

Table 4-3 Slit-lamp examination in male rats

Group	Dose (mg/kg)	Day	Item	Grade	Water for injection	ACQ	ACQ	ACQ	ACQ
						1	10	30	
Pre	No abnormal changes				6	6	6	6	6
25	No abnormal changes				6			6	6

Numerals represent the number of animals.

Table 4-4 Slit-lamp examination in female rats

Group	Water for injection	ACQ	ACQ	ACQ
Dose (mg/kg)		1	10	30
Day	Grade			
Pre	No abnormal changes	6	6	6
25	No abnormal changes	6		6

Numerals represent the number of animals.

Fundusoscopic examination

Grade

- 0 : No abnormal changes
- 1 : Slight
- 2 : Moderate
- 3 : Severe
- P : Non-graded change
- U : Unexamined

Table 4-5 Funduscopic examination in male rats

Group	Dose(mg/kg)	Item	Grade	Water for injection	ACQ	ACQ	ACQ	ACQ
Pre	No abnormal changes			6	6	6	6	6
25	No abnormal changes			6	6	6	6	6

Numerals represent the number of animals.

Table 4-6 Fundusoscopic examination in female rats

Group	Dose(mg/kg)	Day	Item	Grade	Water for injection	ACQ	ACQ	ACQ
Pre			No abnormal changes		6	6	6	6
25			No abnormal changes		6	6	10	30

Numerals represent the number of animals.

Standard Urinalysis

Color 0 : Normal color
1 : Abnormal color

Protein 0 : -
1 : ±
2 : +
3 : ++
4 : +++

(mg/dL)
30
100
300<=

Glucose 0 : -
1 : ±
2 : +
3 : ++
4 : +++

(g/dL)
0.1
0.25
0.5
1<=

Ketone body 0 : -
1 : ±
2 : +
3 : ++
4 : +++

Bilirubin 0 : -
1 : +
2 : ++
3 : +++

(mg/dL)
5
15
40
80

Occult blood 0 : -
1 : ±
2 : +
3 : ++
4 : +++

Urobilinogen 0 : ±
1 : +
2 : ++
3 : +++
4 : ++++

(Ehrlich unit/dL)
0.1
1
2
4
8<=

Table 5-1 Urinalysis in male rats

Group	Dose (mg/kg)	Day	Grade	Water for injection	ACQ	ACQ	ACQ	ACQ
Color		26	0	6	6	6	6	6
			1					
								30
pH		26	5					
			5.5					
			6	2	1	1	1	
			6.5					
			7	2	4	2	2	1
			7.5	2	1	2	2	2
			8			1	1	2
			8.5					1
			9					

Numerals represent the number of animals.
 Not significantly different from Water for injection.

Table 5-2 Urinalysis in male rats

Group	Dose (mg/kg)	Day	Grade	Water for injection	ACQ	ACQ	ACQ	ACQ
Protein	26	0	1					
			2	2				
			3	3	3	2	4	
			4	1	3	4	2	
Glucose	26	0	1					
			2	6				
			3	6	6	6	6	
			4					

Numerals represent the number of animals.
 Not significantly different from Water for injection.

Table 5-3 Urinalysis in male rats

Group	Water for injection	ACQ	ACQ	ACQ
Dose (mg/kg)	Day	Grade	ACQ	ACQ
			1	30
Ketone body	26	0	5	4
	1	1	1	2
	2			
	3			
	4			
Bilirubin	26	0	6	6
	1			
	2			
	3			

Numerals represent the number of animals.
 Not significantly different from Water for injection.

Table 5-4 Urinalysis in male rats

Group	Dose (mg/kg)	Day	Grade	Water for injection	ACQ	ACQ	ACQ
Occult blood	26		0	4	5	6	6
			1	2	1		
			2				
			3				
			4				
Urobilinogen	26		0	2	3	2	2
			1	4	3	4	4
			2				
			3				
			4				

Numerals represent the number of animals.
 Not significantly different from Water for injection.

