

Table 4. Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Male

Signs	Dose level (mg/kg)	B. G.	Administration period (Week)				Recovery period (Week)	
			1	2	3	4	1	2
No. of animals	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
REMOVAL FROM CAGE Ease of removal	0	8	8	10	8	8	5	5
	20	4	4	5	5	3	-	-
	100	5	3	5	4	4	-	-
	500	5	6	9	10	9	5	5
Vocalization	0	2	2	0	2	2	0	0
	20	1	1	0	0	2	-	-
	100	0	2	0	1	1	-	-
	500	5	4	1	0	1	0	0
B. G. : Before grouping	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Male

Signs	Dose level (mg/kg)	Administration period (Week)				Recovery period (Week)		
		B. G.	1	2	3	4	1	2
HANDLING OBSERVATIONS								
Muscle tone	Normal	0	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
Subnormal temperature	Absent	0	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
Piloerection	Absent	0	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
Staining hair	Absent	0	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
Unkempt hair	Absent	0	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
Skin color	Normal	0	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
Lacrimation	Absent	0	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5

B. G.: Before grouping

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Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Sex : Male

Signs	Dose level (mg/kg)	B. G.	Administration period (Week)				Recovery period (Week)	
			1	2	3	4	1	2
Exophthalmos	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
Pupillary size	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
Salivation	0	10	10	10	10	10	5	5
	20	5	5	4	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	8	3	2	5	5
Slight	0	0	0	0	0	0	0	0
	20	0	0	1	0	0	-	-
	100	0	0	0	0	0	-	-
	500	0	0	2	7	6	0	0
Marked	0	0	0	0	0	0	0	0
	20	0	0	0	0	0	-	-
	100	0	0	0	0	0	-	-
	500	0	0	0	0	2	0	0

B. G. : Before grouping

Table 4. --continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Male

Signs	Dose level (mg/kg)	B. G. Administration period (Week)				Recovery period (Week)			
		1	2	3	4	1	2		
OBSERVATIONS IN ARENA									
Posture	Normal	10	10	10	10	10	10	5	5
	0	10	10	10	10	10	10	5	5
	20	5	5	5	5	5	5	5	5
	100	5	5	5	5	5	5	5	5
	500	10	10	10	10	10	10	5	5
Motor activity	Normal	10	10	10	10	10	10	5	5
	0	10	10	10	10	10	10	5	5
	20	5	5	5	5	5	5	5	5
	100	5	5	5	5	5	5	5	5
	500	10	10	10	10	10	10	5	5
Respiration	Normal	10	10	10	10	10	10	5	5
	0	10	10	10	10	10	10	5	5
	20	5	5	5	5	5	5	5	5
	100	5	5	5	5	5	5	5	5
	500	10	10	10	10	10	10	5	5
Lid closure	Wide open	10	10	10	10	10	10	5	5
	0	10	10	10	10	10	10	5	5
	20	5	5	5	5	5	5	5	5
	100	5	5	5	5	5	5	5	5
	500	10	10	10	10	10	10	5	5
Gait	Normal	10	10	10	10	10	10	5	5
	0	10	10	10	10	10	10	5	5
	20	5	5	5	5	5	5	5	5
	100	5	4	5	5	5	5	5	5
	500	10	10	10	10	10	10	5	5
	0	0	0	0	0	0	0	0	0
	20	0	0	0	0	0	0	0	0
	100	0	0	0	0	0	0	0	0
	500	0	1	0	0	0	0	0	0
Tremor	None	10	10	10	10	10	10	5	5
	0	10	10	10	10	10	10	5	5
	20	5	5	5	5	5	5	5	5
	100	5	5	5	5	5	5	5	5
	500	10	10	10	10	10	10	5	5

B. G. : Before grouping

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Table 4. --continued Detailed clinical observations and sensory reactivity to stimuli of different types

Sex : Male

Signs	Dose level (mg/kg)	B. G.	Administration period (Week)				Recovery period (Week)	
			1	2	3	4	1	2
Twitch	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
Convulsion	500	10	10	10	10	10	5	5
	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
Stereotypic behavior	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
	0	10	10	10	10	10	5	5
Abnormal behavior	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5
B. G. : Before grouping	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	10	10	10	10	5	5

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Male

Signs	Dose level (mg/kg)	B. G. Administration period (Week)				Recovery period (Week)	
		1	2	3	4	1	2
SENSORIMOTOR FUNCTION Approach contact	No reaction	0				0	0
		20				0	-
		100				0	-
	Normal a)	500				1	0
		0				10	5
		20				5	-
	Touch response	100				5	-
		500				9	5
		0				0	0
	No reaction	20				0	-
		100				0	-
		500				1	0
	Moderate reaction	0				10	5
		20				5	-
		100				5	-
Freezing	500				8	5	
	0				0	0	
	20				0	-	
Pinna response	100				0	-	
	500				1	0	
	0				10	5	
Normal	20				5	-	
	100				5	-	
	500				10	5	

