1,3,5,7-テトラアザトリシクロ [3.3.1.1<sup>3,7</sup>] デカンの ラット及びマウスを用いた経口投与による がん原性予備試験(混水試験)報告書

## APPENDIX

 $(A1-1\sim A8-3-2)$ 

2週間試験:ラット/0187;マウス/0188

#### APPENDIXES

- APPENDIX A 1-1 CLINICAL OBSERVATION (TWO-WEEK STUDY : SUMMARY)
  RAT : MALE
- APPENDIX A 1-2 CLINICAL OBSERVATION (TWO-WEEK STUDY: SUMMARY)
  RAT: FEMALE
- APPENDIX A 1-3 CLINICAL OBSERVATION (TWO-WEEK STUDY: SUMMARY)
  MOUSE: MALE
- APPENDIX A 1-4 CLINICAL OBSERVATION (TWO-WEEK STUDY : SUMMARY)
  MOUSE : FEMALE
- APPENDIX A 2-1 BODY WEIGHT CHANGES (TWO-WEEK STUDY : SUMMARY)
  RAT : MALE
- APPENDIX A 2-2 BODY WEIGHT CHANGES (TWO-WEEK STUDY : SUMMARY)
  RAT : FEMALE
- APPENDIX A 2-3 BODY WEIGHT CHANGES (TWO-WEEK STUDY : SUMMARY)
  MOUSE : MALE
- APPENDIX A 2-4 BODY WEIGHT CHANGES (TWO-WEEK STUDY : SUMMARY)
  MOUSE : FEMALE
- APPENDIX A 3-1 WATER CONSUMPTION CHANGES (TWO-WEEK STUDY : SUMMARY)
  RAT : MALE
- APPENDIX A 3-2 WATER CONSUMPTION CHANGES (TWO-WEEK STUDY : SUMMARY)
  RAT : FEMALE
- APPENDIX A 3-3 WATER CONSUMPTION CHANGES (TWO-WEEK STUDY : SUMMARY)
  MOUSE : MALE
- APPENDIX A 3-4 WATER CONSUMPTION CHANGES (TWO-WEEK STUDY : SUMMARY)

  MOUSE : FEMALE
- APPENDIX A 4-1 FOOD CONSUMPTION CHANGES (TWO-WEEK STUDY : SUMMARY)
  RAT : MALE
- APPENDIX A 4-2 FOOD CONSUMPTION CHANGES (TWO-WEEK STUDY : SUMMARY)
  RAT : FEMALE
- APPENDIX A 4-3 FOOD CONSUMPTION CHANGES (TWO-WEEK STUDY : SUMMARY)
  MOUSE : MALE
- APPENDIX A 4-4 FOOD CONSUMPTION CHANGES (TWO-WEEK STUDY : SUMMARY)
  MOUSE : FEMALE

#### APPENDIXES (CONTINUED)

- APPENDIX A 5-1 CHEMICAL INTAKE CHANGES (TWO-WEEK STUDY : SUMMARY)
  RAT : MALE
- APPENDIX A 5-2 CHEMICAL INTAKE CHANGES (TWO-WEEK STUDY : SUMMARY)
  RAT : FEMALE
- APPENDIX A 5-3 CHEMICAL INTAKE CHANGES (TWO-WEEK STUDY : SUMMARY)
  MOUSE : MALE
- APPENDIX A 5-4 CHEMICAL INTAKE CHANGES (TWO-WEEK STUDY : SUMMARY)
  MOUSE : FEMALE
- APPENDIX A 6-1 GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)
  RAT : MALE : DEAD AND MORIBUND ANIMALS
- APPENDIX A 6-2 GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)
  RAT : FEMALE : DEAD AND MORIBUND ANIMALS
- APPENDIX A 6-3 GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)
  RAT : FEMALE : SACRIFICED ANIMALS
- APPENDIX A 6-4 GROSS FINDINGS (TWO-WEEK STUDY: SUMMARY)

  MOUSE: FEMALE: DEAD AND MORIBUND ANIMALS
- APPENDIX A 6-5 GROSS FINDINGS (TWO-WEEK STUDY: SUMMARY)
  MOUSE: MALE: SACRIFICED ANIMALS
- APPENDIX A 6-6 GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)
  MOUSE : FEMALE : SACRIFICED ANIMALS
- APPENDIX A 7-1 HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (TWO-WEEK STUDY: SUMMARY)
  RAT: MALE: DEAD AND MORIBUND ANIMALS
- APPENDIX A 7-2 HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (TWO-WEEK STUDY: SUMMARY)
  RAT: FEMALE: DEAD AND MORIBUND ANIMALS
- APPENDIX A 7-3 HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (TWO-WEEK STUDY: SUMMARY)
  RAT: MALE: SACRIFICED ANIMALS
- APPENDIX A 7-4 HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (TWO-WEEK STUDY: SUMMARY)
  RAT: FEMALE: SACRIFICED ANIMALS
- APPENDIX A 7-5 HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (TWO-WEEK STUDY: SUMMARY)
  MOUSE: FEMALE: DEAD AND MORIBUND ANIMALS
- APPENDIX A 7-6 HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (TWO-WEEK STUDY: SUMMARY)
  MOUSE: MALE: SACRIFICED ANIMALS
- APPENDIX A 7-7 HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (TWO-WEEK STUDY: SUMMARY)
  MOUSE: FEMALE: SACRIFICED ANIMALS

#### APPENDIXES (CONTINUED)

- APPENDIX A 8-1 IDENTITY AND PURITY OF TATCD
  PERFORMED AT THE JAPAN BIOASSAY LABORATORY
  (TWO-WEEK STUDIES)
- APPENDIX A 8-2 STABILITY OF TATCD

  AT THE JAPAN BIOASSAY LABORATORY

  (TWO-WEEK STUDIES)
- APPENDIX A 8-3-1 ANALYSIS OF TATCD CONCENTRATION IN DRINKING WATER OF THE TWO-WEEK STUDIES
- APPENDIX A 8-3-2 STABILITY OF TATCD CONCENTRATION IN DRINKING WATER OF THE TWO-WEEK STUDIES

### APPENDIX A 1-1

CLINICAL OBSERVATION (TWO-WEEK STUDY: SUMMARY)

RAT: MALE

STUDY NO.: 0187 ANIMAL: RAT F344 REPORT TYPE: A1 2

CLINICAL OBSERVATION (SUMMARY)

ALL ANIMALS

SEX : MALE

PAGE: 1

linical sign	Group Name		stration We												
		1-1	1-2	1-3	1-4	1-5	1-6	1-7	2-1	2-2	2-3	2-4	2-5	2-6	2-7
		1	1	1	1	1	1	1	1	1	1	1	1	1	1
реатн	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	Õ	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	Ŏ	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	Ö	0	0	0	Ö	Ö	0	0	0	0	0	0	0	0
	50000 ppm	Ŏ	Ö	0	0	0	Ő	0	0	0	0	0	0	0	0
	100000 ppm	0	0	Ö	0	Ö	Ö	5	8	10	-	-	_	_	-
OCOMOTOR MOVEMENT DECR	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	1	0	2	0		-	-	-	-
UNCHBACK POSITION	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	7	7	5	2	0	_	-	-	-	-
ASTING	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0.	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	1	3	2	0	-	-	-	-	-
OILED	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	. 0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	1	1	4	5	2	0	-	-	-	-	-

STUDY NO.: 0187 ANIMAL: RAT F344 REPORT TYPE: A1 2 CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : MALE

PAGE: 2

Clinical sign	Group Name	Admini:	stration We	ek-day											
		1-1	1-2	1-3	1-4	1-5	1-6	1-7	2-1	2-2	2-3	2-4	2-5	2-6	2-7
		1	1.	1	1	1	1	1	1	1	1	1	1	1	1
												, , , , , , , , , , , , , , , , , , , ,			
PILOERECTION	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	Ō	0	Ö
	100000 ppm	0	0	0	1	7	8	5	2	0	-	_	_	_	_
EXOPHTHALMOS	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	o o	Ô	Ö
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	Ô	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	1	1	1	1	1	1	0	0	Ō	-	-	-	-	-
EYE OPACITY	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	Ô	Ô	0	Ö
	25000 ppm	0	0	0	0	0	0	0	0	0	Ô	Ô	0	0	Ö
	50000 ppm	0	0	0	0	Ö	Ö	Ŏ	0	Õ	Õ	0	0	0	0
	100000 ppm	0	0	0	1	1	1	0	Ö	Ö	-	-	_	-	-
ANTERIOS CHAMBER OPACITY	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	Ō	0	Ô	0	0	Ö	0	Ö
	25000 ppm	0	0	0	0	0	0	0	0	Ô	Ô	0	0	0	0
	50000 ppm	0	Ö	Ŏ	Ö	Ö	Ö	Ŏ	0	0	0	0	0	0	0
	100000 ppm	0	0	0	1	1	1	0	Ö	0	-	-	-	-	-
OSE HEMORRHAGIC DISCHA	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	Ō	0	Ô	Ö	0	0	0	0	0	0	0
	12500 ppm	0	0	0	Õ	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	Ŏ	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	Ö	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	Ö	Ö	0	0	0	0	5	2	0	_	_	_	_	V
	100000 PPIII	v	v	V	v	v	V	J	4	v	-	-	_	-	-

