Table 2-2   Clinical signs in female rats

Group		Water for injection					CCA 10					CCA 100					CCA 300				
Dose(mg/kg)																					
	Grade	0	1	2	3	+	0	1	2	3	+	0	1	2	3	+	0	1	2	3	+
Day	Item																				
21	No abnormal signs	6					6					6									
22	No abnormal signs	6					6					6									
23	No abnormal signs	6					6					6									
24	No abnormal signs	6					6					6									
25	No abnormal signs	6					6					6									
26	No abnormal signs	6					6					6									
27	No abnormal signs	6					6					6									
28	No abnormal signs	6					6					6									

Numerals represent the number of animals.

Table 2-3   Clinical signs in female rats (Administration site)

Group	Number of animals	Item	Day of administration (Before administration)																											
			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Water for injection	6		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CCA (10 mg/kg)	6	Crust	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2	2	2	1	1	1	1	2	2	2	3	3	3
CCA (100 mg/kg)	6	Crust	0	0	0	0	0	0	4	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
CCA (300 mg/kg)	6	Crust	0	0	0	0	0	0	1	1	1	1	1	1																		

Numerals represent the number of animals.

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Table 3   Food consumption (g/day) in female rats

Group	Water for injection	CCA	CCA	CCA
Dose(mg/kg)		10	100	300
Day				
Pre	15.8± 3.7(6)	16.7± 2.5(6)	16.8± 1.7(6)	17.0± 2.2(6)
5	19.0± 0.6(6)	18.7± 1.9(6)	18.3± 1.5(6)	6.0 (2)*
12	20.0± 0.6(6)	19.0± 2.0(6)	20.8± 2.5(6)	
19	20.7± 2.7(6)	21.5± 1.9(6)	21.5± 2.3(6)	
26	17.8± 2.1(6)	18.3± 2.1(6)	18.8± 2.1(6)	

Values are expressed as the mean + S.D. (N).
* P<0.05 : significantly different from Water for injection.

41

Table 4-1   Body weight (g) in female rats

Group	Water for injection	CCA	CCA	CCA
Dose(mg/kg)		10	100	300
Day				
Pre	151.2± 6.1(6)	151.7± 6.5(6)	149.7± 6.8(6)	151.0± 5.2(6)
6	176.7± 3.6(6)	172.5± 8.0(6)	165.5+10.8(6)	142.0 (1)
13	194.8± 6.2(6)	191.3± 9.5(6)	186.7+12.8(6)	
20	203.3+10.2(6)	202.5± 8.4(6)	198.2+15.9(6)	
27	216.8+12.4(6)	218.0± 9.7(6)	215.2+18.4(6)	

Values are expressed as the mean + S.D. (N).
Not significantly different from Water for injection.

42

Table 4-2   Body weight gain (g) in female rats

Group	Water for injection	CCA	CCA	CCA
Dose(mg/kg)		10	100	300
Day 6	25.5+ 5.5(6)	20.8+ 5.7(6)	15.8+ 6.2(6)*	-4.0 (1)
13	18.2+ 5.6(6)	18.8+ 3.9(6)	21.2+ 4.3(6)	
20	8.5+ 4.3(6)	11.2+ 3.2(6)	11.5+ 6.7(6)	
27	13.5+ 4.8(6)	15.5+ 3.3(6)	17.0+ 4.4(6)	

Values are expressed as the mean + S.D. (N).
* P<0.05 : significantly different from Water for injection.

Gross ophthalmological & slit-lamp examination

Grade

0 : No abnormal changes

1 : Slight

2 : Moderate

3 : Severe

P : Non-graded change

U : Unexamined

Table 5-1　　　　Gross ophthalmological & slit-lamp examination in female rats

Group	Water for injection	CCA	CCA	CCA
Dose(mg/kg)		10	100	300
Item　　　　　　Grade				
Pre　No abnormal changes	6	6	6	6
4w　No abnormal changes	6	6	6	

Numerals represent the number of animals.

45

Funduscopic examination

Grade

0 : No abnormal changes

1 : slight

2 : Moderate

3 : Severe

P : Non-graded change

U : Unexamined

Table 5-2.   Funduscopic examination in female rats

Group	Water for injection	CCA	CCA	CCA
Dose(mg/kg)		10	100	300
Item	Grade			
Pre No abnormal changes	6	6	6	6
4w No abnormal changes	6	6	6	

Numerals represent the number of animals.

