

Table 8 - 1 Functional tests - Summary data in female rats

Sensorimotor responses at 4 weeks

Dose (mg/kg/day)	Score	Visual placing	Approach response	Touch response	Pain response	Auditory response	Aerial righting reflex
0	-2		0	0	0	0	
	-1		0	0	0	0	
	0	10	10	10	9	10	10
	1	0	0	0	1	0	0
	2	0	0	0	0	0	0
	3						0
1	-2		0	0	0	0	
	-1		0	0	0	0	
	0	10	10	10	8	10	10
	1	0	0	0	2	0	0
	2	0	0	0	0	0	0
	3						0
8	-2		0	0	0	0	
	-1		0	0	0	0	
	0	10	10	10	10	10	10
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3						0
80	-2		0	0	0	0	
	-1		0	0	0	0	
	0	10	10	10	9	10	8
	1	0	0	0	1	0	2
	2	0	0	0	0	0	0
	3						0

Table 8 - 2 Functional tests - Summary data in female rats

Data of quantitative measurements at 4 weeks

Dose (mg/kg/day)		Body temperature (°C)	Landing foot splay (mm)	Grip strength	
				Forelimb (g)	Hindlimb (g)
0	Mean	38.8	94	378	238
	S.D.	0.2	15	62	31
	Num.	10	10	10	10
1	Mean	38.8	90	352	247
	S.D.	0.2	9	46	17
	Num.	10	10	10	10
8	Mean	38.7	89	372	233
	S.D.	0.4	16	48	27
	Num.	10	10	10	10
80	Mean	38.5	82	330	234
	S.D.	0.4	9	62	33
	Num.	10	10	10	10

Table 8 - 3

Functional tests - Summary data in female rats

Motor activity

(counts)

Dose (mg/kg/day)	No. of animals examined	Week	4						Total
			min	0-10	10-20	20-30	30-40	40-50	
0	10	Mean	2157	1729	947	749	476	369	6427
		S.D.	419	654	597	432	517	369	2322
1	10	Mean	1892	1291	1034	625	546	270	5658
		S.D.	339	405	499	355	438	385	1685
8	10	Mean	2090	1265	913	694	330	222	5514
		S.D.	431	385	396	425	383	377	1599
80	10	Mean	1557 **	1150	856	659	535	291	5048
		S.D.	509	511	423	348	238	347	1889

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

Table 9 Body weight - Group mean values in male rats

Dose (mg/kg/day)	Day		(g)															
	0 ^a		3	7	10	14	17	21	24	27								
0	Mean	48	63	85	104	128	147	168	186	201								
	S.D.	6	8	10	12	14	15	18	19	20								
	N	13	13	13	13	13	13	13	13	13	13							
1	Mean	49	64	87	107	133	152	174	193	211								
	S.D.	5	6	8	10	15	18	22	24	27								
	N	13	13	13	13	13	13	13	13	13	13							
8	Mean	49	63	84	103	127	145	166	183	199								
	S.D.	5	6	8	9	11	13	15	16	18								
	N	13	13	13	13	13	13	13	13	13	13							
80	Mean	49	59	78	97	120	134	154	168	174 ^{**}								
	S.D.	5	6	7	8	10	12	14	17	19								
	N	13	13	13	13	13	13	13	13	13	13							

a: Day 0, Initiation of treatment.

S.D.: Standard deviation.

N: Number of animals.

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

Table 10 Body weight - Group mean values in female rats

Dose (mg/kg/day)	Day		(g)															
	0 ^a		3	7	10	14	17	21	24	27								
0	Mean	40	52	70	86	102	113	124	133	142								
	S.D.	5	6	6	9	9	10	13	14	15								
	N	13	13	13	13	13	13	13	13	13								
1	Mean	40	51	69	83	99	111	122	130	139								
	S.D.	5	5	7	9	9	10	11	11	12								
	N	13	13	13	13	13	13	13	13	13								
8	Mean	40	52	70	85	102	114	125	133	142								
	S.D.	5	5	6	6	6	6	7	8	8								
	N	13	13	13	13	13	13	13	13	13								
80	Mean	40	48	63 *	78	95	108	124	133	137								
	S.D.	6	7	6	7	6	5	7	7	7								
	N	13	13	13	13	13	13	13	13	13								

a: Day 0, Initiation of treatment.

S.D.: Standard deviation.

N: Number of animals.

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

Table 11 Food consumption - Group mean values in male rats

Dose (mg/kg/day)	Week					Average
	1	2	3	4		
0	Mean	10.3	14.8	18.0	20.0	15.8
	S.D.	1.0	1.2	1.3	1.3	
	N	13	13	13	13	
1	Mean	10.9	15.7	19.0	21.1	16.7
	S.D.	0.7	1.7	2.5	3.0	
	N	13	13	13	13	
8	Mean	10.4	14.9	18.2	19.9	15.9
	S.D.	0.9	1.6	1.9	2.1	
	N	13	13	13	13	
80	Mean	8.2 **	13.3 *	15.1 **	16.8 **	13.4
	S.D.	1.0	1.2	1.9	2.4	
	N	13	13	13	13	

S.D.: Standard deviation.