CLINICAL OBSERVATION (SUMMARY) ALL ANIMALS

STUDY NO.: 0187 ANIMAL: RAT F344 REPORT TYPE: A1 2

SEX : MALE

PAGE: 3

Clinical sign	Group Name	Admini	stration We	ek-day											
		1-1	1-2	1-3	1-4	1-5	1-6	1-7	2-1	2-2	2-3	2-4	2-5	2-6	2-7
į		1	1	1	1	1	1	1	1	1	1	1	1	1	1
RREGULAR BREATHING	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	Ö	0
	100000 ppm	0	0	0	0	0	0	0	2	0	_	-	_	-	-
BNORMAL RESPIRATION	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	Ö	Ö	0	0
	25000 ppm	0	0	0	0	0	. 0	0	0	0	0	0	0	0	Ő
	50000 ppm	0	0	0	0	0	Õ	0	Ö	0	0	Ö	0	0	0
	100000 ppm	0	0	0	0	0	0	0	2	Ö	-	-	_	-	-
RADYPNEA	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0 .	0	0	0	0	0	0	0	Ô	Ô	0	0
	25000 ppm	0	0	0	0	0	0	0	Ò	0	0	Ô	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	Ŏ	0	Ö	0
	100000 ppm	0	0	0	0	0	0	Ō	1	Ö	-	-	_	-	-
MALL STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	Ô	0	0	0
	12500 ppm	0	0	0	0	0	Ô	0	0	0	0	Ö	0	0	0
	25000 ppm	0	0	Ō	Ö	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	Ö	0	0	0	Ö	Ö	0	0
	100000 ppm	0	0	Ō	8	9	9	5	2	0	-	-	-	-	_
LIGO-STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	Ö	0	0	0	Ö	0	0	. 0
	12500 ppm	Ŏ	Ö	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	Ö	Ö	Ö	0	Ö	0	0	0	0	0	0	0	0	0
	50000 ppm	Ö	0	Ö	. 0	0	0	Ö	0	0	0	0	0	0	0
	100000 ppm	Ö	0	0	8	9	9	4	2	0	_	_	_	_	-

(HAN190)

STUDY NO. : 0187 ANIMAL : RAT F344 REPORT TYPE : A1 2

CLINICAL OBSERVATION (SUMMARY) ALL ANIMALS

SEX : MALE

PAGE: 4

Clinical sign	Group Name	Admini	stration We	eek-day											
		1-1 1	1-2 1	1-3	1-4 1	1-5 1	1-6 1	1-7 1	2-1 1	2-2 1	2-3 1	2-4 1	2-5 1	2-6 1	2-7 1
SUBNORMAL TEMP	Control	0	0	0	0	0	0	٥	^	^					
oodiioming 15th	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	Ö	Ö	Õ	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	Õ	Ö	Ö	0
	100000 ppm	0	0	0	0	0	1	0	0	Λ	_	_	_	_	_

### APPENDIX A 1-2

CLINICAL OBSERVATION (TWO-WEEK STUDY: SUMMARY)

RAT: FEMALE

STUDY NO.: 0187 ANIMAL: RAT F344 REPORT TYPE: A1 2 CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : FEMALE

PAGE: 5

6250 12500 25000 25000 100000 100000  LOCOMOTOR MOVEMENT DECR Cont 6250 12500 25000 100000  HUNCHBACK POSITION Cont 6255 12500 25000 100000  WASTING Cont 6250 12500 25000 100000	ntrol 50 ppm 90 ppm 90 ppm 90 ppm	1-1 1 0 0 0 0 0	stration W 1-2 1 0 0	1-3 1	1-4	1 <b>-</b> 5	1–6 1	1-7 1	2-1 1	2-2 1	2-3 1	2-4 1	2-5 1	2-6 1	2-7 1
### RESTING   Cont   Co	mqq 00 mqq 00 mqq 00	0 0 0 0	0	0			1				1	1	1	1	
COMMOTOR MOVEMENT DECR	mqq 00 mqq 00 mqq 00	0 0 0	0		0									-	
COMMOTOR MOVEMENT DECR	mqq 00 mqq 00 mqq 00	0 0 0	0		0										
12500 25000 100000 100000 100000 100000 125000 125000 1000000	mqq 00 mqq 00	0		0		0	0	0	0	0	0	0	0	0	0
25000 50000 100000 COCOMOTOR MOVEMENT DECR Cont 6250 125000 50000 100000 UNCHBACK POSITION Cont 6250 125000 50000 100000 ASTING Cont 6250 125000 50000 100000 ASTING Cont 6250 50000 50000 50000 50000 50000 50000	Mqq 00	0	0	v	0	0	0	0	0	0	0	0	0	0	0
50000   100000   100000   100000   100000   100000   12500   12500   100000   100000   100000   12500   12500   12500   12500   100000   100000   100000   100000   100000   100000   100000   100000   125000	00 ppm	•	-	0	0	0	0	0	0	0	0	0	0	0	0
100000  COMOTOR MOVEMENT DECR  Conf 6256 12500 50000 100000  UNCHBACK POSITION  Conf 6250 12500 25000 100000  ASTING  Conf 6250 12500 50000 100000  Conf 6250 6250 6250 6250 6250 6250 6250 6250		0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCOMOTOR MOVEMENT DECR 6250 12500 50000 100000 UNCHBACK POSITION 6250 25000 50000 100000 ASTING Cont 6250 12500 50000 50000 50000 50000 50000 50000 50000	00 ppm	•	0	0	0	0	0	0	0	0	0	0	0	0	0
6250 12500 25000 50000 100000 100000  INCHBACK POSITION  Cant 6250 12500 25000 100000  ASTING  Cant 6250 12500 50000 100000  ASTING  Cont 6250 12500 50000 50000 50000		0	0	0	0	0	1	1	4	5	9	9	10	· –	-
12500 25000 50000 100000  NCHBACK POSITION  Cont 6250 25000 50000 100000  STING  Cont 6250 25000 50000 50000 50000 50000 50000	ntrol	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25000 50000 100000 100000 UNCHBACK POSITION Cont 6250 25000 50000 100000 ASTING Cont 6250 12500 52500 52500 52500 52500 52500 52500 52500 52500 55000	50 ppm	0	. 0	0	0	0	0	0	0	0	0	0	0	0	0
ASTING Cont 6250  ASTING Cont 6250  12500  100000  ASTING Cont 6250  12500  1000000	00 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ASTING Cont 6250  ASTING Cont 6250  ASTING Cont 6250  100000  ASTING Cont 6250  12500  12500  12500  12500  12500  12500  12500	00 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
UNCHBACK POSITION Cont 6250 12500 25000 50000 100000 ASTING Cont 6250 12500 25000 50000	00 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6250 12500 25000 50000 100000 STING Cant 6250 12500 25000	mqq 00	0	0	0	0	0	0	0	4	3	1	1	0	_	-
12500 25000 50000 100000 STING Cant 6250 12500 25000 50000	ntrol	0	0	0	0	0	0	0	0	0	0	0	0	0	. 0
12500 25000 50000 100000 STING Cant 6250 12500 25000 50000	50 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50000 100000 ASTING Conn 6250 12500 25000 50000	00 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50000 100000 ASTING Cont 6250 12500 25000 50000	00 ppm	0	0	0	0	0	0	0	0	0	Ô	Ô	0	0	0
100000 ASTING Cont 6250 12500 25000 50000	00 ppm	0	0	0	0	0	Ō	Ô	Ö	Ö	Ö	0	0	0	0
625( 1250( 2500( 5000(	00 ppm	0	0	0	1	4	4	4	2	5	1	1	Ö	-	-
12500 25000 50000	ntrol	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25000 50000	50 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50000	00 ppm	0	0	0	0	0	0	0	0	0	0	Ô	0	Ö	. 0
	00 ppm	0	0	0	0	0	Ō	Ö	Ô	0	Ŏ	0	0	0	. 0
	00 ppm	0	0	0	0	0	0	0	0	0	0	0	Ŏ	0	0
		0	0	0	0	0	1	1	2	3	1	1	0	-	-
PILED Con:	ntrol	0	0	0	0	0	0	0	0	0	0	0	0	0	. 0
	50 ppm	0	0	0	0	0	0	0	0	Ô	0	0	0	0	0
	00 ppm	Õ	Ô	Ö	Ö	ő	0	0	0	0	0	0	0	0	0
	00 ppm	0	0	0	0	0	0	0	0	0	٥	0	0	0 .	0
50000		0	0	0	0	0	0	0	0	0	0	0	0	0	-
100000		0	0	0	3	3	3	7	4	5	1	1	0	U	0

