アセト酢酸メチルのラットを用いた経口投与による 13週間毒性試験 (混水試験)報告書

試験番号: 0426

# **APPENDIXES**

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# APPENDIX A 1

CLINICAL OBSERVATION : SUMMARY, RAT : MALE

CLINICAL OBSERVATION (SUMMARY)

ANIMAL : RAT F344/DuCrj

ALL ANIMALS

REPORT TYPE : A1 13

SEX : MALE

PAGE: 1

Clinical sign	Group Name	Admini	stration We	eek-day										
·		1-7	2-7	3-7	4-7	5-7	6-7	7-7	8-7	9-7	10-7	11-7	12-7	13-7
					-									
PILOERECTION	Control	0	0	0 .	0	0	0	0	0	0	0	0	0	0
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	5000 ppm	0	0	0	0	0	0	0	0	0	0	0	0.	0
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	20000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	40000 ppm	5	0	0	0	0	0	0	0	0	0	0	0	0
SMALL STOOL	Control	0	0	0	0	0	0	0	0	0	0 .	0	0	0
	2500 ppm	0	0	0	0	0	0	0	0	0	. 0	0	0	0
	5000 ppm	0	0	0	0	0	0	0	0	0	0	0	. 0	0
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	20000 բբա	0	0	0	0	0	0	0	0	0	0	0	0	0
	40000 ppm	9	3	0	0	0	0	0	0	0	0	0	0	1
OLIGO-STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	5000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	20000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	40000 ppm	10	1	0	0	0	0	0	0	0	0	0	0	0

(HAN190)

## APPENDIX A 2

CLINICAL OBSERVATION : SUMMARY, RAT : FEMALE

CLINICAL OBSERVATION (SUMMARY)

ANIMAL : RAT F344/DuCrj

ALL ANIMALS REPORT TYPE: A1 13

SEX : FEMALE

\*\*\*\*\*\*\*

PAGE: 2

. . . . .

Clinical sign Group Name Administration Week day 6-7 7-7 8-7 9-7 10-7 11-7 12 - 713-7 2-7 4-7 5-7 1-7 3-7 MORIBUND SACRIFICE Control 2500 ppm 5000 ppm 10000 ppm 20000 ppm 40000 ppm LOCOMOTOR MOVEMENT DECR Control 2500 ppm 5000 ppm 10000 ppm 20000 ppm 40000 ppm HUNCHBACK POSITION Control 2500 ppm 5000 ppm 10000 ppm 20000 ppm 40000 ppm PILOERECTION Control 2500 ppm 5000 ppm 10000 ppm 20000 ppm 40000 ppm SOILED PERI GENITALIA Control 2500 ppm 5000 ppm 10000 բբա 20000 ppm 40000 ppm ABNORMAL RESPIRATION Control 2500 ppm 5000 ppm 10000 ppm 20000 ppm 40000 ppm 

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1 13

#### CLINICAL OBSERVATION (SUMMARY)

ALL ANIMALS

SEX : FEMALE

PAGE: 3

Clinical sign	Group Name	Admini	stration We	eek-day											
		1-7	2-7	3-7	4-7	5-7	6-7	7–7	8-7	9-7	10-7	11-7	12-7	13-7	
BRADYPNEA	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	
	2500 բբա	0	0	0	0	0	0	0	0	0	0	0	0	0	
	5000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	10000 ppm	0	0	0	0	0	0	0	0	0	0	. 0	0	0	
	20000 ppm	0	0 .	0	0	0	0	0	0	0	0	0	0	0	
	40000 ppm	1	0	0	0	0	0	0	0	0	0	0	0	0	
SMALL STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	5000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	20000 բբա	0	0	0	0	0	0	0	0	0	0	0	0	0	
	40000 ppm	5	1	0	0	0	0	0	0	0	0	0	0	0	
OLIGO-STOOL	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	5000 բրա	0	0	0	0	0	- 0	0	0	0	0	0	0	0	
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	20000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	40000 ppm	10	0	0	0	0	0	0	0	0	0	0	0	0	
SUBNORMAL TEMP	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	5000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	20000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	
	40000 ppm	1	Ö	Ö	Õ	0	ő	0	Ö	0	0	0	0	Ö	

(HAN190)

## APPENDIX B 1

BODY WEIGHT CHANGES : SUMMARY, RAT : MALE

ANIMAL : RAT F344/DuCrj UNIT : g REPORT TYPE : A1 13

BODY WEIGHT CHANGES ALL ANIMALS

(SUMMARY)

SEX : MALE

roup Name	Adminis	tration	week												
	0		1		2		3		4		5		6		
Control	127±	4	159±	6	190±	9	216±	9	237±	8	251±	8	261±	11	
2500 ррт	127±	4	156±	7	185±	11	209±	13	229±	12	244±	12	254±	12	
5000 բրա	127±	4	154±	7	183±	8	209±	8	228±	7	242±	8	249±	8	
10000 ppm	127±	4	154±	7	185±	8	210±	8	229±	9	242±	9	250±	11	
20000 ppm	127±	5	148±	6*	180±	10	204±	13	225±	13*	238±	12*	243±	14**	
40000 ppm	127±	4	107±	17**	. 144±	17**	177±	12**	200±	12**	216±	12**	221±	11**	