B. G. : Before grouping

a) Rat slowly approaches and sniffs at object or turns away

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Male

Signs	Dose level (mg/kg)	B. G.	Administration period (Week)				Recovery period (Week)	
			1	2	3	4	1	2
Pain response (Tail pinch)	0					1		0
	20					0		-
	100					0		-
	500					0		0
Normal	0					9		5
	20					5		-
	100					5		-
	500					10		5
Pupillary reflex	0					10		5
	20					5		-
	100					5		-
	500					10		5
Air righting reflex	0					10		5
	20					5		-
	100					5		-
	500					10		5

B. G. : Before grouping

Table 4. —continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Female

Signs	Dose level (mg/kg)	B. G.	Administration period (Week)				Recovery period (Week)		
			1	2	3	4	1	2	
REMOVAL FROM CAGE Ease of removal	Very easy	0	10	10	10	10	10	5	5
		20	5	5	5	5	5	—	—
		100	5	5	5	5	5	—	—
	Easy	500	10	9	8	8	8	5	5
		0	8	10	7	10	10	5	5
		20	3	5	3	5	5	—	—
	Moderately difficult	100	4	5	4	5	5	—	—
		500	9	7	6	7	8	5	5
		0	2	0	3	0	0	0	0
	None	20	2	0	2	0	0	—	—
		100	1	0	1	0	0	—	—
		500	1	1	2	1	0	0	0
Vocalization	0	0	0	0	0	0	0	0	
	20	0	0	0	0	0	—	—	
	100	0	0	0	0	0	—	—	
B. G. : Before grouping	500	0	1	0	0	0	0	0	
	0	10	10	10	10	10	5	5	
	20	5	5	5	5	5	—	—	
	100	5	5	5	5	5	—	—	
	500	10	9	8	8	8	5	5	

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Female

Signs	Dose level (mg/kg)	B. G.	Administration period (Week)				Recovery period (Week)		
			1	2	3	4	1	2	
HANDLING OBSERVATIONS									
Muscle tone	Normal	10	10	10	10	10	10	5	5
		20	5	5	5	5	5	-	-
		100	5	5	5	5	5	-	-
		500	10	9	8	8	8	5	5
Subnormal temperature	Absent	0	10	10	10	10	10	5	5
		20	5	5	5	5	5	-	-
		100	5	5	5	5	5	-	-
		500	10	9	8	8	8	5	5
Piloerection	Absent	0	10	10	10	10	10	5	5
		20	5	5	5	5	5	-	-
		100	5	5	5	5	5	-	-
		500	10	9	8	8	8	5	5
Staining hair	Absent	0	10	10	10	10	10	5	5
		20	5	5	5	5	5	-	-
		100	5	5	5	5	5	-	-
		500	10	7	8	8	8	5	5
	Very soiled	0	0	0	0	0	0	0	0
		20	0	0	0	0	0	-	-
		100	0	0	0	0	0	-	-
		500	0	2	0	0	0	0	0
Unkempt hair	Absent	0	10	10	10	10	10	5	5
		20	5	5	5	5	5	-	-
		100	5	5	5	5	5	-	-
		500	10	9	8	8	8	5	5
Skin color	Normal	0	10	10	10	10	10	5	5
		20	5	5	5	5	5	-	-
		100	5	5	5	5	5	-	-
		500	10	9	8	8	8	5	5

B. G. : Before grouping

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Sex : Female

Signs	Dose level (mg/kg)	B. G.	Administration period (Week)				Recovery period (Week)	
			1	2	3	4	1	2
Lacrimation	Absent	10	10	10	10	10	5	5
		20	5	5	5	5	-	-
		100	5	5	5	5	-	-
		500	10	9	8	8	5	5
Exophthalmos	Absent	10	10	10	10	10	5	5
		20	5	5	5	5	-	-
		100	5	5	5	5	-	-
		500	10	9	8	8	5	5
Pupillary size	Normal	10	10	10	10	10	5	5
		20	5	5	5	5	-	-
		100	5	5	5	5	-	-
		500	10	9	8	8	5	5
Salivation	Absent	10	10	10	10	10	5	5
		20	5	5	5	5	-	-
		100	5	5	5	5	-	-
		500	10	8	5	5	5	5
Slight		0	0	0	0	0	0	0
		20	0	0	0	0	-	-
		100	0	0	0	0	-	-
		500	0	1	3	3	0	0

B. G. : Before grouping

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Sex : Female	Signs	Dose level (mg/kg)	Administration period (Week)				Recovery period (Week)		
			B. G.	1	2	3	4	1	2
OBSERVATIONS IN ARENA									
	Posture	Normal	10	10	10	10	10	5	5
	Motor activity	Normal	5	5	5	5	5	-	-
			10	9	8	8	8	5	5
			10	10	10	10	10	5	5
			5	5	5	5	5	-	-
			10	8	8	8	8	5	5
		Low	0	0	0	0	0	0	0
			20	0	0	0	0	-	-
			100	0	0	0	0	-	-
			500	0	1	0	0	0	0
	Respiration	Normal	10	10	10	10	10	5	5
			20	5	5	5	5	-	-
			100	5	5	5	5	-	-
			500	10	9	8	8	5	5
	Lid closure	Wide open	10	10	10	10	10	5	5
			20	5	5	5	5	-	-
			100	5	5	5	5	-	-
			500	10	9	8	8	5	5
	Gait	Normal	10	10	10	10	10	5	5
			20	5	5	5	5	-	-
			100	5	5	5	5	-	-
			500	10	9	8	8	5	5
	Tremor	None	10	10	10	10	10	5	5
			20	5	5	5	5	-	-
			100	5	5	5	5	-	-
			500	10	9	8	8	5	5