# STUDY NO.: 0187 CLINICAL OBSERVATION (SUMMARY) ANIMAL: RAT F344 REPORT TYPE: A1 2

SEX : FEMALE

FAGE: 6

Clinical sign	Group Name	Admini:	stration We	eek-day											
		1-1	1-2	1-3	1-4	1-5	1-6	1-7	2-1	2-2	2-3	2-4	2-5	2-6	2-7
		1	1	1	1	1	1	1	1	1	1	1	1	1	1
								• <del></del>							
ILOERECTION	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	1	0	0	0	0	0	0	0	0	Ö	0	Ö	Ö	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	Ó	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	Ô	0
	100000 ppm	0	0	0	4	5	4	8	6	5	1	1	0	-	-
DILED PERI GENITALIA	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	Ô	Ō	Ô	0
	100000 ppm	0	0	0	1	2	2	2	1	1	0	0	Ō	-	_
OSE HEMORRHAGIC DISCHA	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	Ô	Ŏ	Ô	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	Ö	Ö	Ö	Ô	Õ	0	0	0	Ő	0
	100000 ppm	0	0	0	0	0	0	7	4	5	1	1	Ö	-	_
RREGULAR BREATHING	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	Ö	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	Ô	0	0	0	0
	50000 ppm	0	0	Ō	0	0	0	Ö	ő	ŏ	0	0	0	0	0
	100000 ppm	. 0	0	0	0	0	Ō	0	2	2	Ö	Ö	0	_	_
BNORMAL RESPIRATION	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	Ŏ	0	0	0	Ó	0	0	0
	12500 ppm	0	0	0	0	.0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	٥	0	0
	50000 ppm	Ö	0	Ö	Ö	0	0	0	0	0	0	0	0	0	-
	100000 ppm	0	0	. 0	0	0	0	0	2	2	0	. 0	0	v	0

(HAN190)

STUDY NO.: 0187
ANIMAL: RAT F344
REPORT TYPE: A1 2

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : FEMALE

PAGE: 7

Clinical sign	Group Name	Admini	stration We	eek-day											
		1-1	1-2	1-3	1-4	1-5	1-6	1-7	2-1	2-2	2-3	2-4	2-5	2-6	2-7
		1	1	1	1	1	1	1	1	1	1	1	1	1	1
RADYPNEA	Control	0	0	٥	0	•	•	•	•						
AND IT NUM	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	•	0	0	=	•	0	0	0	0	0	0
	25000 ppm	0	0	0	0	•	0	0	0	0	0	0	0	0	0
	50000 ppm	•	0	•	0	0	V	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10000 ppm	U	U	0	0	0	0	0	0	2	0	0	0	-	-
MALL STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	. 0
	6250 ppm	0	0	0	0	Ö	0	Ö	Ŏ	Ö	Õ	0	0	ő	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	٥
	50000 ppm	0	0	0	0	0	0	0	Ő	Ö	0	ŏ	0	0	0
	100000 ppm	0	0	0	9	9	9	9	6	5	1	1	0	_	-
LIGO-STOOL	Control	0	0	0	0	0	0	0	0	0	^	0	•	•	
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	٨	0	0	0	0	0	0	0	U	U	U	0	0
	50000 ppm	0	0	n	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	10	10	9	9	6	5	1	1	0	-	V
	10000 ppili	V	V	V	10	10	ฮ	ð	р	Э	1	1	U	_	_
UBNORMAL TEMP	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	Ō	0	0	0	0	0	0
	50000 ppm	0	. 0	0	0	0	0	0	Ŏ	0	Ö	Õ	Ö	0	0
	100000 ppm	0	0	0	0	0	0	0	Ô	0	Ô	1	0	_	_

(HAN190)

### APPENDIX A 1-3

CLINICAL OBSERVATION (TWO-WEEK STUDY: SUMMARY)

MOSUE: MALE

STUDY NO.: 0188

ANIMAL : MOUSE BDF1

REPORT TYPE : A1 2

CLINICAL OBSERVATION (SUMMARY) ALL ANIMALS

SEX : MALE

PAGE: 1

		1-1	1-2	1-3											
			- 4	1-0	1-4	1-5	1–6	1-7	2-1	2-2	2-3	2-4	2-5	2-6	2-7
		1	1	1	1	1	1	1	1	1	1	1	1	1	1
ILOERECTION	Combine	0	0	0	•	0	0	0	0	•	0	0	•	۰	0
ILULIEUI IUN	Control	0	0	0	0	0	0	0	0	0	0	0	U	0	0
	6250 ppm	0	0	U	0	0	0	U	0	0	0	Ü	0	Ü	U
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	0	0	0	0	2	2	3	3	3
LIGO-STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	Ö	0	Ó	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	Ô	Ó	0	Ô	0	0
	100000 ppm	Ö	0	0	Ö	Ö	Ö	0	8	8	8	7	7	7	7

(HAN190)

### APPENDIX A 1-4

CLINICAL OBSERVATION (TWO-WEEK STUDY: SUMMARY)

MOSUE: FEMALE

STUDY NO. : 0188
ANIMAL : MOUSE BDF1
REPORT TYPE : A1 2

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : FEMALE

PAGE: 2

linical sign	Group Name	Admini	stration We	ek-day											-
		1-1	1-2	1-3	1-4	1-5	1-6	1-7	2-1	2-2	2-3	2-4	2-5	2-6	2-7
		1	1	1	1	1	1	1	1	1	1	1	1	1	1
EATH	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	0	0	0	1	1	1	1	1	1
TERAL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	1
INCHBACK POSITION	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	0	1	1	0	0	0	1	1	0
ASTING	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0 -	0	0	0	0	0	0	1	1	1
ILOERECTION	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	.0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	0	1	1	1	2	2	2	2	1

(HAN190)

STUDY NO.: 0188
ANIMAL: MOUSE BDF1
REPORT TYPE: A1 2

CLINICAL OBSERVATION (SUMMARY) ALL ANIMALS

SEX : FEMALE

PAGE: 3

Clinical sign	Group Name	Admini	stration We	ek-day											
		1-1	1-2	1-3	1-4	1-5	1-6	1-7	2-1	2-2	2-3	2-4	2-5	2-6	2-7
		1	1 		1		1	<u> </u>	. 1	1	<u> </u>		<u> </u>		
SMALL STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	0	0	0	0	0	0	2	2	1
OLIGO-STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
•	6250 ppm	0	0.	0	0	0	0	0	0	0	0	0	0	0	0
	12500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100000 ppm	0	0	0	0	0	0	0	9	9	5	5	5	5	5

(HAN190)

### APPENDIX A 2-1

BODY WEIGHT CHANGES (TWO-WEEK STUDY:SUMMARY)

RAT: MALE

STUDY NO. : 0187

ANIMAL : RAT F344

UNIT : g

REPORT TYPE : A1 2

SEX : MALE

BODY WEIGHT CHANGES ALL ANIMALS

(SUMMARY)

PAGE: 1

DUP Name	Admini	stration	week-day											
	0-0		1-1		1-2		1-4		1-7		2-3		2-7	
Control	123±	4	126±	4	128±	5	136±	5	147±	7	159±	8	176±	10
6250 ppm	123±	4	127±	4	128±	5	134土	8	144±	12	158±	8	176±	9
12500 ppm	123±	4	126±	4	128±	4	136±	4	147±	5	158±	6	174±	8
25000 ppm	123±	4	125±	5	127±	5	134±	6	144±	8	156±	7	170±	7
50000 ppm	123±	4	121±	4*	122±	4**	129±	4*	139±	4	148±	6**	155±	14**
100000 ppm	123±	4	114±	3**	105±	4**	95±	5**	77±	4**	-		-	
														,
Significant differen	nce; *:P≦0	.05	**: P ≤ 0.0	1			Test of Dur	nett						

(HAN260)

#### APPENDIX A 2-2

BODY WEIGHT CHANGES (TWO-WEEK STUDY: SUMMARY)

RAT: FEMALE

STUDY NO. : 0187 ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 2
SEX : FEMALE

BODY WEIGHT CHANGES ALL ANIMALS

(SUMMARY)

PAGE: 2

roup Name	Admini:	stration	week-day											
	0-0		1-1		1-2		1-4		17		2-3		2-7	
Control	101±	3	103±	4	103±	3	108±	3	115±	3	121±	Л	130±	5
	141_		100_	•	1001	Ü	1001	Ü	1102	Ü	1212	4	100	Ü
6250 ppm	101±	3	102±	5	102±	3	106±	4	114±	3	120±	4	131±	5
12500 ppm	101±	3	102±	3	102±	3	105±	5	113±	4	119±	4	128±	4
25000 ppm	101±	3	100±	4	102±	3	106±	2	113±	2	119±	2	128±	2
50000 ppm	101±	3	98±	3*	99±	3**	101±	3**	109±	2**	115±	2**	122±	2**
100000 ppm	101±	3	91 土	2**	85±	3**	78±	4**	68±	5**	63±	0 ?	-	
Significant differer	nce; *:P≦0	.05	** : P ≦ 0.0	)1			Test of Du	innett						

<sup>?:</sup> Significant test is not applied, because No. of data in this group is less than 3.