Table 5-5 Urinalysis in female rats

Group	Dose(mg/kg)	Day	Grade	Water for injection	ACQ	ACQ	ACQ	ACQ
Color		26	0	6	6	6	6	6
			1					
pH		26	5			1		
			5.5					3
			6		1			
			6.5					
			7	2	1	2		3
			7.5	3	3	1		
			8	1	1	2		
			8.5					
			9					

Numerals represent the number of animals.
 Not significantly different from Water for injection.

Table 5-6 Urinalysis in female rats

Group	Dose (mg/kg)	Day	Grade	Water for injection	ACQ	ACQ	ACQ	ACQ
Protein		26	0	2	2	1	10	5
			1	1	1			
			2	2	3	4	1	
			3	1				
			4			1		
Glucose		26	0	6	6	6	6	6
			1					
			2					
			3					
			4					

Numerals represent the number of animals.
 Not significantly different from Water for injection.

Table 5-7 Urinalysis in female rats

Group	Dose (mg/kg)	Day	Grade	Water for Injection	ACQ	ACQ	ACQ	ACQ
Ketone body		26	0	4	5	6	6	6
			1	2	1			
			2					
			3					
			4					
Bilirubin		26	0	6	6	6	6	6
			1					
			2					
			3					

Numerals represent the number of animals.
 Not significantly different from Water for Injection.

Table 5-8 Urinalysis in female rats

Group	Dose (mg/kg)	Day	Grade	Water for injection	ACQ	ACQ	ACQ	ACQ	
Occult blood	26	0	5	4	1	10	30		
		1				2		5	
		2		1		1	1		
		3	1	1		1	1	1	
		4				1	1		
Urobilinogen	26	0	3	2	4	4	5		
		1	3	4		2		1	
		2							
		3							
		4							

Numerals represent the number of animals.
 Not significantly different from Water for injection.

Hematology

RBC	($10^6/\text{mm}^3$)	Number of red blood cells
WBC	($10^3/\text{mm}^3$)	Number of white blood cells
Ht	(%)	Hematocrit value
Hb	(g/dL)	Hemoglobin concentration
Plat.	($10^3/\text{mm}^3$)	Number of blood platelets
MCV	(fL)	Mean corpuscular volume
MCH	(pg)	Mean corpuscular hemoglobin
MCHC	(g/dL)	Mean corpuscular hemoglobin concentration
Ret.	(%)	Reticulocyte ratio
Hemogram		
Eosino.	($10^3/\text{mm}^3$)	Number of eosinophilic leukocytes
Eosino.	(%)	Eosinophilic leukocyte ratio
Baso.	($10^3/\text{mm}^3$)	Number of basophilic leukocytes
Baso.	(%)	Basophilic leukocyte ratio
Mono.	($10^3/\text{mm}^3$)	Number of monocytes
Mono.	(%)	Monocyte ratio
Lymph.	($10^3/\text{mm}^3$)	Number of lymphocytes
Lymph.	(%)	Lymphocyte ratio
Neutro.	($10^3/\text{mm}^3$)	Number of neutrophilic leukocytes
Neutro.	(%)	Neutrophilic leukocyte ratio
LUC	($10^2/\text{mm}^3$)	Number of large unstained cells
LUC	(%)	Large unstained cell ratio
Blood coagulation test		
PT	(Sec)	Prothrombin time
APTT	(Sec)	Activated partial thromboplastin time