B. G. : Before grouping

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Female

Signs	Dose level (mg/kg)	Administration period (Week)				Recovery period (Week)		
		B.G.	1	2	3	4	1	2
Twitch	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
Convulsion	500	10	9	8	8	8	5	5
	0	10	10	10	10	10	5	5
	20	5	5	5	5	5	-	-
Stereotypic behavior	100	5	5	5	5	5	-	-
	500	10	9	8	8	8	5	5
	0	10	10	10	10	10	5	5
Abnormal behavior	20	5	5	5	5	5	-	-
	100	5	5	5	5	5	-	-
	500	10	9	8	8	8	5	5
Other	0	0	0	0	0	0	0	0
	20	0	0	0	0	0	-	-
	100	0	0	0	0	0	-	-
Loose stool	100	0	0	0	0	0	-	-
	500	0	1	0	0	0	0	0

B.G. : Before grouping

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Female

Signs	Dose level (mg/kg)	Administration period (Week)				Recovery period (Week)		
		B. G.	1	2	3	4	1	2
SENSORIMOTOR FUNCTION								
Approach contact	0					10		5
	20					5		-
	100					5		-
	500					8		5
Touch response	0					10		5
	20					5		-
	100					5		-
	500					8		5
Pinna response	0					10		5
	20					5		-
	100					5		-
	500					8		5
Pain response (Tail pinch)	0					0		0
	20					0		-
	100					0		-
	500					0		1
						0		2
						0		-
						0		-
						0		0
						10		3
						5		-
						5		-
						8		4
Pupillary reflex	0					10		5
	20					5		-
	100					5		-
	500					8		5
						10		5
						5		-
						5		-
						8		5

B. G. : Before grouping
a) Rat slowly approaches and sniffs at object or turns away

Table 4. -continued Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 9933 (115-212)

Sex : Female

Signs	Dose level (mg/kg)	Administration period (Week)				Recovery period (Week)		
		B. G. 1	2	3	4	1	2	
Air righting reflex	0				10			5
	20				5			-
	100				5			-
	500				8			5

B. G. : Before grouping

Table 5. Summary of number of defecation

Exp. No. 9933 (115-212)

Sex	Dose level (mg/kg)	No. of animals	B.G.	Administration period (week)				Recovery period (week)					
				1	2	3	4	1	2				
Male	0	10	0.3 ± 0.7 a)	0.4 ± 0.8	0.1 ± 0.3	0.2 ± 0.6	0.0 ± 0.0	0.0 ± 0.0	(5)	0.0 ± 0.0	(5)	0.0 ± 0.0	(5)
	20	5	0.6 ± 0.9	0.6 ± 0.5	0.0 ± 0.0	0.4 ± 0.9	0.2 ± 0.4						
	100	5	0.6 ± 0.9	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.4	0.0 ± 0.0						
Female	500	10	1.0 ± 1.1	0.9 ± 1.5	0.4 ± 1.3	0.5 ± 1.6	0.0 ± 0.0	1.4 ± 1.9	(5)	0.0 ± 0.0	(5)		
	0	10	0.1 ± 0.3	0.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	(5)	0.6 ± 0.9	(5)		
	20	5	1.0 ± 1.4	0.2 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0						
Before grouping	100	5	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.4						
	500	10	0.3 ± 0.7	0.6 ± 0.9 (9)	0.5 ± 1.1 (8)	0.0 ± 0.0 (8)	0.0 ± 0.0 (8)	0.6 ± 1.3 (5)	0.0 ± 0.0 (5)				

B.G. : Before grouping
 a) Mean ± S. D.
 Values in parentheses are expressed no. of animals examined

Table 6. Summary of number of pools of urine

Exp. No. 9933 (115-212)

Sex	Dose level (mg/kg)	No. of animals	B.G.	Administration period (week)				Recovery period (week)	
				1	2	3	4	1	2
Female	0	10	0.3 ± 0.5	a) 0.6 ± 0.8	0.2 ± 0.6	0.1 ± 0.3	0.4 ± 0.7	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)
	20	5	0.4 ± 0.5	0.0 ± 0.0	0.4 ± 0.9	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4 (5)	0.2 ± 0.4 (5)
	100	5	0.8 ± 0.8	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)
Male	0	10	0.5 ± 0.8	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.4	0.2 ± 0.4 (5)	0.2 ± 0.4 (5)
	20	5	0.2 ± 0.4	0.4 ± 0.8	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)
	100	5	0.2 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 0.5	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)
Female	0	10	0.2 ± 0.4	0.4 ± 0.8	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)
	20	5	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.4 (5)	0.2 ± 0.4 (5)
	100	5	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)
Male	0	10	0.2 ± 0.6	0.4 ± 0.5 (9)	0.4 ± 0.5 (8)	0.1 ± 0.4 (8)	0.1 ± 0.4 (8)	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)
	20	5	0.2 ± 0.6	0.4 ± 0.5 (9)	0.4 ± 0.5 (8)	0.1 ± 0.4 (8)	0.1 ± 0.4 (8)	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)
	100	5	0.2 ± 0.6	0.4 ± 0.5 (9)	0.4 ± 0.5 (8)	0.1 ± 0.4 (8)	0.1 ± 0.4 (8)	0.0 ± 0.0 (5)	0.0 ± 0.0 (5)