(HAN260)

### APPENDIX A 2-3

BODY WEIGHT CHANGES (TWO-WEEK STUDY:SUMMARY)

MOSUE: MALE

STUDY NO. : 0188

ANIMAL : MOUSE BDF1

UNIT : g
REPORT TYPE : A1 2

SEX : MALE

BODY WEIGHT CHANGES ALL ANIMALS

(SUMMARY)

PAGE: 1

oup Name	Administration week-day							
	0-0	1-1	1-2	1-4	1-7	2-3	2-7	
Control	24.2± 0.8	23.8± 0.8	24.0± 0.7	24.5± 0.7	25.0± 0.9	25.6± 0.8	26.2± 0.5	
6250 ppm	24.2± 0.8	23.7± 1.0	24.2± 0.8	24.8± 1.0	25.2± 0.8	25.7± 1.0	26.6± 1.1	
12500 ppm	24.2± 0.7	23.6± 0.7	24.0± 0.5	24.2± 0.7	24.7± 0.6	25.5± 0.7	26.2± 0.6	
25000 ppm	24,2± 0.8	23.6± 0.8	23.9± 0.9	24.4± 0.9	24.8± 0.8	25.4± 1.0	26.3± 1.1	
50000 ppm	24.2± 0.7	22.9± 0.9	22.1± 1.3**	24.2± 0.6	24.6± 0.7	25.3± 0.6	26.2± 0.7	
100000 ppm	24.2± 0.7	21.4± 0.7**	20.6± 0.6**	20.0± 0.8**	19.5± 1.3**	19.9± 2.5**	18.8± 2.8**	
			10.1					
Significant differen	nce; *: P ≤ 0.05	**: P ≤ 0.01		Test of Dunnett				

(HAN260)

#### APPENDIX A 2-4

BODY WEIGHT CHANGES (TWO-WEEK STUDY: SUMMARY)

MOSUE: FEMALE

STUDY NO. : 0188

ANIMAL : MOUSE BDF1

UNIT : g

REPORT TYPE : A1 2

SEX : FEMALE

BODY WEIGHT CHANGES

ALL ANIMALS

(SUMMARY)

Group Name Administration week-day\_ 0-0 1-1 1-2 1-4 1-7 2-7 2-3 Control 19.3± 0.6 18.8± 0.6 19.1± 0.7 19.3± 0.8 19.6± 0.7  $20.2 \pm 0.7$ 20.7± 0.6 6250 ppm 19.3± 0.7 17.9± 1.2 19.0± 0.6 19.7± 0.9 19.6± 0.8  $20.4 \pm 0.7$  $21.0 \pm 0.6$ 12500 ppm 19.3± 0.6 17.2± 0.7\*\* 18.7± 1.1  $19.2 \pm 0.8$ 19.5± 1.0  $20.0 \pm 0.9$  $20.7 \pm 1.0$ 25000 ppm  $19.3 \pm 0.7$ 17.2± 0.9\*\*  $18.1 \pm 1.3$ 19.1± 0.8 19.1± 0.5 19.9± 1.1 20.7± 0.9 50000 ppm  $19.3 \pm 0.6$ 17.6± 0.9\*\*  $18.6 \pm 0.5$  $19.1 \pm 0.7$ 19.4生 0.7  $20.2 \pm 0.7$  $20.6 \pm 1.0$ 100000 ppm 19.3± 0.7 16.8± 0.7\*\* 16.0± 0.6\*\* 15.8± 0.8\*\* 15.6± 1.8\*\* 16.5± 2.0\*\* 14.9± 2.3\*\* Significant difference;  $*: P \leq 0.05$ \*\*:  $P \leq 0.01$ Test of Dunnett

(HAN260)

BAIS 2

PAGE: 2

### APPENDIX A 3-1

WATER CONSUMPTION CHANGES (TWO-WEEK STUDY: SUMMARY)

RAT: MALE

STUDY NO.: 0187

ANIMAL : RAT F344

UNIT : g
REPORT TYPE : A1 2

SEX : MALE

WATER CONSUMPTION CHANGES (SUMMARY)

ALL ANIMALS

PAGE: 1

iroup Name	Administratio	n week-day(effective)_		
	1-3(3)	1-7(4)	2-3(3)	2-7(4)
4 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -				
Control	18.4± 1.2	18.7± 1.3	19.2± 2.2	19.6± 2.5
6250 ppm	10.14 1.1	17.04 5.0	20 24 2 1	90 94 1 4
0200 ppiii	19.1± 1.1	17.8± 5.6	20.3± 3.1	20.3± 1.4
12500 ppm	20.5± 0.9	21.0± 2.3	20.5± 1.4	20.5± 1.4
05000		01.11.00		
25000 ppm	21.6± 2.1**	21.4± 2.6	21.2± 1.9	21.0± 1.9
50000 ppm	20.5± 2.6	20.6± 1.5	22.6± 4.9	24.1± 5.9
100000 ppm	14.2± 2.4	$8.0 \pm 4.6$	-	-
<del>*************************************</del>				
Significant difference;	*: $P \le 0.05$	**: $P \leq 0.01$		Test of Dunnett
(UANGCO)				

(HAN260)

#### APPENDIX A 3-2

WATER CONSUMPTION CHANGES (TWO-WEEK STUDY: SUMMARY)

RAT: FEMALE

STUDY NO. : 0187

WATER CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 2
SEX : FEMALE

PAGE: 2

roup Name	Administration	week-day(effective)_			
	1-3(3)	1-7(4)	2-3(3)	2-7(4)	
Control	15.6± 1.0	16.3± 0.7	16.3± 1.3	16.4± 2.2	
6250 ppm	16.6± 1.8	17.7± 2.3	18.1± 2.2	18.3± 2.8	
12500 ppm	18.0± 1.5	17.2± 2.9	18.2± 1.8	18.4± 1.4*	
25000 ppm	17.9± 2.1	18.8± 1.6*	17.7± 1.6	18.0± 1.7	
50000 ppm	17.9± 7.1	19.9± 6.0	18.5± 3.3	19.7± 4.3*	
100000 ppm	8.6± 2.0*	10.5± 2.8	13.5± 3.1	11.3± 0.0 ?	
Significant difference;	*: $P \le 0.05$	** : P ≤ 0.01		Test of Dunnett	

(HAN260)

### APPENDIX A 3-3

WATER CONSUMPTION CHANGES (TWO-WEEK STUDY: SUMMARY)

MOUSE: MALE

STUDY NO. : 0188

ANIMAL : MOUSE BDF1
UNIT : g

REPORT TYPE : A1 2

SEX : MALE

WATER CONSUNPTION CHANGES (SUMMARY) ALL ANIMALS

oup Name	Administration	week-day(effective)			
	1-3(3)	1-7(4)	2-3(3)	2-7(4)	
Control	4.5± 0.3	4.6± 0.4	4.7± 0.4	4.2± 0.5	
6250 ppm	4.9± 1.0	4.8± 1.0	4.8± 0.9	4.5± 1.1	
12500 ppm	5.1± 0.7	5.1± 0.9	5.2± 0.7	4.7± 0.8	
25000 ppm	5.8± 1.5*	5.7± 1.1	5.4± 1.0	4.8± 0.9	
50000 ppm	5.0± 0.7	5.6± 0.6	5.2± 0.3	4.8± 0.5	
100000 ppm	4.0± 1.3	7.9± 1.8**	8.6± 2.8**	6.3± 2.5	
Significant difference;	*: P ≤ 0.05	**: P ≤ 0.01		Test of Dunnett	

(HAN260)

BAIS 2

PAGE: 1

### APPENDIX 3-4

WATER CONSUMPTION CHANGES(TWO-WEEK STUDY: SUMMARY)

MOUSE: FEMALE

STUDY NO. : 0188

ANIMAL : MOUSE BDF1
UNIT : g
REPORT TYPE : A1 2
SEX : FEMALE

WATER CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

PAGE: 2

roup Name	Administration (	week-day(effective)				
	1-3(3)	1-7(4)	2-3(3)	2-7(4)		
						· · · · · ·
Control	4.2± 0.4	4.8± 0.7	4.9± 0.7	5.1± 1.1		
0000						
6250 ppm	4.5± 0.6	5.0± 0.4	5.0± 0.9	4.7± 0.4		
12500 ppm	4.4± 0.4	4.9± 0.5	5.2生 0.7	4.9± 0.4		
25000 ppm	4.6± 0.7	5.5± 0.7	$5.6 \pm 0.4$	5.1± 0.9		
50000 ppm	5.8± 0.6**	6.0± 0.7**	6.2± 0.6**	5.8± 0.8		
		•••	0.52	0.02 0.0		
100000 ppm	4.5± 0.9	7.9± 1.1**	9.9± 2.8**	5.2± 3.2		
Significant difference	ce; *:P≦0.05 *	$*: P \leq 0.01$		Test of Dunnett		

(HAN260)

### APPENDIX A 4-1

FOOD CONSUMPTION CHANGES (TWO-WEEK STUDY: SUMMARY)

RAT: MALE

STUDY NO. : 0187

ANIMAL : RAT F344 UNIT : g

REPORT TYPE : A1 2

SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)

ALL ANIMALS

Group Name	Administration 1-7(7)	week-day(effective) 2-7(7)		
Control	14.3± 0.5	14.9± 1.1		
6250 ppm	13.8± 1.4	15.3± 0.9		
12500 ppm	14.3± 0.5	15.0± 0.7		
25000 ppm	13.7± 1.2	14.5± 0.9		
50000 ppm	12.1± 0.5**	12.4± 1.5**		
100000 ppm	3.8± 0.7**	-		
Significant differe	ence; *: P ≤ 0.05	**: P ≤ 0.01	Test of Dunnett	
(HAN260)				BAIS