Significant difference; \*: P ≤ 0.05

\*\* : P ≤ 0.01

Test of Dunnett

(HAN260)

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ANIMAL : RAT F344/DuCrj UNIT : g

REPORT TYPE : A1 13

SEX : MALE

BODY WEIGHT CHANGES ALL ANIMALS

(SUMMARY)

Admini	Administration week												
7 		8		9						12		13	
277±	12	290±	12	300±	13	310±	12	315±	12	323±	12	326±	11
270±	11	281±	13	288±	14	297±	14	302±	14	308±	15	310±	16
264±	8	274±	9*	282±	10**	288±	10**	292±	12**	296±	10**	299±	11**
263±	11*	274±	13*	281±	13**	286±	14**	290±	13**	297±	13**	299±	14**
258±	13**	267±	13**	273±	13**	280±	16**	281±	16**	285±	16**	287±	15**
235±	13**	245±	14**	250±	13**	253±	13**	256±	16**	264±	17**	264±	22**
	$7$ $277\pm$ $270\pm$ $264\pm$ $263\pm$	$7$ $277\pm 12$ $270\pm 11$ $264\pm 8$ $263\pm 11*$ $258\pm 13**$	7 8  277± 12 290±  270± 11 281±  264± 8 274±  263± 11* 274±  258± 13** 267±	7 8  277± 12 290± 12  270± 11 281± 13  264± 8 274± 9*  263± 11* 274± 13*  258± 13** 267± 13**	7 8 9  277 $\pm$ 12 290 $\pm$ 12 300 $\pm$ 270 $\pm$ 11 281 $\pm$ 13 288 $\pm$ 264 $\pm$ 8 274 $\pm$ 9* 282 $\pm$ 263 $\pm$ 11* 274 $\pm$ 13* 281 $\pm$ 258 $\pm$ 13** 267 $\pm$ 13** 273 $\pm$	7 8 9  277± 12 290± 12 300± 13  270± 11 281± 13 288± 14  264± 8 274± 9* 282± 10**  263± 11* 274± 13* 281± 13**  258± 13** 267± 13** 273± 13**	7 8 9 10  277± 12 290± 12 300± 13 310±  270± 11 281± 13 288± 14 297±  264± 8 274± 9* 282± 10** 288±  263± 11* 274± 13* 281± 13** 286±  258± 13** 267± 13** 273± 13** 280±	7 8 9 10  277± 12 290± 12 300± 13 310± 12  270± 11 281± 13 288± 14 297± 14  264± 8 274± 9* 282± 10** 288± 10**  263± 11* 274± 13* 281± 13** 286± 14**  258± 13** 267± 13** 273± 13** 280± 16**	7 8 9 10 11  277± 12 290± 12 300± 13 310± 12 315±  270± 11 281± 13 288± 14 297± 14 302±  264± 8 274± 9* 282± 10** 288± 10** 292±  263± 11* 274± 13* 281± 13** 286± 14** 290±  258± 13** 267± 13** 273± 13** 280± 16** 281±	7 8 9 10 11  277± 12 290± 12 300± 13 310± 12 315± 12  270± 11 281± 13 288± 14 297± 14 302± 14  264± 8 274± 9* 282± 10** 288± 10** 292± 12**  263± 11* 274± 13* 281± 13** 286± 14** 290± 13**  258± 13** 267± 13** 273± 13** 280± 16** 281± 16**	7 8 9 10 11 12  277± 12 290± 12 300± 13 310± 12 315± 12 323±  270± 11 281± 13 288± 14 297± 14 302± 14 308±  264± 8 274± 9* 282± 10** 288± 10** 292± 12** 296±  263± 11* 274± 13* 281± 13** 286± 14** 290± 13** 297±  258± 13** 267± 13** 273± 13** 280± 16** 281± 16** 285±	7 8 9 10 11 12  277± 12 290± 12 300± 13 310± 12 315± 12 323± 12  270± 11 281± 13 288± 14 297± 14 302± 14 308± 15  264± 8 274± 9* 282± 10** 288± 10** 292± 12** 296± 10**  263± 11* 274± 13* 281± 13** 286± 14** 290± 13** 297± 13**  258± 13** 267± 13** 273± 13** 280± 16** 281± 16** 285± 16**	7 8 9 10 11 12 13  277± 12 290± 12 300± 13 310± 12 315± 12 323± 12 326±  270± 11 281± 13 288± 14 297± 14 302± 14 308± 15 310±  264± 8 274± 9* 282± 10** 288± 10** 292± 12** 296± 10** 299±  263± 11* 274± 13* 281± 13** 286± 14** 290± 13** 297± 13** 299±  258± 13** 267± 13** 273± 13** 280± 16** 281± 16** 285± 16** 287±