N: Number of animals.

Significantly different from control: *, $p <= 0.05$; **, $p <= 0.01$.

Table 12 Food consumption - Group mean values in female rats

Dose (mg/kg/day)	Week				Average	
	1	2	3	4		
0	Mean	8.5	12.6	14.3	14.6	12.5
	S.D.	1.0	1.1	1.5	1.8	
	N	13	13	13	13	
1	Mean	8.5	12.8	14.7	14.8	12.7
	S.D.	1.1	1.2	1.3	1.3	
	N	13	13	13	13	
8	Mean	8.6	13.0	15.0	14.5	12.8
	S.D.	1.1	0.9	1.3	1.4	
	N	13	13	13	13	
80	Mean	6.5 **	11.1 **	12.5 **	13.3	10.9
	S.D.	1.0	0.8	1.3	1.7	
	N	13	13	13	13	

S.D.: Standard deviation.

N: Number of animals.

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

Key to Tables 13 and 14
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
<u>Differential leukocyte count</u>	
L	Lymphocyte
N	Neutrophil
M	Monocyte
E	Eosinophil
B	Basophil
LUC	Large unstained cell

Table 13 - 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	8 Mean	41.4	14.1	7.18	57.8	19.7	34.1	1138	282.5	15.0	19.2
	S.D.	0.9	0.4	0.31	1.8	0.8	0.4	81	38.3	0.3	1.2
1	8 Mean	43.4 *	14.9	7.34	59.2	20.3	34.3	1245	320.0	15.0	19.8
	S.D.	1.5	0.6	0.39	2.9	1.0	0.3	138	49.5	0.9	1.2
8	8 Mean	43.3	14.9	7.36	59.0	20.3	34.4	1254	302.7	15.0	19.5
	S.D.	1.8	0.7	0.44	1.6	0.7	0.3	163	34.4	0.5	0.9
80	8 Mean	40.0	13.4	7.42	53.9 **	18.1 **	33.6	1353	266.3	16.7 *	20.3
	S.D.	2.8	1.0	0.56	2.3	1.3	1.0	353	83.6	1.3	2.5

S.D. : Standard deviation.

Significantly different from control : *, $p <= 0.05$; **, $p <= 0.01$.

Table 13 - 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	8	Mean	5.70	0.83	0.11	0.04	0.02	0.06	
		S.D.	0.85	0.50	0.06	0.01	0.01	0.02	
1	8	Mean	6.11	0.65	0.09	0.03	0.02	0.06	
		S.D.	0.73	0.22	0.03	0.01	0.01	0.01	
8	8	Mean	5.39	0.54	0.08	0.03	0.01	0.05	
		S.D.	1.24	0.15	0.02	0.01	0.01	0.03	
80	8	Mean	7.25 *	0.85	0.13	0.02	0.03	0.08	
		S.D.	1.54	0.47	0.09	0.01	0.02	0.04	

S.D. : Standard deviation.

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

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

Table 13 - 3

Dose (mg/kg/day)	No. of animals examined	Nucleated cell count of bone marrow ($10^5/\mu\text{L}$)
0	8	Mean 30.1 S.D. 2.6
1	8	Mean 29.5 S.D. 2.7
8	8	Mean 28.9 S.D. 2.4
80	8	Mean 27.3 S.D. 1.7

S.D. : Standard deviation.

Table 14 - 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	8	Mean 43.1	14.7	7.32	58.8	20.1	34.1	1324	203.7	15.5	16.4
		S.D. 1.0	0.4	0.27	1.3	0.6	0.6	93	55.4	0.6	1.4
1	8	Mean 42.5	14.5	7.51	56.7	19.4	34.2	1287	182.3	15.9	15.8
		S.D. 0.7	0.2	0.28	1.8	0.8	0.5	115	30.0	0.8	1.0
8	8	Mean 43.1	14.7	7.49	57.5	19.6	34.1	1276	204.4	15.3	16.3
		S.D. 1.8	0.6	0.23	0.9	0.4	0.3	131	54.2	0.6	0.9
80	8	Mean 39.8 **	13.1 **	7.40	53.9 **	17.7 **	32.8 **	1308	273.8 *	15.2	16.7
		S.D. 0.5	0.2	0.44	2.7	0.8	0.4	126	72.4	0.8 (7)	0.8 (7)

S.D. : Standard deviation.

() : Available number of animals for the parameter.

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

Table 14 - 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	8	Mean	3.50	0.62	0.06	0.03	0.01	0.01	0.02
		S.D.	0.79	0.31	0.04	0.01	0.01	0.01	0.01
1	8	Mean	3.74	0.52	0.06	0.04	0.01	0.01	0.03
		S.D.	0.79	0.17	0.03	0.01	0.01	0.01	0.01
8	8	Mean	4.22	0.56	0.07	0.04	0.02	0.02	0.03
		S.D.	1.37	0.21	0.04	0.03	0.01	0.01	0.02
80	8	Mean	5.18 *	0.46	0.09	0.02 *	0.01	0.01	0.05
		S.D.	1.97	0.35	0.07	0.01	0.01	0.01	0.03

S.D. : Standard deviation.