B.G. : Before grouping
a) Mean ± S.D.
Values in parentheses are expressed no. of animals examined

Table 7. Summary of grip strength

Exp. No. 9933(115-212)

4 week of administration				Unit : g
Sex	Dose level (mg/kg)	No. of animals	Forelimb	Hindlimb
	0	10	944 ± 197 a)	389 ± 81
Male	20	5	968 ± 220	450 ± 34
	100	5	877 ± 277	527 ± 180
	500	10	813 ± 185	417 ± 91
	0	10	802 ± 69	465 ± 61
Female	20	5	868 ± 145	549 ± 83
	100	5	743 ± 95	492 ± 91
	500	8	692 ± 168	473 ± 78

a) Mean ± S. D.

Table 7. -continued Summary of grip strength

Exp. No. 9933(115-212)

2 week of recovery		Unit : g		
Sex	Dose level (mg/kg)	No. of animals	Forelimb	Hindlimb
Male	0	5	1125 ± 118 a)	652 ± 96
	500	5	1210 ± 373	672 ± 113
Female	0	5	768 ± 209	422 ± 141
	500	5	655 ± 119	417 ± 106

a) Mean ± S. D.

Table 8. Summary of motor activity

Exp. No. 9933 (115-212)

4 week of administration		Dose level (mg/kg)	No. of animals	Motor activity (counts)						Total (0-60)
				0-10 a)	10-20	20-30	30-40	40-50	50-60	
Male		0	10	176 ± 54 b)	147 ± 33	138 ± 42	105 ± 36	105 ± 42	91 ± 41	760 ± 202
		20	5	173 ± 45	134 ± 20	127 ± 35	117 ± 21	94 ± 37	66 ± 41	710 ± 111
		100	5	164 ± 43	99 ± 57	111 ± 44	87 ± 48	66 ± 39	42 ± 50	571 ± 203
Female		500	10	155 ± 50	99 ± 52	66 ± 43**	41 ± 28**	17 ± 24**	20 ± 18**	397 ± 165**
		0	10	128 ± 28	93 ± 41	85 ± 37	69 ± 31	71 ± 28	75 ± 27	520 ± 141
		20	5	126 ± 25	90 ± 29	80 ± 40	80 ± 30	80 ± 47	58 ± 19	513 ± 124
Female		100	5	132 ± 14	84 ± 27	93 ± 30	92 ± 12	82 ± 40	86 ± 21	570 ± 83
		500	8	140 ± 31	90 ± 33	75 ± 27	67 ± 38	48 ± 33	58 ± 45	478 ± 163

a) Interval time (minutes)

b) Mean ± S.D.

Significantly different from control group **: $p \leq 0.01$ (Dunnett)

Table 8. --continued Summary of motor activity

Exp. No. 9933. (115-212)

2 week of recovery		Motor activity (counts)								Total (0-60)
Dose level (mg/kg)	No. of animals	0-10 a)	10-20	20-30	30-40	40-50	50-60			
Male										
0	5	170 ± 59 b)	128 ± 46	96 ± 47	84 ± 34	77 ± 30	41 ± 34	595 ± 176		
500	5	194 ± 32	137 ± 43	112 ± 36	101 ± 37	90 ± 33	55 ± 31	689 ± 141		
Female										
0	5	118 ± 22	79 ± 21	66 ± 33	101 ± 22	84 ± 24	72 ± 23	520 ± 119		
500	5	127 ± 44	105 ± 44	82 ± 28	79 ± 25	73 ± 24	64 ± 25	529 ± 160		

a) interval time (minutes)

b) Mean ± S.D.