PAGE: 1

### APPENDIX A 4-2

FOOD CONSUMPTION CHANGES (TWO-WEEK STUDY: SUMMARY)

RAT: FEMALE

STUDY NO.: 0187 ANIMAL : RAT F344

UNIT : g
REPORT TYPE : A1 2
SEX : FEMALE

(HAN260)

FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

PAGE: 2

BAIS 2

	1-7(7)  11.6± 0.4  11.4± 0.7	2-7(7)  12.0± 0.6  11.9± 0.8			
6250 ppm	11.4± 0.7	11.9± 0.8			
6250 ppm	11.4± 0.7	11.9± 0.8			
19500	11 1 2 4 1	11 01 04			
12500 ppm	11.1± 1.1	11.9± 0.4			
25000 ppm	11.2± 0.4	11.6± 0.6			
50000 ppm	10.2± 0.4**	10.7± 0.3**			
100000 ppm	3.8± 0.4**	3.0± 0.0 ?			
	······································				
Significant difference; *	: P ≤ 0.05	** : P ≤ 0.01	Test of Dunnett		

# APPENDIX A 4-3

FOOD CONSUMPTION CHANGES (TWO-WEEK STUDY: SUMMARY)

MOSUE: MALE

ANIMAL : MOUSE BDF1

UNIT : g REPORT TYPE : A1 2

FOOD CONSUMPTION CHANGES (SUMMARY)

ALL ANIMALS

TOUR Name	Administration	week-day(effective)		 · · · · · · · · · · · · · · · · · · ·
Cap Trains	1-7(7)	2-7(7)		
Contral	4.1± 0.3	4.1± 0.1		
6250 ppm	4.1± 0.3	4.0± 0.3		
12500 ppm	3.9± 0.2	4.1± 0.2		
25000 ppm	3.9± 0.2	4.1± 0.3		
	3.8± 0.2**	4.1± 0.3		
mqq 00000	2.4± 0.2**	3.2± 0.7*		
Significant differen	nce; *: P ≤ 0.05	**: P ≤ 0.01	Test of Dunnett	
IAN260)				 BAIS 2

# APPENDIX A 4-4

FOOD CONSUMPTION CHANGES (TWO-WEEK STUDY: SUMMARY)

MOSUE: FEMALE

ANIMAL : MOUSE BDF1

UNIT : g
REPORT TYPE : A1 2

SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

PAGE: 2

	week-day(effective)		
1-7(7)	2-7(7)		
3.3± 0.3	3.6± 0.2		
2 2 1	2.64.00		
3.3± 0.2	3.6± 0.2		
3.3± 0.2	$3.7 \pm 0.2$		
2 1 4 0 0	2.64 0.9		
3.1± U.Z	3.6± 0.2		
3.2± 0.2	3.6± 0.3		
2 2+ 1 2**	27+ 06**		
2.21 0.0	D.7 - V.0		
; *:P≦0.05 *	* : P ≤ 0.01	Test of Dunnett	
	3.3± 0.3 3.3± 0.2 3.3± 0.2 3.1± 0.2 3.2± 0.2 2.2± 0.3**	$3.3\pm 0.3$ $3.6\pm 0.2$ $3.6\pm 0.2$ $3.3\pm 0.2$ $3.7\pm 0.2$ $3.1\pm 0.2$ $3.6\pm 0.2$ $3.2\pm 0.2$ $3.6\pm 0.3$ $2.2\pm 0.3**$ $2.7\pm 0.6**$	$3.3\pm 0.3$ $3.6\pm 0.2$ $3.6\pm 0.2$ $3.3\pm 0.2$ $3.7\pm 0.2$ $3.1\pm 0.2$ $3.6\pm 0.2$ $3.6\pm 0.2$ $3.2\pm 0.2$ $3.6\pm 0.3$ $2.2\pm 0.3**$ $2.7\pm 0.6**$

(HAN260)

BAIS 2

# APPENDIX A 5-1

CHEMICAL INTAKE CHANGES (TWO-WEEK STUDY: SUMMARY)

RAT: MALE

ANIMAL : RAT F344

UNIT : g/kg/day
REPORT TYPE : A1 2
SEX : MALE

CHEMICAL INTAKE CHENGES (SUMMARY)
ALL ANIMALS

SEX : MALE						PAGE: 1
Group Name	Administ 1	tration	(weeks)2			 
Control	0.000± (	0.000	0.000± 0.000			
6250 ppm	0.759± (	0.221	0.718± 0.046			
12500 ppm	1.785± (	0.170	1.476± 0.059			
25000 ppm	3.702± (	0.299	3.089± 0.206			
50000 ppm	7.398± (	0.395	7.935± 2.777			
100000 ppm	13.489± 7	7.411	-			
						1

(HAN300)

BAIS 2

# APPENDIX A 5-2

CHEMICAL INTAKE CHANGES (TWO-WEEK STUDY: SUMMARY)

RAT: FEMALE

ANIMAL : RAT F344
UNIT : g/kg/day
REPORT TYPE : A1 2

SEX : FEMALE

CHEMICAL INTAKE CHENGES (SUMMARY)

ALL ANIMALS

Group Name	Administration	(weeks)		
	1	2		
Control	0.000± 0.000	0.000± 0.000		
6250 ppm	0.972± 0.118	0.878± 0.129		
12500 ppm	1.900± 0.278	1.798± 0.145		
25000 ppm	4.180± 0.407	3.505± 0.360		
mqq 00003	9.092± 2.615	8.126± 1.720		
100000 ppm	15.524± 3.987	-		

(HAN300)

BAIS 2

# APPENDIX A 5-3

CHEMICAL INTAKE CHANGES (TWO-WEEK STUDY: SUMMARY)

MOUSE: MALE

ANIMAL : MOUSE BDF1

UNIT : g/kg/day REPORT TYPE : A1 2

CHEMICAL INTAKE CHENGES (SUMMARY)
ALL ANIMALS

roup Name	Administration				
	1	2			
Control	0.000± 0.000	0.000± 0.000			
6250 ppm	1.199± 0.234	1.065± 0.245			
12500 ppm	2.565± 0.421	2.214± 0.388			
25000 ppm	5.794± 1.023	4.548± 0.785			
50000 ppm	11.337± 1.173	9.063± 0.856			
100000 ppm	40.802± 10.672	34.813± 16.210			

(HAN300)

BAIS 2

# APPENDIX A 5-4

CHEMICAL INTAKE CHANGES (TWO-WEEK STUDY: SUMMARY)

MOUSE: FEMALE

ANIMAL : MOUSE BDF1
UNIT : g/kg/day
REPORT TYPE : A1 2
SEX : FEMALE

CHEMICAL INTAKE CHENGES (SUMMARY)

ALL ANIMALS

Group Name	Administration	(weeks)	 	
	1	2	 	
Control	0.000± 0.000	0.000± 0.000		
6250 ppm	1.582± 0.111	1.399± 0.112		
12500 ppm	3.133± 0.293	2.961± 0.267		
25000 ppm	7.240± 0.970	6.187± 1.210		
50000 ppm	15.543± 1.581	14.128± 1.719		
100000 ppm	52.131± 11.500	35.906± 23.680		

(HAN300)

BAIS 2

### APPENDIX A 6-1

GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)

RAT: MALE: DEAD AND MORIBUND ANIMALS

ANIMAL : RAT F344

REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY) DEAD AND MORIBUND ANIMALS (0- 2W)

0rgan	Findings	Group Name NO. of Animals	Control 0 (%)	6250 ppm 0 (%)	12500 ppm 0 (%)	25000 ppm 0 (%)
subcutis	dry		- ( -)	- ( -)	- ( -)	- ( -)
thymus	atrophic		- ( -)	- ( -)	- ( -)	- ( -)
	red		- ( -)	- ( -)	- ( -)	- ( -)
	red zone		- ( -)	- ( -)	- ( -)	- ( -)
(HPT080)						BAI

STUDY NO. : 0187 ANIMAL

: RAT F344

REPORT TYPE : A1 : MALE SEX

GROSS FINDINGS (SUMMARY)

DEAD AND MORIBUND ANIMALS (0- 2W)

Group Name 50000 ppm 100000 ppm Findings\_ 0 (%) 10 (%) Organ\_\_ NO. of Animals - ( -) subcutis dгу 10 (100) thymus - ( -) 10 (100) atrophic

- ( -)

- ( -)

4 (40)

4 (40)

(HPT080)

red

red zone

BAIS 2

### APPENDIX A 6-2

GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)

RAT: FEMALE: DEAD AND MORIBUND ANIMALS

ANIMAL : RAT F344

REPORT TYPE : A1 : FEMALE SEX

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 2W)

PAGE: 3

Organ	Findings	Group Name NO. of Animals	Control 0 (%)	6250 ppm 0 (%)	12500 ppm 0 (%)	25000 ppm 0 (%)
subcutis	dry		- ( -)	- ( -)	- ( -)	- ( -)
thymus	atrophic		- ( -)	- ( -)	- ( -)	- ( -)
	red		- "( -)	- ( -)	- ( -)	- ( -)
gl stomach	ulcer		- ( -)	- ( -)	- ( -)	- ( -)
adrenal	red		- ( <b>-</b> )	- ( -)	- ( -)	- ( -)