Table 6-1 Hematology in male rats

Group	Dose (mg/kg)	N	Water for injection	ACQ		ACQ		ACQ	
				1	6	10	6	30	6
RBC	(10 ⁶ /mm ³)		8.178±0.422	8.090±0.486	8.188±0.311	7.973±0.403			
WBC	(10 ³ /mm ³)		7.842±1.522	9.012±3.333	8.775±1.454	7.630±2.295			
Ht	(%)		47.28±1.85	46.98±2.02	47.10±1.48	46.07±2.46			
Hb	(g/dL)		16.50±0.56	16.45±0.73	16.50±0.44	16.17±0.88			
Plat.	(10 ³ /mm ³)		1164.2±159.0	1137.2±109.4	1113.7±79.3	1098.0±103.8			
MCV	(fL)		57.63±1.79	58.13±2.19	57.55±1.04	57.75±1.29			
MCH	(pg)		20.13±0.49	20.38±0.84	20.15±0.39	20.27±0.54			
MCHC	(g/dL)		34.85±0.48	35.07±0.24	35.02±0.49	35.13±0.27			
Ret.	(%)		1.97±0.40	2.03±0.25	1.98±0.19	2.52±0.20**			
Eosino.	(10 ³ /mm ³)		0.102±0.040	0.097±0.034	0.110±0.048	0.072±0.015			
Eosino.	(%)		1.33±0.47	1.10±0.28	1.27±0.54	1.00±0.29			
Baso.	(10 ³ /mm ³)		0.028±0.008	0.033±0.020	0.028±0.012	0.027±0.012			
Baso.	(%)		0.33±0.08	0.35±0.12	0.32±0.08	0.32±0.10			
Mono.	(10 ³ /mm ³)		0.148±0.043	0.133±0.074	0.137±0.051	0.122±0.049			
Mono.	(%)		1.87±0.42	1.40±0.42	1.58±0.54	1.58±0.31			
Lymph.	(10 ³ /mm ³)		6.175±1.515	7.683±3.139	7.175±1.594	5.612±2.143			
Lymph.	(%)		78.17±5.76	84.13±5.55	81.18±5.96	72.07±7.17			
Neutro.	(10 ³ /mm ³)		1.347±0.374	1.013±0.332	1.293±0.354	1.758±0.405			
Neutro.	(%)		17.72±5.38	12.47±5.95	15.28±5.44	24.57±7.51			
LUC	(10 ³ /mm ³)		0.048±0.038	0.055±0.046	0.032±0.015	0.038±0.046			
LUC	(%)		0.60±0.42	0.55±0.29	0.35±0.08	0.45±0.44			
PT	(Sec)		12.95±1.87	14.05±2.42	12.83±1.06	11.08±0.53			
APTT	(Sec)		25.10±2.14	25.03±3.13	23.73±1.00	22.28±0.94*			

Values are expressed as the mean ± S.D.
 * P<0.05 , ** P<0.01 : Significantly different from Water for injection.

Table 6-2 Hematology in female rats

Group	Dose (mg/kg)	N	Water for injection		ACQ		ACQ		ACQ	
			6	6	1	6	10	6	30	6
RBC	(10 ⁶ /mm ³)		7.433±0.492	7.295±0.468	7.713±0.343	7.463±0.362				
WBC	(10 ³ /mm ³)		7.428±2.072	7.445±3.527	6.587±1.221	6.208±0.704				
Ht	(%)		41.83±2.22	41.63±1.30	41.93±1.09	41.90±1.70				
Hb	(g/dL)		14.83±0.81	15.05±0.63	14.98±0.57	14.77±0.58				
Plat.	(10 ⁹ /mm ³)		1202.0±187.9	1193.5±140.8	1201.3±162.8	1198.2±97.2				
MCV	(fL)		56.30±0.97	57.15±2.01	54.40±1.39	56.18±1.23				
MCH	(pg)		19.98±0.63	20.67±0.77	19.43±0.50	19.82±0.46				
MCHC	(g/dL)		35.47±0.64	36.13±0.67	35.77±0.67	35.27±0.16				
Ret.	(%)		2.73±1.03	2.52±0.91	2.06±0.43	2.77±0.42				
Eosino.	(10 ³ /mm ³)		0.095±0.034	0.100±0.028	0.122±0.038	0.135±0.058				
Eosino.	(%)		1.27±0.39	1.48±0.44	1.83±0.36	2.17±0.84*				
Baso.	(10 ³ /mm ³)		0.018±0.008	0.023±0.015	0.018±0.004	0.017±0.008				
Baso.	(%)		0.25±0.08	0.27±0.08	0.30±0.09	0.28±0.08				
Mono.	(10 ³ /mm ³)		0.110±0.037	0.120±0.051	0.107±0.051	0.093±0.026				
Mono.	(%)		1.55±0.64	1.62±0.17	1.63±0.65	1.48±0.29				
Lymph.	(10 ³ /mm ³)		5.902±1.695	5.813±2.459	4.905±1.189	4.347±0.934				
Lymph.	(%)		79.53±7.68	79.30±4.54	74.12±7.71	69.85±11.67				
Neutro.	(10 ³ /mm ³)		1.262±0.631	1.335±0.979	1.397±0.492	1.598±0.704				
Neutro.	(%)		16.80±7.32	16.67±4.75	21.63±8.18	25.87±11.62				
LUC	(10 ³ /mm ³)		0.045±0.033	0.057±0.057	0.035±0.038	0.022±0.012				
LUC	(%)		0.53±0.24	0.62±0.32	0.52±0.41	0.33±0.19				
PT	(Sec)		7.75±0.34	8.02±0.31	8.22±0.39	7.95±0.50				
APTT	(Sec)		17.62±1.00	17.17±0.67	17.72±1.63	17.77±1.10				