Table 9-1. Hematology
 ---Administration period---

Sex	Dose level (mg/kg)	No. of animals	HCT (%)	HGB (g/dL)	RBC ($\times 10^6/\text{mm}^3$)	MCV (μm^3)	MCH (pg)	MCHC (%)
Male	0	5	41.8 ± 1.5	15.2 ± 0.4	7.53 ± 0.22	55.6 ± 2.2	20.2 ± 0.5	36.3 ± 0.6
	20	5	41.8 ± 0.5	15.2 ± 0.2	7.47 ± 0.18	56.0 ± 1.2	20.3 ± 0.4	36.3 ± 0.4
	100	5	42.0 ± 0.5	15.3 ± 0.3	7.63 ± 0.23	55.0 ± 1.2	20.1 ± 0.4	36.5 ± 0.3
	500	5	41.8 ± 3.2	14.9 ± 1.3	7.39 ± 0.55	56.7 ± 3.3	20.2 ± 1.1	35.7 ± 0.5
Female	0	5	40.5 ± 1.5	15.1 ± 0.5	7.77 ± 0.37	52.2 ± 1.7	19.5 ± 0.6	37.4 ± 0.3
	20	5	39.5 ± 1.3	14.8 ± 0.4	7.48 ± 0.23	52.8 ± 0.9	19.7 ± 0.4	37.3 ± 0.5
	100	5	40.1 ± 1.1	15.0 ± 0.3	7.39 ± 0.27	54.2 ± 1.1	20.3 ± 0.5	37.5 ± 0.3
	500	3	36.0 ± 0.9**	13.1 ± 0.4**	6.81 ± 0.27**	52.8 ± 1.3	19.2 ± 0.4	36.4 ± 0.4**

Mean ± S.D.
 Significantly different from control group; **; $P \leq 0.01$ (Dunnett)

Table 9-1. ---continued Hematology
---Administration period---

Sex	Dose level (mg/kg)	No. of animals	WBC ($\times 10^3/\text{mm}^3$)	Differential leukocyte counts (%)					
				NEUT	LYMPH	MONO	EOSN	BASO	LUC
Male	0	5	12.23 \pm 2.20	14.9 \pm 5.2	81.8 \pm 5.6	2.0 \pm 0.4	0.7 \pm 0.2	0.2 \pm 0.1	0.5 \pm 0.1
	20	5	12.55 \pm 2.07	15.3 \pm 6.2	81.4 \pm 6.4	2.1 \pm 0.4	0.4 \pm 0.1	0.1 \pm 0.1	0.7 \pm 0.3
	100	5	12.22 \pm 2.88	13.4 \pm 1.7	83.6 \pm 2.4	1.8 \pm 0.7	0.6 \pm 0.2	0.2 \pm 0.1	0.5 \pm 0.1
	500	5	13.66 \pm 1.33	20.3 \pm 7.5	75.5 \pm 8.0	3.1 \pm 0.4**	0.5 \pm 0.2	0.1 \pm 0.0	0.5 \pm 0.1
Female	0	5	7.13 \pm 2.09	17.0 \pm 3.8	78.7 \pm 3.2	2.3 \pm 0.5	1.4 \pm 0.6	0.1 \pm 0.0	0.5 \pm 0.2
	20	5	6.32 \pm 2.01	15.3 \pm 6.8	81.6 \pm 6.3	1.6 \pm 0.7	0.9 \pm 0.4	0.1 \pm 0.0	0.5 \pm 0.1
	100	5	7.39 \pm 3.66	13.3 \pm 3.1	83.7 \pm 2.7	1.4 \pm 0.3	0.9 \pm 0.5	0.1 \pm 0.1	0.6 \pm 0.2
	500	3	9.01 \pm 1.43	17.3 \pm 4.8	79.3 \pm 5.6	2.0 \pm 0.7	0.9 \pm 0.2	0.1 \pm 0.1	0.5 \pm 0.0

NEUT: Neutrophil LYMPH: Lymphocyte MONO: Monocyte EOSN: Eosinophil BASO: Basophil LUC: Large unstained cells
Mean \pm S.D.
Significantly different from control group; **: $P \leq 0.01$ (Dunnett)

Table 9-1. ---continued Hematology
---Administration period---

Sex	Dose level (mg/kg)	No. of animals	NEUT (x10 ⁹ /mm ³)	Lymph (x10 ⁹ /mm ³)	MONO (x10 ⁹ /mm ³)	EOSN (x10 ⁹ /mm ³)	BASO (x10 ⁹ /mm ³)	IJC (x10 ⁹ /mm ³)
Male	0	5	1.86 ± 0.89	9.96 ± 1.57	0.25 ± 0.08	0.08 ± 0.03	0.02 ± 0.01	0.06 ± 0.02
	20	5	1.90 ± 0.71	10.25 ± 2.11	0.26 ± 0.02	0.05 ± 0.02	0.02 ± 0.00	0.08 ± 0.02
	100	5	1.63 ± 0.37	10.23 ± 2.56	0.21 ± 0.06	0.07 ± 0.04	0.02 ± 0.00	0.06 ± 0.02
	500	5	2.75 ± 1.01	10.32 ± 1.70	0.42 ± 0.06**	0.08 ± 0.03	0.02 ± 0.01	0.07 ± 0.02
Female	0	5	1.19 ± 0.37	5.64 ± 1.75	0.17 ± 0.07	0.09 ± 0.03	0.00 ± 0.01	0.03 ± 0.02
	20	5	0.87 ± 0.25	5.25 ± 1.94	0.11 ± 0.07	0.06 ± 0.04	0.00 ± 0.01	0.03 ± 0.01
	100	5	0.97 ± 0.46	6.21 ± 3.16	0.10 ± 0.04	0.06 ± 0.02	0.01 ± 0.01	0.05 ± 0.04
	500	3	1.57 ± 0.53	7.12 ± 1.13	0.18 ± 0.08	0.08 ± 0.03	0.01 ± 0.01	0.05 ± 0.01