BAIS 2

ANIMAL : RAT F344

REPORT TYPE : A1 : FEMALE SEX

GROSS FINDINGS (SUMMARY)

DEAD AND MORIBUND ANIMALS (0- 2W)

50000 ppm 0 (%) Group Name 100000 ppm Organ\_\_ Findings\_ 10 (%) NO. of Animals - ( -) subcutis dгу 10 (100) thymus - ( -) atrophic 9 (90) red - ( -) 4 (40) gl stomach ulcer - ( -) 1 (10) adrenal red - ( -) 1 (10) (HPT080)

BAIS 2

### APPENDIX A 6-3

GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)

RAT: FEMALE: SACRIFICED ANIMALS

STUDY NO. : 0187 ANIMAL : RAT F344
REPORT TYPE : A1

: FEMALE

SEX

GROSS FINDINGS (SUMMARY) SACRIFICED ANIMALS ( 2W)

0rgan	Findings	Group Name NO. of Animals	Control 10 (%)	6250 ppm 10 (%)	12500 ppm 10 (%)	25000 ppm 10 (%)
liver	herniation		1 (10)	0 ( 0)	0 ( 0)	0 ( 0)
(HPT080)						BAIS 2

STUDY NO. : 0187 ANIMAL : RAT F344

REPORT TYPE : A1 SEX : FEMALE

GROSS FINDINGS (SUMMARY)

SACRIFICED ANIMALS ( 2W)

0rgan	Findings	Group Name NO. of Animals	50000 ppm 10 (%)	100000 ppm 0 (%)	
liver	herniation		0 ( 0)	- ( -)	
(HPT080)					BAIS 2

### APPENDIX A 6-4

GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)

MOUSE: FEMALE: DEAD AND MORIBUND ANIMALS

ANIMAL : MOUSE BDF1

REPORT TYPE : A1 : FEMALE SEX

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 2W)

Group Name Contral 25000 ppm 0 (%) 6250 ppm 12500 ppm Findings\_ 0 (%) 0 (%) 0 (%) Organ\_\_\_\_ NO. of Animals - ( -) subcutis - ( -) - ( -) - ( -) dгу (HPT080) BAIS 2

STUDY NO. : 0188 ANIMAL

: MOUSE BDF1

REPORT TYPE : A1 : FEMALE SEX

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 2W)

100000 ppm Group Name 50000 ppm Findings\_ 0 (%) 1 (%) Organ\_\_\_ NO. of Animals subcutis dry - ( -) 1 (100) (HPT080) BAIS 2

### APPENDIX A 6-5

GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)

MOUSE: MALE: SACRIFCED ANIMALS

ANIMAL : MOUSE BDF1

REPORT TYPE : A1 SEX : MALE

GROSS FINDINGS (SUMMARY) SACRIFICED ANIMALS ( 2W)

0rgan	Findings	Group Name NO. of Animals 10	Control (%)	6250 ppm 10 (%)	12500 ppm 10 (%)	25000 ppm 10 (%)
spleen	black zone	1	( 10)	3 (30)	1 (10)	1 (10)
kidney	hydronephrosis	0	( 0)	0 ( 0)	0 ( 0)	1 (10)

BAIS 2

ANIMAL : MOUSE BDF1

REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY) SACRIFICED ANIMALS ( 2W)

rgan	Findings	Group Name NO. of Animals	50000 ppm 10 (%)	100000 ppm 10 (%)	
pleen	black zone		2 (20)	0 ( 0)	
dney	hydronephrasis		0 ( 0)	1 (10)	

### APPENDIX A 6-6

GROSS FINDINGS (TWO-WEEK STUDY : SUMMARY)

MOUSE: FEMALE: SACRIFCED ANIMALS

ANIMAL : MOUSE BDF1

REPORT TYPE : A1 : FEMALE GROSS FINDINGS (SUMMARY) SACRIFICED ANIMALS ( 2W)

Organ	Findings	Group Name Control NO. of Animals 10 (%)	6250 ppm 10 (%)	12500 ppm 10 (%)	25000 ppm 10 (%)
subcutis	dry	0 ( 0)	0 ( 0)	0 ( 0)	0 ( 0)
hymus	atrophic	0 ( 0)	0 ( 0)	0 ( 0)	0 ( 0)
spleen	black zone	1 (10)	0 ( 0)	0 ( 0)	0 ( 0)

ANIMAL : MOUSE BDF1

REPORT TYPE : A1

GROSS FINDINGS (SUMMARY) SACRIFICED ANIMALS ( 2W)

SEX : FEMALE

Organ	Findings	Group Name NO. of Animals	50000 ppm 10 (%)	100000 ppm 9 (%)	
subcutis	dry		0 ( 0)	1 ( 11)	
thymus	atrophic		0 ( 0)	1 (11)	
spleen	black zone		2 (20)	1 (11)	
(HPT080)					BAIS 2

#### APPENDIX A 7-1

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS

(TWO-WEEK STUDY: SUMMARY)

RAT: MALE: DEAD AND MORIBUND ANIMALS

STUDY NO. : 0187 ANIMAL

: RAT F344

REPORT TYPE : A1 SEX : MALE HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

PAGE: 1

DEAD AND MORIBUND ANIMALS (0- 2W)

Group Name 6250 ppm Control 12500 ppm 25000 ppm No. of Animals 0 0 0 ⟨2⟩ ⟨3⟩ <1> (4) 〈2〉 〈3〉 <4> <2> <3> ⟨2⟩ ⟨3⟩ ⟨4⟩ 0rgan\_ Findings (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) [Hematopoietic system] bone marrow congestion ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) thymus atrophy ( -) ( -) ( -) ( -) ( -) ( -) ( '-) ( -) ( -) hemorrhage ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) spleen atrophy ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) [Digestive system] tongue inflammation ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) stomach vacuolic change:parietal cell ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) [Urinary system] mineralization:cortico-medullary junction kidney ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) [Endocrine system] adrena L hemorrhage ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) ( -) <1>:Slight <3>:Marked <2>:Moderate <4>:Severe (HPT150) BAIS2

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY) DEAD AND MORIBUND ANIMALS (0- 2W)

ANIMAL : RAT F344
REPORT TYPE : A1

: MALE SEX

PAGE: 2

		Group Name 50000 ppm No. of Animals 0 <1> <2> <3> <4>	100000 ppm 3 <1> <2> <3> <4>	
Organ	Findings	(%) (%) (%) (%)	(%) (%) (%) (%)	
[Hematopoieti	c system]			
bone marrow	congestion	( -) ( -) ( -)	0 3 0 0 ( 0) (100) ( 0) ( 0)	
thymus	atrophy	( -) ( -) ( -) ( -)	1 2 0 0 (33) (67) (0) (0)	
	hemorrhage	( -) ( -) ( -) ( -)	0 0 3 0 ( 0) (100) ( 0)	
spleen	atrophy	( -) ( -) ( -) ( -)	2 0 0 0 (67) (0) (0) (0)	
[Digestive sy	rstem]			
tongue	inflammation	( -) ( -) ( -) ( -)	1 0 0 0 (33) (0) (0) (0)	
stomach	vacuolic change:parietal cell	( -) ( -) ( -) ( -)	2 0 0 0 0 (67) (0) (0) (0)	
[Urinary syst	rem]			
kidney	mineralization:cortico-medullary junction	( -) ( -) ( -) ( -)	1 0 0 0 (33) (0) (0) (0)	
[Endocrine sy	rstem]			
adrenal	hemorrhage	( -) ( -) ( -) ( -)	0 2 1 0 (0) (67) (33) (0)	
<1>	:Slight <2>:Moderate <3>:Marked	<4>:Severe		
(HPT150)				Dito

(HPT150)

#### APPENDIX A 7-2

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS

(TWO-WEEK STUDY: SUMMARY)

RAT: FEMALE: DEAD AND MORIBUND ANIMALS

STUDY NO. : 0187 ANIMAL : RAT F344 REPORT TYPE : AI SEX : FEMALE HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 2W)

Organ	Findings	Group Name Control No. of Animals 0 <pre></pre>	6250 ppm 0 <1> <2> <3> <4> (%) (%) (%) (%)	12500 ppm 0 <1> <2> <3> <4> (%) (%) (%) (%)	25000 ppm 0 <1> <2> <3> <4> (%) (%) (%) (%)
[Hematopoieti	c system]				
one marrow	congestion	( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)
thymus	atrophy	( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	
	hemorrhage	( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)
spleen	atrophy	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -)
Digestive sy	rstem]				
tomach	vacuolic change:parietal cell	( -) ( -) ( -) ( -)	( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -)
Urinary syst	rem]				
cidney	mineralization:cortico-medullary junction	( -) ( -) ( -) ( -)		( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)
(Endocrine sy	rstem]				
adrenal	hemorrhage	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)
<1>	:Slight <2>:Moderate <3>:Marked	<4>:Severe			
(HPT150)					<u></u>

STUDY NO. : 0187 ANIMAL : RAT H

: RAT F344

REPORT TYPE : A1 SEX : FEMALE HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 2W)

HORIDURD ANIMALS (U- ZW)