Values are expressed as the mean ± S.D.
* P<0.05 : Significantly different from Water for injection.

Blood Chemistry

ASAT	(IU/L)	Aspartate aminotransferase
ALAT	(IU/L)	Alanine aminotransferase
ALP	(IU/L)	Alkaline phosphatase
LDH	(IU/L)	Lactate dehydrogenase
CPK	(IU/L)	Creatine phosphokinase
T.Bil.	(mg/dL)	Total bilirubin
T.Prot.	(g/dL)	Total protein
Albumin	(g/dL)	Albumin
T.Chol.	(mg/dL)	Total cholesterol
TGL	(mg/dL)	Triglyceride
Glucose	(mg/dL)	Glucose
BUN	(mg/dL)	Blood urea nitrogen
Creat.	(mg/dL)	Creatinine
IP	(mg/dL)	Inorganic phosphorus
Ca	(mg/dL)	Calcium
Na	(mEq/L)	Sodium
K	(mEq/L)	Potassium
Cl	(mEq/L)	Chloride
Protein fraction		
Albumin	(%)	Albumin
A1-glob.	(%)	Alpha-1 globulin
A2-glob.	(%)	Alpha-2 globulin
B-glob.	(%)	Beta globulin
G-glob.	(%)	Gamma globulin
A/G		Albumin / Globulin

Table 7-1 Blood chemistry in male rats

Group	Dose(mg/kg)	Water for injection	ACQ		ACQ		ACQ	
			N	1	6	10	30	6
ASAT (IU/L)	82.2±14.9	79.8±12.7	99.8±14.3	103.2±19.9				
ALAT (IU/L)	29.7±3.1	33.5±4.5	32.8±3.1	37.8±8.5*				
ALP (IU/L)	601.2±104.7	553.7±105.0	585.5±74.4	589.0±70.4				
LDH (IU/L)	713.8±687.1	403.3±299.4	1098.7±661.8	762.5±388.7				
CPK (IU/L)	310.3±229.2	207.5±69.7	384.5±187.1	292.2±65.9				
T.Bil. (mg/dL)	0.062±0.008	0.067±0.014	0.063±0.005	0.067±0.010				
T.Prot. (g/dL)	5.53±0.39	5.40±0.17	5.50±0.14	5.40±0.09				
Albumin (g/dL)	4.25±0.31	4.15±0.23	4.25±0.19	4.15±0.08				
T.Chol. (mg/dL)	48.2±8.2	51.0±12.5	43.8±8.1	46.3±6.7				
TGL (mg/dL)	27.5±14.5	24.0±7.9	21.5±6.0	14.0±4.4*				
Glucose (mg/dL)	149.7±11.4	150.0±11.6	146.0±11.6	139.0±4.3				
BUN (mg/dL)	17.33±2.81	17.77±1.74	17.05±2.16	19.58±1.63				
Creat. (mg/dL)	0.197±0.027	0.212±0.029	0.203±0.018	0.223±0.022				
IP (mg/dL)	8.348±0.473	8.037±0.506	8.342±0.682	7.423±0.713*				
Ca (mg/dL)	10.05±0.23	10.05±0.18	10.10±0.38	9.87±0.47				
Na (mEq/L)	143.2±1.3	144.2±1.2	144.5±1.0	144.3±1.0				
K (mEq/L)	4.00±0.20	4.02±0.28	4.00±0.09	3.95±0.22				
Cl (mEq/L)	104.0±3.0	104.5±2.0	104.3±1.8	105.3±1.4				
Albumin (%)	53.20±1.73	52.35±1.13	54.15±1.10	53.67±2.19				
A1-glob. (%)	19.95±2.02	20.95±1.49	20.52±2.01	19.50±1.43				
A2-glob. (%)	7.33±0.55	7.37±0.46	6.47±0.60*	7.53±0.30				
B-glob. (%)	14.38±0.55	15.03±0.82	14.80±1.21	15.13±0.78				
G-glob. (%)	5.13±0.36	4.30±0.99	4.07±0.72	4.17±1.21				
A/G	1.138±0.077	1.102±0.050	1.182±0.053	1.165±0.103				