NEUT: Neutrophil Lymph: Lymphocyte MONO: Monocyte EOSN: Eosinophil BASO: Basophil IJC: Large unstained cells
Mean ± S.D.
Significantly different from control group; **; P ≤ 0.01 (Dunnett)

Table 9-1. --continued Hematology
 ---Administration period---

Sex	Dose level (mg/kg)	No. of animals	PLT (x10 ⁶ /mm ³)	Reticulocyte (%)
Male	0	5	1252 ± 166	3.1 ± 0.4
	20	5	1194 ± 74	3.3 ± 0.2
	100	5	1337 ± 156	2.9 ± 0.7
	500	5	1235 ± 133	6.5 ± 2.3
Female	0	5	1248 ± 63	1.9 ± 0.3
	20	5	1156 ± 123	2.1 ± 0.3
	100	5	1305 ± 95	2.4 ± 0.4
	500	3	1289 ± 199	4.9 ± 2.8

Mean ± S.D.

Table 9-2. Hematology
 ---Recovery period---

Exp. No. 9933 (115-212)

Sex	Dose level (mg/kg)	No. of animals	HCT (%)	HGB (g/dL)	RBC ($\times 10^6/\text{mm}^3$)	MCV (μm^3)	MCH (pg)	MCHC (%)
Male	0	5	42.8 \pm 1.8	16.3 \pm 0.6	8.20 \pm 0.32	52.2 \pm 1.8	19.9 \pm 0.5	38.1 \pm 0.3
	500	5	42.9 \pm 1.0	16.2 \pm 0.4	7.67 \pm 0.33*	56.0 \pm 2.6*	21.1 \pm 0.9*	37.6 \pm 0.2*
Female	0	5	40.0 \pm 1.3	15.7 \pm 0.5	7.73 \pm 0.13	51.7 \pm 1.0	20.2 \pm 0.4	39.1 \pm 0.4
	500	5	41.9 \pm 1.7	16.1 \pm 0.6	7.82 \pm 0.25	53.6 \pm 2.0	20.6 \pm 0.9	38.4 \pm 0.7

Mean \pm S.D.
 Significantly different from control group; *: $P \leq 0.05$ (Dunnett)

Table 9-2. ---continued Hematology
---Recovery period---

Exp. No. 9933 (115-212)

Sex	Dose level (mg/kg)	No. of animals	WBC ($\times 10^3/\text{mm}^3$)	Differential leukocyte counts (%)					
				NEUT	LYMPH	MONO	EOSN	BASO	LJC
Male	0	5	11.37 \pm 2.07	13.6 \pm 4.0	82.4 \pm 4.9	2.3 \pm 0.8	0.9 \pm 0.3	0.1 \pm 0.0	0.7 \pm 0.6
	500	5	9.82 \pm 2.46	13.4 \pm 2.8	82.1 \pm 3.4	2.7 \pm 0.9	1.1 \pm 0.1	0.1 \pm 0.1	0.5 \pm 0.2
Female	0	5	6.27 \pm 1.05	14.2 \pm 4.6	81.6 \pm 4.4	2.4 \pm 0.8	1.2 \pm 0.2	0.1 \pm 0.1	0.5 \pm 0.3
	500	5	7.94 \pm 2.32	14.1 \pm 5.2	81.2 \pm 5.6	2.3 \pm 0.7	1.5 \pm 0.6	0.2 \pm 0.1	0.7 \pm 0.1

NEUT: Neutrophil LYMPH: Lymphocyte MONO: Monocyte EOSN: Eosinophil BASO: Basophil LJC: Large unstained cells
Mean \pm S.D.

Table 9-2. ---continued Hematology
---Recovery period---

Exp. No. 9933 (115-212)

Sex	Dose level (mg/kg)	No. of animals	NEUT ($\times 10^3/\text{mm}^3$)	LYMPH ($\times 10^3/\text{mm}^3$)	MONO ($\times 10^3/\text{mm}^3$)	EOSN ($\times 10^3/\text{mm}^3$)	BASO ($\times 10^3/\text{mm}^3$)	LUC ($\times 10^3/\text{mm}^3$)
Male	0	5	1.60 ± 0.66	9.29 ± 1.23	0.27 ± 0.13	0.10 ± 0.05	0.01 ± 0.01	0.09 ± 0.09
	500	5	1.33 ± 0.50	8.05 ± 1.90	0.27 ± 0.12	0.10 ± 0.03	0.02 ± 0.01	0.06 ± 0.04
Female	0	5	0.87 ± 0.20	5.13 ± 1.03	0.15 ± 0.06	0.08 ± 0.02	0.00 ± 0.00	0.03 ± 0.02
	500	5	1.07 ± 0.42	6.50 ± 2.23	0.18 ± 0.05	0.12 ± 0.07	0.01 ± 0.01*	0.05 ± 0.00

NEUT: Neutrophil LYMPH: Lymphocyte MONO: Monocyte EOSN: Eosinophil BASO: Basophil LUC: Large unstained cells
Mean ± S.D.
Significantly different from control group; *: $P \leq 0.05$ (Dunnett)

Table 9-2. ---continued Hematology
 ---Recovery period---

Sex	Dose level (mg/kg)	No. of animals	PLT ($\times 10^3/\text{mm}^3$)	Reticulocyte (%)
Male	0	5	1117 \pm 125	2.1 \pm 0.4
	500	5	1065 \pm 134	2.4 \pm 0.5
Female	0	5	1229 \pm 48	1.9 \pm 0.4
	500	5	1208 \pm 83	1.4 \pm 0.5

Mean \pm S.D.