Group Name 50000 ppm 100000 ppm No. of Animals 0 4 <1> ⟨2⟩ ⟨3⟩ ⟨4⟩ 〈2〉 〈3〉 〈4〉 Findings\_ (%) (%) (%) (%) (%) (%) (%) (%) [Hematopoietic system] bone marrow congestion ( -) ( -) ( -) ( -) (0)(100)(0)(0) thymus atrophy ( -) ( -) ( -) ( -) (0)(100)(0)(0) hemorrhage 0 0 2 0 ( -) ( -) ( -) ( -) (0)(0)(50)(0) spleen atrophy 4 0 ( -) ( -) ( -) ( -) (100) ( 0) ( 0) ( 0) [Digestive system] stomach vacuolic change:parietal cell ( -) ( -) ( -) ( -) (0)(25)(0)(0) [Urinary system] kidney mineralization:cortico-medullary junction ( -) ( -) ( -) ( -) (100) ( 0) ( 0) ( 0) [Endocrine system] adrenal hemorrhage 1 2 1 0 ( -) ( -) ( -) ( -) (25) (50) (25) (0) <1>:Slight <2>:Moderate <3>:Marked <4>:Severe (HPT150)

BAIS2

# APPENDIX A 7-3

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS

(TWO-WEEK STUDY: SUMMARY)

RAT: MALE: SACRIFICED ANIMALS

STUDY NO. : 0187 ANIMAL : RAT F344

REPORT TYPE : A1 : MALE HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 2W)

	Group Name No. of Animals	Control 2	6250 ppm 2	12500 ppm 2	25000 ppm 2
organFindings	(%)	<2> <3> <4> (%) (%) (%)	<1> <2> <3> <4> (%) (%) (%) (%) (%)	<1> <2> <3> <4> (%) (%) (%) (%) (%)	<1> <2> <3> <4> (%) (%) (%) (%)
Hematopoietic system]					
thymus hemorrhage	1 ( 50)	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)
[Digestive system]					
stomach vacuolic change:parietal cell	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) (0)
<1>:Slight <2>:Moderate <3>:Ma	ked <4>:Severe				
(HPT150)					

BAIS2

STUDY NO. : 0187 ANIMAL

SEX

: RAT F344 REPORT TYPE : A1 : MALE

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

PAGE: 2

SACRIFICED ANIMALS ( 2W)

Group Name 50000 ppm 100000 ppm No. of Animals 2 0 <2> <3> <4> <2> <3> <4> (1) (%) (%) (%) (%) (%) (%) Findings\_ (%) (%) [Hematopoietic system] thymus hemorrhage 0 0 0 (0)(0)(0)(0) ( -) ( -) ( -) ( -) [Digestive system] stomach vacuolic change:parietal cell 1 0 0 0 ( -) ( -) ( -) ( -) (50) (0) (0) (0) <1>:Slight <2>:Moderate <3>:Marked <4>:Severe (HPT150) BAIS2

# APPENDIX A 7-4

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS

(TWO-WEEK STUDY: SUMMARY)

RAT: FEMALE: SACRIFICED ANIMALS

STUDY NO. : 0187 ANIMAL

: RAT F344

REPORT TYPE : A1 SEX : FEMALE HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 2W)

Group Name 6250 ppm 12500 ppm 25000 ppm Control 2 No. of Animals 2 2 2 <1> 〈2〉 〈3〉 <2> <3> <4> <1> 〈2〉 〈3〉 <1> 〈2〉 〈3〉 〈4〉 <4> (%) 0rgan Findings\_ (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) [Hematopoietic system] thymus congestion 0 0 0 0 0 (0)(0)(0)(0) (50) (0) (0) (0) ( 0) ( 0) ( 0) ( 0) (0)(0)(0)(0) [Digestive system] stomach vacuolic change:parietal cell 0 0 0 (0)(0)(0)(0) (0)(0)(0)(0) (0)(0)(0)(0) (0)(0)(0)(0) Liver herniation 0 0 0 0 0 (50) (0) (0) (0) (0)(0)(0)(0) (0)(0)(0)(0) (0)(0)(0)(0) [Urinary system] kidney mineralization:cortico-medullary junction 0 0 2 0 0 0 2 0 0 0 2 0 0 0 (100) ( 0) ( 0) ( 0) (100) ( 0) ( 0) ( 0) (100) ( 0) ( 0) ( 0) (100) ( 0) ( 0) ( 0) <1>:Slight <2>:Moderate <3>:Marked <4>:Severe (HPT150) BAIS2

STUDY NO. : 0187

ANIMAL : RAT F344

REPORT TYPE : A1 SEX

: FEMALE

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 2W)

Organ	Findings	Group Name 50000 ppm No. of Animals 2	100000 ppm 0 <1> <2> <3> <4> (%) (%) (%)	
[Hematopoie	· rtic system]			
thymus	congestion	0 0 0 0 0 (0) (0)	( -) ( -)	
[Digestive :	system]			
stomach	vacuolic change:parietal cell	1 0 0 0 (50) ( 0) ( 0) ( 0)	( -) ( -) ( -) ( -)	
liver	herniation	0 0 0 0 0 (0) (0)	( -) ( -) ( -) ( -)	
[Urinary sy:	stem]			
kidney	mineralization:cortico-medullary junction	2 0 0 0 0 (100) ( 0) ( 0) ( 0)	( -) ( -) ( -) ( -)	
<	1>:Slight <2>:Moderate <3>:Marked	<4>:Seuere		
(HPT150)				 BAIS

# APPENDIX A 7-5

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS

(TWO-WEEK STUDY: SUMMARY)

MOUSE: FEMALE: DEAD AND MORIBUNDANIMALS

STUDY NO. : 0188

ANIMAL : MOUSE BDF1

REPORT TYPE : A1 : FEMALE SEX

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 2W)

	Group Name Control No. of Animals 0	6250 ppm 0	12500 ppm 0	25000 ppm 0
gan Findings	(1) (2) (3) (4) (%) (%) (%) (%)	<1> <2> <3> <4>         (%)       (%)       (%)       (%)	(1)       (2)       (3)       (4)         (%)       (%)       (%)       (%)	<1> <2> <3> <4> (%) (%) (%) (%)
dematopoietic system]				
hymus atrophy	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)		( -) ( -) ( -) ( -)
pleen atrophy	( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)
Digestive system]				
stomach vacuolic change:parietal cell	( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)
<1>:Slight <2>:Moderate <3>:Man	rked <4>:Severe			
(HPT150)				

STUDY NO. : 0188 ANIMAL

: MOUSE BDF1

REPORT TYPE : A1 SEX : FEMALE HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

DEAD AND MORIBUND ANIMALS (0- 2W)

Group Name 50000 ppm 100000 ppm No. of Animals 0 <1> ⟨2⟩ ⟨3⟩ ⟨4⟩ (1) (2) (3) (4) Findings\_ (%) (%) (%) (%) (%) (%) (%) (%) 0rgan\_\_ [Hematopoietic system] thymus atrophy ( -) ( -) ( -) ( -) (0)(0)(100)(0) spleen atrophy ( -) ( -) ( --) ( --) (100) ( 0) ( 0) ( 0) [Digestive system] ( -) ( -) ( -) ( -) stomach vacuolic change:parietal cell 0 1 0 0 ( 0) (100) ( 0) ( 0) <1>:Slight <2>:Moderate <3>:Marked <4>:Severe (HPT150) BAIS2

# APPENDIX A 7-6

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS

(TWO-WEEK STUDY: SUMMARY)

MOUSE: MALE: SACRIFICED ANIMALS

STUDY NO. : 0188

ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 2W)

		Group Name Control No. of Animals 2	6250 ppm 2	12500 ppm 2	25000 ppm 2
rgan	Findings	(1) (2) (3) (4) (%) (%) (%) (%)	<1> <2> <3> <4> (%) (%) (%) (%)	<1> <2> <3> <4> (%) (%) (%) (%)	<1> <2> <3> <4> <4> <6 <6 <6 <6 <6 <6 <6 <6 <6 <6 <6 <6 <6
lematopo	ietic system]				
eleen	deposit of melanin	0 0 0 0 0 (0) (0)	1 0 0 0 (50) (0) (0) (0)	1 0 0 0 (50) ( 0) ( 0). ( 0)	0 0 0 0 0 (0) (0) (0)
igestiv	e system]				
omach	vacuolic change:parietal cell	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)
ver	granulation	1 0 0 0 (50)(0)(0)(0)	1 0 0 0 (50) (0) (0) (0)	1 0 0 0 (50) (0) (0) (0)	1 0 0 0 (50) (0) (0) (0)

STUDY NO. : 0188

ANIMAL : MOUSE BDF1

REPORT TYPE : A1 SEX : MALE HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 2W)

Group Name 50000 ppm 100000 ppm No. of Animals 2 2 <1> <2> <3> <4> <1> <2> <3> <4> Organ\_ Findings\_ (%) (%) (%) (%) (%) (%) (%) (%) [Hematopoietic system] spleen deposit of melanin 0 0 0 0 (0)(0)(0)(0) (0)(0)(0)(0) [Digestive system] stomach vacuolic change:parietal cell 0 0 0 0 1 0 0 0 ( 0) ( 0) ( 0) ( 0) (50) (0) (0) (0) liver granulation 1 0 0 0 0 0 0 0 (50) (0) (0) (0) (0)(0)(0)(0) <1>:Slight <2>:Moderate <3>:Marked <4>:Severe (HPT150) BAIS2