47

Standard Urinalysis

Color   0 : Normal color
        1 : Abnormal color

Protein   (mg/dL)
0 : -
1 : +-
2 : +   30
3 : ++   100
4 : +++   300<=

Glucose   (g/dL)
0 : -
1 : +-   0.1
2 : +   0.25
3 : ++   0.5
4 : +++   1<=

Ketone body   (mg/dL)
0 : -
1 : +-   5
2 : +   15
3 : ++   40
4 : +++   80

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

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

Urobilinogen   (Ehrlich unit/dL)
0 : +-   0.1
1 : +   1
2 : ++   2
3 : +++   4
4 : ++++   8<=

48

Number of Animals

Item : Urinalysis
Sex : Female

Group	Water for injection	CCA	CCA	CCA
Dose(mg/kg)	0	10	100	300
4w	6	6	6	

Table 6-1   Urinalysis in female rats

Group		Water for injection	CCA	CCA	CCA
Dose(mg/kg)			10	100	300
	Grade				
Color	4w				
	0				
	1	6	6	6	
pH	4w				
	5				
	5.5				
	6				
	6.5	1	2		
	7	1			
	7.5	2	1	1	
	8	1	2	3	
	8.5	1	1	1	
	9			1	

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

50

Table 6-2   Urinalysis in female rats

Group		Water for injection	CCA	CCA	CCA
Dose(mg/kg)			10	100	300
	Grade				
Protein	4w				
	0	4	·3	4	
	1	1	1	1	
	2	1	2	1	
	3				
	4				
Glucose	4w				
	0	6	6	6	
	1				
	2				
	3				
	4				

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

51

Table 6-3   Urinalysis in female rats

Group			Water for injection	CCA	CCA	CCA
Dose(mg/kg)				10	100	300
	Grade					
Ketone body	4w	0	6	6	6	
		1				
		2				
		3				
		4				
Bilirubin	4w	0	6	6	6	
		1				
		2				
		3				

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

52

Table 6-4   Urinalysis in female rats

Group		Water for injection	CCA	CCA	CCA
Dose(mg/kg)			10	100	300
	Grade				
Occult blood	4w				
	0	2	3	6	
	1	1	1		
	2	2	2		
	3	1			
	4				
Urobilinogen	4w				
	0	5	5	2	
	1	1	1	4	
	2				
	3				
	4				

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

53

Hematology

RBC	$(10^6/mm^3)$	Number of red blood cells
WBC	$(10^3/mm^3)$	Number of white blood cells
Ht	(%)	Hematocrit value
Hb	(g/dL)	Hemoglobin concentration
Plat.	$(10^3/mm^3)$	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.	$(10^3/mm^3)$	Number of eosinophilic leukocytes
Eosino.	(%)	Eosinophilic leukocyte ratio
Baso.	$(10^3/mm^3)$	Number of basophilic leukocytes
Baso.	(%)	Basophilic leukocyte ratio
Mono.	$(10^3/mm^3)$	Number of monocytes
Mono.	(%)	Monocyte ratio
Lymph.	$(10^3/mm^3)$	Number of lymphocytes
Lymph.	(%)	Lymphocyte ratio
Neutro.	$(10^3/mm^3)$	Number of neutrophilic leukocytes
Neutro.	(%)	Neutrophilic leukocyte ratio
LUC	$(10^3/mm^3)$	Number of large unstained cells
LUC	(%)	Large unstained cell ratio