Table 10-1. Coagulation
 ---Administration period---

Sex	Dose level (mg/kg)	No. of animals	PT (sec.)	APTT (sec.)
Male	0	5	17.7 ± 0.9	26.0 ± 2.0
	20	5	18.0 ± 1.5	25.1 ± 0.8
	100	5	17.9 ± 1.6	26.4 ± 2.9
	500	5	17.3 ± 1.1	25.2 ± 5.3
Female	0	5	16.0 ± 0.3	17.4 ± 1.5
	20	5	16.2 ± 0.6	16.9 ± 1.2
	100	5	16.0 ± 0.6	18.2 ± 2.5
	500	3	16.2 ± 0.5	15.9 ± 1.8

Mean ± S.D.

Table 10-2. Coagulation
---Recovery period---

Sex	Dose level (mg/kg)	No. of animals	PT (sec.)	APTT (sec.)
Male	0	5	18.9 ± 2.2	25.4 ± 1.3
	500	5	17.2 ± 0.9	23.6 ± 1.6
Female	0	5	17.4 ± 0.6	18.0 ± 2.0
	500	5	17.0 ± 0.6	19.4 ± 1.1

Mean ± S.D.

Table 11-1. Blood chemistry
---Administration period---

Sex	Dose level (mg/kg)	No. of animals	T. protein (g/dL)	Glucose (mg/dL)	Triglyceride (mg/dL)	T. cholesterol (mg/dL)
Male	0	5	5.65 ± 0.21	154 ± 16	55.8 ± 27.6	61 ± 5
	20	5	5.52 ± 0.19	152 ± 5	64.7 ± 13.1	61 ± 10
	100	5	5.52 ± 0.13	145 ± 10	33.1 ± 16.0	58 ± 8
	500	5	5.75 ± 0.15	135 ± 11*	45.2 ± 22.1	56 ± 12
Female	0	5	5.78 ± 0.22	117 ± 26	13.4 ± 7.2	62 ± 13
	20	5	5.54 ± 0.07	113 ± 14	14.3 ± 6.4	52 ± 7
	100	5	5.64 ± 0.09	108 ± 12	19.8 ± 11.4	69 ± 7
	500	3	5.33 ± 0.30**	97 ± 10	38.1 ± 11.1**	62 ± 14

Mean ± S.D.
Significantly different from control group; * : P ≤ 0.05 ** : P ≤ 0.01 (Dunnnett)

Table 11-1. -continued Blood chemistry
 ---Administration period---

Sex	Dose level (mg/kg)	No. of animals	BUN (mg/dL)	Creatinine (mg/dL)	T.bilirubin (mg/dL)	Total bile acid (μ mol/L)
Male	0	5	9.0 \pm 1.0	0.21 \pm 0.02	0.02 \pm 0.01	19.2 \pm 14.4
	20	5	8.4 \pm 0.9	0.20 \pm 0.02	0.03 \pm 0.01	18.9 \pm 15.4
	100	5	9.5 \pm 1.5	0.20 \pm 0.04	0.03 \pm 0.00	24.9 \pm 10.5
	500	5	10.5 \pm 1.5	0.24 \pm 0.02	0.06 \pm 0.04	46.1 \pm 45.6
Female	0	5	11.6 \pm 1.7	0.23 \pm 0.03	0.03 \pm 0.01	12.3 \pm 5.8
	20	5	12.5 \pm 1.8	0.25 \pm 0.05	0.03 \pm 0.01	25.1 \pm 12.5
	100	5	12.2 \pm 3.0	0.25 \pm 0.11	0.02 \pm 0.01	16.1 \pm 9.9
	500	3	11.2 \pm 3.0	0.19 \pm 0.04	0.06 \pm 0.03	16.7 \pm 4.1

Mean \pm S.D.

Table 11-1. -continued Blood chemistry
---Administration period---

Sex	Dose level (mg/kg)	No. of animals	AST (U/L)	ALT (U/L)	ALP (U/L)	Gamma-GTP (U/L)
Male	0	5	78 ± 5	25 ± 2	762 ± 156	0.6 ± 0.1
	20	5	81 ± 9	30 ± 4#	828 ± 183	0.7 ± 0.1
	100	5	74 ± 5	34 ± 8	908 ± 295	0.6 ± 0.2
	500	5	73 ± 4	45 ± 12#	724 ± 156	1.3 ± 0.4
Female	0	5	84 ± 11	23 ± 2	505 ± 70	0.8 ± 0.1
	20	5	86 ± 13	22 ± 3	468 ± 105	0.9 ± 0.1
	100	5	76 ± 6	23 ± 5	455 ± 157	0.9 ± 0.1
	500	3	88 ± 5	40 ± 24	804 ± 265*	2.0 ± 0.7

