in male rats  
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	WBC ( $10^3/\mu\text{L}$ )	Differential leukocyte count ( $10^3/\mu\text{L}$ )						
			L	N	M	E	B	LUC	
0	10	Mean	5.78	1.17	0.10	0.06	0.03	0.05	
		S.D.	0.79	0.29	0.04	0.03	0.01	0.02	
1	10	Mean	6.19	1.33	0.12	0.06	0.04	0.05	
		S.D.	1.44	0.43	0.04	0.04	0.02	0.02	
8	10	Mean	5.39	1.21	0.13	0.07	0.03	0.07	
		S.D.	0.98	0.40	0.08	0.01	0.01	0.07	
40	4	Mean	6.24	1.75	0.13	0.08	0.03	0.07	
		S.D.	1.51	0.43	0.03	0.04	0.02	0.03	

S.D. : Standard deviation.

Table 19 - 3 Hematology - Group mean values in male rats  
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	Nucleated cell count of bone marrow ( $10^5/\mu\text{L}$ )	
		Mean	S.D.
0	10	25.8	1.4
1	10	27.0	2.3
8	10	27.4	3.5
40	4	26.5	1.5

S.D. : Standard deviation.

Table 20 - 1  
Hematology - Group mean values in female rats  
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	Ht (%)	Hb (g/dL)	RBC ( $10^6/\mu\text{L}$ )	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ( $10^3/\mu\text{L}$ )	Retics ( $10^9/\text{L}$ )	PT (sec)	APTT (sec)
0	10	Mean	15.1	7.84	54.2	19.3	35.6	1276	201.0	16.6	20.2
		S.D.	0.7 (8)	0.3 (8)	0.8 (8)	0.4 (8)	0.3 (8)	132 (8)	41.0 (8)	0.6 (8)	1.3 (8)
1	10	Mean	15.0	8.01	52.6 *	18.8	35.8	1231	189.0	16.7	19.8
		S.D.	1.0	0.3	1.1	0.5	0.5	90	45.9	0.5	0.5
8	9	Mean	15.2	8.00	53.1	19.0	35.8	1331	168.3	17.0	19.1
		S.D.	1.2	0.4	1.4	0.5	0.6	111	38.3	0.4	0.8
40	5	Mean	16.3	8.41 *	53.6	19.4	36.1	1267	188.1	16.4	18.9
		S.D.	3.8 (4)	1.6 (4)	1.3 (4)	0.9 (4)	0.8 (4)	160 (4)	108.8 (4)	0.4 (4)	1.6 (4)

S.D. : Standard deviation.

( ) : Available number of animals for the parameter.

Significantly different from control : \* ,  $p \leq 0.05$ ; \*\* ,  $p \leq 0.01$ .

Table 20 - 2  
Hematology - Group mean values in female rats  
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	WBC ( $10^3/\mu\text{L}$ )	Differential leukocyte count ( $10^3/\mu\text{L}$ )						
			L	N	M	E	B	LUC	
0	10	Mean	4.58	1.17	0.09	0.08	0.02	0.04	
		S.D.	0.98 (8)	0.22 (8)	0.03 (8)	0.06 (8)	0.01 (8)	0.02 (8)	
1	10	Mean	4.42	1.01	0.09	0.07	0.02	0.04	
		S.D.	1.35	0.39	0.03	0.04	0.02	0.02	
8	9	Mean	4.98	1.38	0.10	0.08	0.02	0.03	
		S.D.	1.69	0.90	0.04	0.03	0.01	0.02	
40	5	Mean	5.32	1.67	0.16 *	0.06	0.03	0.02	
		S.D.	1.39 (4)	0.28 (4)	0.05 (4)	0.06 (4)	0.01 (4)	0.01 (4)	

S.D. : Standard deviation.

( ) : Available number of animals for the parameter.

Significantly different from control : \* ,  $p \leq 0.05$ ; \*\* ,  $p \leq 0.01$ .

Table 20 - 3  
 Hematology - Group mean values in female rats  
 After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	Nucleated cell count of bone marrow ( $10^5/\mu\text{L}$ )
0	10	Mean 27.3 S.D. 2.8
1	10	Mean 26.0 S.D. 2.5
8	9	Mean 28.5 S.D. 2.8
40	5	Mean 24.5 S.D. 4.9

S.D. : Standard deviation.

Key to Tables 21 and 22  
Standard key to blood biochemistry data

Blood Biochemistry:

ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGTP	$\gamma$ -Glutamyl transpeptidase
Creat	Creatinine
BUN	Blood urea nitrogen
TP	Total protein
Alb	Albumin
Glob	Globulin
A/G ratio	Albumin/globulin ratio
Gluc	Glucose
T.Chol	Total cholesterol
TG	Triglyceride
T.Bil	Total bilirubin
Ca	Calcium
P	Inorganic phosphorus
Na	Sodium
K	Potassium
Cl	Chloride