Blood coagulation test

PT	(Sec)	Prothrombin time
APTT	(Sec)	Activated partial thromboplastin time

Table 7   Hematology in female rats

Group		Water for injection	CCA	CCA	CCA
Dose(mg/kg)			10	100	300
N		6	6	6	0
RBC	$(10^6/mm^3)$	8.235+0.272	7.933+0.217	7.928+0.412	
WBC	$(10^3/mm^3)$	5.825+1.290	7.527+2.615	10.450+2.768**	
Ht	(%)	46.77+1.34	44.68+1.16	42.37+2.46**	
Hb	(g/dL)	16.48+0.31	16.03+0.45	14.70+1.12**	
Plat.	$(10^3/mm^3)$	1034.7+40.6	1200.0+136.0	1532.8+176.4**	
MCV	(fL)	56.78+1.24	56.37+1.27	53.47+2.76*	
MCH	(pg)	20.03+0.52	20.27+0.52	18.58+1.39	
MCHC	(g/dL)	35.25+0.44	35.92+0.44	34.72+0.95	
Ret.	(%)	1.67+0.27	2.08+0.17	4.18+0.96**	
Eosino.	$(10^3/mm^3)$	0.108+0.054	0.148+0.102	0.072+0.027	
Eosino.	(%)	1.83+0.77	2.05+1.38	0.75+0.33*	
Baso.	$(10^3/mm^3)$	0.008+0.004	0.015+0.008	0.022+0.012*	
Baso.	(%)	0.13+0.05	0.17+0.08	0.18+0.12	
Mono.	$(10^3/mm^3)$	0.087+0.028	0.112+0.047	0.132+0.055	
Lymph.	$(10^3/mm^3)$	4.340+1.034	5.810+2.143	8.220+2.246**	
Lymph.	(%)	74.50+6.31	76.87+5.43	78.80+5.10	
Neutro.	$(10^3/mm^3)$	1.227+0.390	1.385+0.552	1.905+0.759	
Neutro.	(%)	21.05+5.43	18.65+4.13	18.05+5.09	
LUC	$(10^3/mm^3)$	0.053+0.015	0.055+0.028	0.102+0.051	
LUC	(%)	0.97+0.23	0.72+0.13	0.93+0.34	
PT	(sec)	7.88+0.32	7.87+0.26	8.05+0.40	
APTT	(sec)	17.55+1.21	17.42+0.71	17.90+0.53	

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

Blood Chemistry

ASAT	(IU/L)	Aspartate aminotransferase
ALAT	(IU/L)	Alanine aminotransferase
ALP	(IU/L)	Alkaline phosphatase
G-GTP	(IU/L)	Gamma – glutamyl transpeptidase
T.Bil.	(mg/dL)	Total bilirubin
T.Prot.	(g/dL)	Total protein
Albumin	(g/dL)	Albumin
A/G		Albumin / Globulin
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
Globlin	(g/dL)	Globlin

Table 8   Blood chemistry in female rats

Group		Water for injection	CCA	CCA	CCA
Dose(mg/kg)			10	100	300
N		6	6	6	0
ASAT	(IU/L)	106.8+15.2	102.0+15.2	139.5+30.4*	
ALAT	(IU/L)	24.3+2.9	24.0+4.2	21.2+1.9	
ALP	(IU/L)	432.3+60.1	378.2+73.2	308.7+19.5**	
G-GTP	(IU/L)	1.3+1.0	1.8+1.3	1.7+1.2	
T.Bil.	(mg/dL)	0.052+0.012	0.040+0.013	0.017+0.023**	
T.Prot.	(g/dL)	5.65+0.26	5.75+0.14	5.33+0.22*	
Albumin	(g/dL)	4.38+0.13	4.33+0.18	3.80+0.23**	
A/G	(g/dL)	3.582+0.783	3.130+0.549	2.527+0.435*	
T.Chol.	(mg/dL)	50.5+13.5	48.7+10.0	62.0+6.4	
TGL	(mg/dL)	9.0+2.8	9.3+2.9	14.2+4.2*	
Glucose	(mg/dL)	122.0+13.0	139.2+6.8*	138.2+10.7*	
BUN	(mg/dL)	17.03+3.11	18.70+3.31	20.10+3.21	
Creat.	(mg/dL)	0.225+0.021	0.232+0.041	0.190+0.026	
IP	(mg/dL)	8.668+0.944	8.555+0.760	8.823+0.574	
Ca	(mg/dL)	9.48+0.13	9.55+0.16	9.35+0.23	
Na	(mEq/L)	143.8+0.8	143.3+0.8	143.5+1.0	
K	(mEq/L)	3.58+0.21	3.68+0.26	4.28+0.21**	
Cl	(mEq/L)	109.2+1.5	108.3+0.8	109.2+0.8	
Globlin	(g/dL)	1.27+0.24	1.42+0.22	1.53+0.21	

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

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Gross Autopsy Findings

Grade

0 : No abnormal changes

1 : Slight

2 : Moderate

3 : Marked

P : Non-graded changes