Mean ± S.D.
* : P ≤ 0.05 (Dunnett)
: P ≤ 0.05 (Steel)

Table 11-1. -continued Blood chemistry
 ---Administration period---

Sex	Dose level (mg/kg)	No. of animals	Calcium (mg/dL)	I. phosphorus (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)
Male	0	5	9.79 ± 0.16	8.61 ± 1.06	141.4 ± 1.3	4.64 ± 0.29	106.6 ± 1.7
	20	5	9.70 ± 0.26	8.81 ± 0.67	142.3 ± 0.7	4.67 ± 0.29	106.9 ± 1.7
	100	5	9.83 ± 0.29	8.58 ± 0.62	141.9 ± 1.1	4.60 ± 0.23	106.4 ± 0.6
	500	5	10.04 ± 0.37	9.69 ± 0.94	140.2 ± 0.9	5.06 ± 0.25	106.8 ± 2.1
Female	0	5	9.80 ± 0.43	8.06 ± 1.28	141.3 ± 0.9	4.59 ± 0.25	108.9 ± 1.4
	20	5	9.51 ± 0.25	7.98 ± 0.69	142.3 ± 1.1	4.28 ± 0.11	110.4 ± 0.9
	100	5	9.53 ± 0.24	7.27 ± 0.38	142.1 ± 1.7	4.26 ± 0.17*	108.6 ± 1.3
	500	3	9.61 ± 0.33	8.41 ± 0.73	141.1 ± 2.3	4.82 ± 0.23	107.4 ± 1.4

Mean ± S.D.
 Significantly different from control group; * : P ≤ 0.05 (Dunnett)

Table 11-2. Blood chemistry
---Recovery period---

Sex	Dose level (mg/kg)	No. of animals	T. protein (g/dL)	Glucose (mg/dL)	Triglyceride (mg/dL)	T. cholesterol (mg/dL)
Male	0	5	5.98 ± 0.22	161 ± 8	55.5 ± 12.0	72 ± 16
	500	5	5.65 ± 0.22*	142 ± 10*	48.8 ± 10.6	60 ± 12
Female	0	5	5.82 ± 0.18	116 ± 20	11.2 ± 4.4	69 ± 10
	500	5	5.78 ± 0.17	127 ± 11	30.7 ± 14.5#	89 ± 8**

Mean ± S.D.
 * : P ≤ 0.05 ** : P ≤ 0.01 (Dunnett)
 † : Significantly different from control group;
 ‡ : Significantly different from control group; # : P ≤ 0.05 (Steel)

Table 11-2. -continued Blood chemistry
 ---Recovery period---

Sex	Dose level (mg/kg)	No. of animals	BUN (mg/dL)	Creatinine (mg/dL)	T. bilirubin (mg/dL)	Total bile acid (μ mol/L)
Male	0	5	12.5 \pm 2.0	0.22 \pm 0.03	0.04 \pm 0.01	20.4 \pm 13.5
	500	5	12.9 \pm 1.4	0.23 \pm 0.01	0.03 \pm 0.01	35.7 \pm 19.3
Female	0	5	16.5 \pm 2.4	0.25 \pm 0.03	0.04 \pm 0.02	14.5 \pm 8.2
	500	5	16.0 \pm 0.8	0.26 \pm 0.04	0.03 \pm 0.01	20.3 \pm 21.1

Mean \pm S.D.

Table 11-2. -continued Blood chemistry
 ---Recovery period---

Sex	Dose level (mg/kg)	No. of animals	AST (U/L)	ALT (U/L)	ALP (U/L)	Gamma-GTP (U/L)
Male	0	5	78 ± 13	31 ± 4	487 ± 94	0.6 ± 0.1
	500	5	75 ± 6	30 ± 6	631 ± 71*	0.8 ± 0.3
Female	0	5	88 ± 7	26 ± 3	354 ± 91	1.1 ± 0.4
	500	5	87 ± 17	27 ± 3	307 ± 80	1.1 ± 0.3

Mean ± S.D.
 Significantly different from control group; *: P ≤ 0.05 (Dunnett)

Table 11-2. --continued Blood chemistry
---Recovery period---

Sex	Dose level (mg/kg)	No. of animals	Calcium (mg/dL)	I. phosphorus (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)
Male	0	5	10.05 ± 0.22	7.57 ± 0.35	142.0 ± 0.6	4.64 ± 0.48	106.2 ± 0.8
	500	5	9.99 ± 0.19	8.35 ± 0.17**	143.3 ± 1.5	4.63 ± 0.16	106.7 ± 1.9
Female	0	5	9.55 ± 0.16	6.60 ± 0.93	141.7 ± 1.1	4.73 ± 0.21	111.0 ± 1.2
	500	5	9.71 ± 0.13	6.97 ± 0.77	141.4 ± 1.2	4.44 ± 0.31	109.1 ± 1.0*

Mean ± S.D.
Significantly different from control group; *: P ≤ 0.05 **; P ≤ 0.01 (Dunnett)