Table 21 - 1  
 Blood biochemistry - Group mean values in male rats  
 After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	ALP (U/L)	AST (U/L)	ALT (U/L)	GGTP (U/L)	Creat (mg/dL)	BUN (mg/dL)	TP (g/dL)	Alb (g/dL)	Glob (g/dL)	A/G ratio	Gluc (mg/dL)
0	10	Mean	67	23	0	0.33	20.7	6.24	4.25	1.99	2.16	166
		S.D.	8	2	1	0.02	3.0	0.22	0.12	0.21	0.26	12
1	10	Mean	66	24	1	0.33	18.9	6.30	4.21	2.08	2.02	158
		S.D.	6	4	0	0.03	2.3	0.18	0.10	0.10	0.07	11
8	10	Mean	69	26	1	0.35	20.1	6.18	4.18	2.01	2.09	158
		S.D.	4	3	1	0.02	2.8	0.09	0.07	0.10	0.12	15
40	4	Mean	69	30	0	0.35	16.7	5.81 **	4.07 *	1.75	2.33	164
		S.D.	12	7	1	0.03	2.0	0.15	0.09	0.07	0.06	15

S.D. : Standard deviation.

Significantly different from control : \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ .

Table 21 - 2  
 Blood biochemistry - Group mean values in male rats  
 After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	T.Chol (mg/dL)	TG (mg/dL)	T.Bil (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	10	Mean	60	0.06	9.9	6.5	146.0	3.34	108.0
	8	S.D.	27	0.01	0.2	0.6	1.0	0.20	1.3
1	10	Mean	65	0.06	10.0	6.2	145.8	3.32	108.3
	9	S.D.	40	0.01	0.2	0.6	1.0	0.17	1.5
8	10	Mean	46	0.05	9.7 *	6.0	145.8	3.23	108.6
	8	S.D.	14	0.01	0.2	0.4	0.8	0.18	1.6
40	4	Mean	74	0.07	9.7	5.7	144.7	3.13	108.2
	7	S.D.	17	0.01	0.1	0.5	0.5	0.22	0.5

S.D. : Standard deviation.  
 Significantly different from control : \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ .

Table 22 - 1  
 Blood biochemistry - Group mean values in female rats  
 After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	ALP (U/L)	AST (U/L)	ALT (U/L)	GGTP (U/L)	Creat (mg/dL)	BUN (mg/dL)	TP (g/dL)	Alb (g/dL)	Glob (g/dL)	A/G ratio	Gluc (mg/dL)
0	10	Mean 212	77	25	0	0.35	20.8	6.41	4.55	1.86	2.46	116
		S.D. 46 (8)	28 (8)	4 (8)	0 (8)	0.03 (8)	2.8 (8)	0.30 (8)	0.32 (8)	0.10 (8)	0.24 (8)	11 (8)
1	10	Mean 246	78	22	0	0.38	22.8	6.34	4.39	1.94	2.27	112
		S.D. 77	11	4	0	0.06	4.3	0.21	0.21	0.13	0.21	5
8	9	Mean 194	75	21	0	0.37	22.5	6.21	4.35	1.86	2.36	122
		S.D. 43	13	4	0	0.05	2.7	0.29	0.39	0.16	0.37	12
40	5	Mean 304	94	30	0	0.38	21.6	6.20	4.28	1.92	2.23	130
		S.D. 160 (4)	20 (4)	12 (4)	1 (4)	0.03 (4)	3.3 (4)	0.08 (4)	0.08 (4)	0.09 (4)	0.13 (4)	23 (4)

S.D. : Standard deviation.

( ) : Available number of animals for the parameter.

Table 22 - 2  
 Blood biochemistry - Group mean values in female rats  
 After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined	T.Chol (mg/dL)	TG (mg/dL)	T.Bil (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	10	Mean	48	10	0.07	9.8	145.6	3.22	110.9
		S.D.	12 (8)	4 (8)	0.01 (8)	0.3 (8)	0.9 (8)	0.17 (8)	1.7 (8)
1	10	Mean	50	8	0.06	9.6	145.3	3.00	110.6
		S.D.	7	3	0.01	0.2	0.7	0.19	1.1
8	9	Mean	48	8	0.07	9.6	145.0	3.03	109.6
		S.D.	7	3	0.01	0.1	1.2	0.25	1.6
40	5	Mean	49	19	0.07	9.6	145.8	2.87 *	106.8 **
		S.D.	18 (4)	9 (4)	0.01 (4)	0.3 (4)	1.0 (4)	0.18 (4)	1.5 (4)

S.D. : Standard deviation.

( ) : Available number of animals for the parameter.

Significantly different from control : \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ .

Table 23 Cellularity - Group mean values in male rats

Dose (mg/kg/day)	No. of animals examined		/mg ( $\times 10^6$ ) <sup>a</sup>		/rat ( $\times 10^7$ )	
			Thymus	Spleen	Thymus	Spleen
0	10	Mean	2.180	0.445	81.5	24.5
		S.D.	0.246	0.063	22.5	5.1
1	10	Mean	2.239	0.457	92.7	26.3
		S.D.	0.222	0.038	22.2	3.2
8	10	Mean	2.067	0.516	76.7	27.6
		S.D.	0.469	0.107	29.7	4.3
40	4	Mean	2.172	0.445	78.2	22.2
		S.D.	0.246	0.036	9.7	2.7

S.D.: Standard deviation.

a: Number of lymphocytes/mg organ weight.