# APPENDIX A 7-7

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS

(TWO-WEEK STUDY: SUMMARY)

MOUSE: FEMALE: SACRIFICED ANIMALS

STUDY NO. : 0188 ANIMAL

: MOUSE BDF1

REPORT TYPE : A1 SEX : FEMALE HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 2W)

Group Name Control 6250 ppm 12500 ppm 25000 ppm No. of Animals 2 2 <1> <2> <3> <4> <1> ⟨2⟩ ⟨3⟩ ⟨4⟩ ⟨2⟩ ⟨3⟩ ⟨4⟩ <1> 〈2〉 〈3〉 〈4〉 <1> Findings\_ (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) [Digestive system] stomach ulcer:forestomach 1 0 0 0 0 0 0 0 0 0 (50) (0) (0) (0) (0)(0)(0)(0) (0)(0)(.0)(0) (0)(0)(0)(0) liver granulation 1 0 0 0 2 0 0 2 0 1 0 0 0 (50) (0) (0) (0) (100) ( 0) ( 0) ( 0) (100) ( 0) ( 0) ( 0) (50) (0) (0) (0) <1>:Slight <2>:Moderate <3>: Marked <4>:Severe (HPT150) BAIS2

STUDY NO. : 0188

ANIMAL

SEX

: FEMALE

: MOUSE BDF1 REPORT TYPE : A1

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 2W)

PAGE: 4 Group Name 50000 ppm 100000 ppm No. of Animals 2 〈2〉 〈3〉 〈4〉 <1> <1> <2> <3> <4> Organ\_\_\_\_ (%) (%) (%) (%) Findings\_ (%) (%) (%) (%) [Digestive system] stomach ulcer:forestomach 0 0 0 0 0 0 0 0 (0)(0)(0)(0) (0)(0)(0)(0) liver granulation 2 0 0 0 0 0 0 0 (100) ( 0) ( 0) ( 0) ( 0) ( 0) ( 0) ( 0) <1>:Slight <2>: Moderate <3>:Marked <4>:Severe (HPT150) BAIS2

# APPENDIX A 8-1 IDENTITY AND PURITY OF TATCD PERFORMED AT THE JAPAN BIOASSAY LABORATORY (TWO-WEEK STUDIES)

IDENTITY OF 1,3,5,7-TETRAAZATRICYCLO[3.3.1.13,7]DECANE PERFORMED AT THE JAPAN BIOASSAY LABORATORY (TWO-WEEK STUDIES)

Lot no. DSJ7468

### 1. Spectral data

## Mass Spectrometry

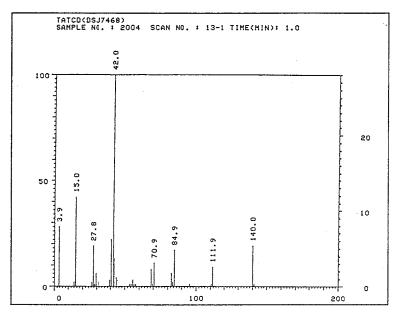
Instrument

: Hitachi M-80B

Ionization

: EI(Electron Ionization)

Ionization Voltage : 70eV



Mass Spectrum of 1,3,5,7-Tetraazatricyclo[3.3.1.1<sup>3,7</sup>]decane

Result:

Molecular Weight

Theoretical Value

140.1(Calculated)

Determined

140.0

### Infrared Spectrum

Instrument

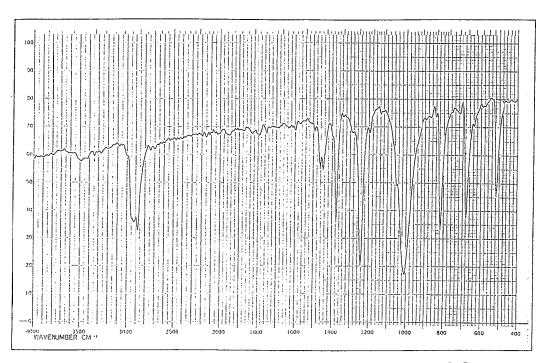
: Hitachi 270-30

Cell

: KBr

Slit

: Medium



Infrared Spectrum of 1,3,5,7-Tetraazatricyclo[3.3.1.1<sup>3.7</sup>]decane

Results:

Wave Number (CM - 1)

Determined	Literature Value
100 500	
$480 \sim 530$	480~ 530
640 ~ 700	640~ 700
780~ 830	780~ 830
910~1100	910~1100
$1200 \sim 1270$	1200~1270
$1350 \sim 1420$	$1350 \sim 1420$
1420 ~ 1490	1420~1490
$2800 \sim 3000$	$2800 \sim 3000$
	(Performed by the WAKO PURE CHEMICAL INDUSTRIES,
	LTD.)

2. Conclusions: The result of the mass spectrum agreed with the theoretical value and the infrared spectrum agreed with the literature value.

# APPENDIX A 8-2 STABILITY OF TATCD AT THE JAPAN BIOASSAY LABORATORY (TWO-WEEK STUDIES)

STABILITY OF 1,3,5,7-TETRAAZATRICYCLO[3.3.1.13,7]DECANE AT THE JAPAN BIOASSAY LABORATORY (TWO-WEEK STUDIES)

Lot no. DSJ7468

1. Sample storage: 1,3,5,7-Tetraazatricyclo[3.3.1.1<sup>3,7</sup>]decane was stored for about 6 weeks at 5°C.

### 2. Infrared Spectrum

Instrument : Hitachi 270-30

Cell

: KBr

Slit

: Medium

Results:

Wave Number (CM<sup>-1</sup>)

11/08/91	12/17/91
480∼ 530	480∼ 530
$640 \sim 700$	640~ 700
780∼ 830	780∼ 830
910~1100	910~1100
$1200 \sim 1270$	$1200 \sim 1270$
$1350 \sim 1420$	$1350 \sim 1420$
$1420 \sim 1490$	$1420 \sim 1490$
$2800 \sim 3000$	2800~3000

3. Conclusions: No notable differrence was observed between infrared spectrums of pre- and post-examination of the study.

Consequently, 1, 3, 5, 7-tetraazatricyclo[3.3.1.1<sup>3, 7</sup>]decane was stable as the chemical when stored for about 6 weeks at 5°C.

# APPENDIX A 8-3-1 ANANLYSIS OF TATCD CONCENTRATION IN DRINKING WATER OF THE TOW-WEEK STUDIES

ANALYSIS OF 1,3,5,7-TETRAAZATRICYCLO[3.3.1.13.7] DECANE CONCENTRATION IN DRINKING WATER OF THE TWO-WEEK STUDIES

(	R	a	t	)

	ncentration of 1,3, r Target Concentrat		lo[3.3.1.1 <sup>3.7</sup> ]deca	ne in Drinking Water
6250 ( a )	12500 ( a )	25000 ( a )	50000 ( a )	100000 ( a )
6403.6(102.5)	12880,1(103.0)	25561.8(102.2)	51397.3(102.8)	107539.8(107.5)

### (Mouse)

Concentration of 1,3,5,7-Tetraazatricyclo[3.3.1.1 <sup>3.7</sup> ]decane in Drinking for Target Concentration(ppm)				
6250 ( a )	12500 ( a )	25000 ( a )	50000 ( a )	100000 ( a )
6131.4( 98.1)	12499.2(100.0)	25693.3(102.8)	51292.0(102.6)	98991.2( 99.0)

# (a) Percent of target concentration

Analytical method: The sample were analyzed by the Ultra Violet Spectrophotometry.

Instrument

: SHIMADZU UV-240

Slit

: 2 nm

Cell

: 10 mm Cell

Range

: 0 - 2

Solvent

: Distilled Water

Wave Length

: 200 nm

# APPENDIX A 8-3-2 STABILITY OF TATCD CONCENTRATION IN DRINKING WATER OF THE TWO-WEEK STUDIES

STABILITY OF 1,3,5,7-TETRAAZATRICYCLO[3.3.1.13.7] DECANE IN DRINKING WATER OF THE TWO-WEEK STUDIES (Rat)

	Concentration of 1,3,5,7-Tetraazatricyclo[3.3.1.1 $^{3,7}$ ]decane in Drinking Water for Target Concentration(ppm)				
Date	6250 ( b )	100000 ( b )			
11/08/91(a)	6022.7(100)	102759.8(100)			
11/12/91	6112.9(101.5)	97507.7( 94.9)			

### (Mouse)

	Concentration of 1,3,5,7-Tetraazatricyclo[3.3.1.1 $^{3.7}$ ]decane in Drinking Water for Target Concentration(ppm)				
Date	6250 ( b )	100000 ( b )			
11/08/91(a)	6022.7(100)	102759.8(100)			
11/12/91	5983.5( 99.3)	96453.2( 93.9)			

<sup>(</sup>a) Date of preparation

Analytical method: The sample were analyzed by the Ultra Violet Spectrophotometry.

Instrument

: SHIMADZU UV-240

Slit

: 2 nm

Cell

: 10 mm Cell

Range

: 2 nm : 0 - 2

Solvent : Distilled Water

Wave Length

: 200 nm

<sup>(</sup>b) Percent of concentration on preparation day