Values are expressed as the mean ± S.D.

* P<0.05 : Significantly different from Water for injection.

Table 7-2 Blood chemistry in female rats

Group	Dose (mg/kg)	N	Water for injection		ACQ		ACQ		ACQ	
			6	6	1	6	10	6	30	6
ASAT (IU/L)			127.3±34.0		116.7±36.1		122.0±33.2		109.7±21.2	
ALAT (IU/L)			27.3±4.8		28.0±5.8		32.3±4.5		31.0±3.4	
ALP (IU/L)			341.0±70.1		371.2±35.2		446.5±94.5*		428.0±66.6	
LDH (IU/L)			2567.7±1014.9		2328.2±1404.9		1661.3±1108.2		1483.7±832.8	
CPK (IU/L)			760.2±258.5		677.7±324.9		540.2±288.1		465.0±241.6	
T.Bil. (mg/dL)			0.038±0.016		0.042±0.008		0.047±0.014		0.032±0.015	
T.Prot. (g/dL)			5.50±0.31		5.53±0.16		5.45±0.23		5.38±0.26	
Albumin (g/dL)			4.22±0.22		4.20±0.15		4.22±0.22		4.23±0.29	
T.Chol. (mg/dL)			52.3±12.4		58.3±13.7		50.3±14.4		49.3±11.4	
TGL (mg/dL)			9.5±1.6		10.5±4.5		8.3±2.9		8.8±2.2	
Glucose (mg/dL)			137.0±9.5		138.3±13.0		128.5±12.1		124.0±10.6	
BUN (mg/dL)			17.33±1.40		18.15±4.12		20.20±3.17		20.52±2.60	
Creat. (mg/dL)			0.233±0.029		0.262±0.029		0.257±0.020		0.250±0.018	
IP (mg/dL)			7.390±1.038		7.588±0.799		7.728±0.872		7.928±0.852	
Ca (mEq/L)			9.38±0.30		9.45±0.30		9.40±0.21		9.35±0.40	
Na (mEq/L)			143.2±1.2		142.2±1.2		141.8±1.0		142.8±0.8	
K (mEq/L)			3.95±0.16		3.88±0.23		3.90±0.39		3.70±0.19	
Cl (mEq/L)			106.0±1.7		105.7±1.4		105.5±1.8		106.3±0.8	
Al-glob. (%)			54.25±2.84		56.07±1.74		54.50±2.39		53.43±1.44	
A1-glob. (%)			18.45±1.01		17.58±1.36		17.93±1.26		19.20±1.19	
A2-glob. (%)			6.13±0.64		5.27±0.53*		5.78±0.59		6.93±0.28*	
B-glob. (%)			16.17±1.70		15.33±0.98		16.85±1.16		16.32±0.98	
G-glob. (%)			5.00±1.04		5.75±1.02		4.93±1.04		4.12±0.40	
A/G			1.193±0.129		1.278±0.090		1.202±0.109		1.148±0.070	

Values are expressed as the mean ± S.D.

* P<0.05 : Significantly different from Water for injection.