Significantly different from control : *, $p <= 0.05$; **, $p <= 0.01$.

Table 14 - 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	8	Mean 27.8 S.D. 2.5
1	8	Mean 28.7 S.D. 2.6
8	8	Mean 28.6 S.D. 2.1
80	8	Mean 27.1 S.D. 2.5

S.D. : Standard deviation.

Key to Tables 15 and 16
Standard key to blood biochemistry data

Blood Biochemistry:

ALP	Alkaline phosphatase
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
GGTP	γ -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 15 - 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)	GOT (U/L)	GPT (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	8	Mean 690	77	20	1	0.22	12.7	5.33	3.71	1.62	2.28	105
		S.D. 177	10	2	0	0.02	2.5	0.26	0.19	0.08	0.06	14
1	8	Mean 751	72	20	0 *	0.20	12.4	5.26	3.67	1.59	2.31	119
		S.D. 213	9	3	0	0.02	2.9	0.19	0.15	0.06	0.05	19
8	8	Mean 630	74	22	1	0.20	13.5	5.44	3.80	1.64	2.32	122
		S.D. 211	10	3	1	0.02	2.9	0.38	0.29	0.09	0.09	21
80	8	Mean 546	102	40 **	2	0.21	18.4 **	5.17	3.66	1.52	2.42 **	112
		S.D. 124	53	29	2	0.03	4.6	0.34	0.23	0.12	0.09	13

S.D. : Standard deviation.

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

Table 15 - 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	8 Mean	67	33	0.05	9.7	7.2	146.6	3.14	108.4
	S.D.	10	15	0.01	0.3	0.5	1.5	0.18	1.4
1	8 Mean	66	50	0.05	9.7	7.4	146.7	3.14	108.2
	S.D.	13	23	0.01	0.4	0.6	1.3	0.12	1.1
8	8 Mean	65	32	0.05	10.1	7.8	146.1	3.19	108.7
	S.D.	11	13	0.01	0.7	0.9	1.4	0.15	1.1
80	8 Mean	71	34	0.08 *	10.2	9.2 **	145.4	3.62	108.2
	S.D.	12	16	0.03	0.6	1.5	0.6	0.99	1.8

S.D. : Standard deviation.

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

Table 16 - 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)	GOT (U/L)	GPT (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	8	Mean 471	72	16	1	0.24	17.5	5.59	3.94	1.65	2.38	103
		S.D. 172	7	2	0	0.03	3.7	0.33	0.26	0.11	0.14	15
1	8	Mean 435	78	18	1	0.25	18.3	5.60	3.97	1.63	2.44	109
		S.D. 141	10	4	0	0.02	3.5	0.18	0.13	0.06	0.06	13
8	8	Mean 375	78	17	1	0.25	17.5	5.65	4.00	1.65	2.42	103
		S.D. 116	10	3	1	0.02	2.1	0.15	0.13	0.03	0.07	14
80	8	Mean 313	74	25	3 **	0.20 **	19.2	4.93 **	3.51 **	1.42 **	2.48	120
		S.D. 89	7	9	1	0.02	2.2	0.25	0.18	0.08	0.10	14

S.D. : Standard deviation.

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

Table 16 - 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	8	Mean 65	19	0.04	10.0	7.4	145.8	3.14	110.7
		S.D. 3	12	0.01	0.4	0.6	1.7	0.19	1.6
1	8	Mean 75	12	0.04	10.0	7.2	145.3	3.20	111.4
		S.D. 12	4	0.01	0.2	0.8	2.3	0.17	3.6
8	8	Mean 79 **	17	0.05	9.9	7.5	147.2	3.22	112.1
		S.D. 11	9	0.01	0.2	0.7	1.4	0.31	1.2
80	8	Mean 74	28	0.05	9.8	8.9 **	146.7	3.36	110.6
		S.D. 8	14	0.02	0.3	1.0	1.5	0.30	1.9

S.D. : Standard deviation.

Significantly different from control : * , $p <= 0.05$; ** , $p <= 0.01$.

Table 17

Cellularity - Group mean values in male rats

Dose (mg/kg/day)	Number of animals examined		<u>/mg($\times 10^6$)^a</u>		<u>/rat($\times 10^7$)</u>	
			Thymus	Spleen	Thymus	Spleen
0	8	Mean	3.347	0.656	211.4	33.2
		S.D.	0.111	0.107	21.6	7.9
1	8	Mean	3.030 *	0.658	190.1	36.8
		S.D.	0.266	0.045	28.1	4.8
8	8	Mean	3.235	0.656	177.6 *	33.6
		S.D.	0.165	0.081	30.9	7.1
80	8	Mean	2.774 **	0.646	92.1 **	20.7 **
		S.D.	0.354	0.072	18.3	5.4

^a: Number of lymphocytes/mg organ weight.

S.D.: Standard deviation.

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