(HAN260)

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## APPENDIX B 2

BODY WEIGHT CHANGES: SUMMARY, RAT: FEMALE

BODY WEIGHT CHANGES ALL ANIMALS

(SUMMARY)

ANIMAL : RAT F344/DuCrj UNIT : g

REPORT TYPE : A1 13

SEX : FEMALE

PAGE: 3

oup Name	Administ	ration	week										,
·· · · · · · · · · · · · · · · · · · ·	. 0		1		2		3	4		5		6	
Control	100±	3	113±	4	123±	5	132± 5	140±	6	147±	6	150±	7
2500 թթտ	100±	3	115±	5	126生	5	135± 6	142±	8	149±	8	150±	8
5000 ррт	100±	3	114±	3.	126±	5	135± 4	142±	5	147±	5	149±	7
10000 ррт	100±	3	112±	3	124±	5	132± 4	141±	5	147±	7	147±	5
. 20000 ppm	100±	3	110±	5	121±	5	131± 6	137±	7	141±	6	141±	7*
40000 ppm	100±	3	91±	17**	114±	7**	128± 7	136±	8	139±	11	139±	10**
Significant differen	nce; $*: P \leq 0$ .	05	** : P ≤ 0.0	1			Test of Dunnett						

(HAN260)

ANIMAL : RAT F344/DuCrj

UNIT : g

REPORT TYPE: A1 13

SEX : FEMALE

BODY WEIGHT CHANGES ALL ANIMALS

162± 7

153± 10

151 ± 13

(SUMMARY)

165± 8

156± 10

153± 15\*

166± 7

158± 11

154± 14\*

(SUMMULI

Group Name Administration week\_ 10 11 12 13 170± 11 156± 160± 10 162± 10 166± 10 167± 11 166± 13 Control 8 171± 10 166± 169± 10 170± 10 157±  $160 \pm$ 163± 9 2500 ppm 5000 ppm 156± 7 159 ± 7 162± 8 165± 7 165± 7 168± 7 170± 8

Significant difference;  $*: P \le 0.05$   $\implies: P \le 0.01$  Test of Dunnett

(HAN260)

10000 ppm

20000 ppm

40000 ppm

155±

147±

145± 12\*

7

8

158± 7

150± 9

147土 13\*

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170± 8

160± 12

158± 15

170± 6

160± 10

160± 13

## APPENDIX C 1

WATER CONSUMPTION CHANGES : SUMMARY, RAT : MALE

WATER CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

STUDY NO. : 0426

ANIMAL : RAT F344/DuCrj

UNIT : g

REPORT TYPE : A1 13

SEX : MALE .

oup Name		week-day(effective)	3-7(4)	4-7(4)	5-7(4)	6-7(4)	7-7(4)
-	1-7(4)	2-7(4)	3-7(4)	4-7(4)	5-7 (4)	0-1(4)	1-7 (4)
Control	17.6± 0.8	18.7± 0.9	19.6± 1.0	19.3± 1.4	18.6± 0.9	17.0± 1.0	18.4± 0.7
2500 ppm	14.5± 1.3	15.4± 1.5**	16.0± 1.5**	15.6± 1.5	15.2± 1.4	14.1± 1.3**	15.5± 1.3**
5000 ррш	13. 2± 1. 1**	14.7± 1.1**	15.4± 0.9**	14.8± 0.4*	14.1± 0.5	12.3± 0.4**	13.5± 0.7**
10000 mqq 00001	13.4± 0.7**	14.5± 0.7**	14.8± 0.7**	14.2± 0.7**	13.4生 0.5**	11.9± 0.7**	12.8± 0.5**
20000 ppm	13.0± 0.9★★	13.7± 1.1**	13.9± 0.9**	13.1± 0.8**	12.6± 0.7**	10.6生 0.8**	11.9± 1.0**
40000 ppm	6.4± 4.3**	11.9± 1.6**	12.6± 0.9**	12.1± 1.1**	11.3± 1.2**	9.5± 0.8**	10.4± 1.0**
Significant differe	ence; *: P ≤ 0.05	<b>**</b> : P ≤ 0.01		Test of Dunnett		•	

(HAN260)

BAIS 3

PAGE: 1

WATER CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

ANIMAL : RAT F344/DuCrj

UNIT : g

STUDY NO. : 0426

REPORT TYPE : A1 13

SEX : MALE

oup Name	Administration 8-7(4)	week-day(effective) 9-7(4)	10-7(4)	11-7(4)	12-7 (4)	13-7(4)	· · · · · · · · · · · · · · · · · · ·
Control	18.6± 0.5	18.1± 0.8	17.9± 1.0	17.3± 0.7	16.9± 0.9	18.2± 2.9	
2500 ppm	14.9± 1.3**	14.3± 1.1**	14.4± 0.7**	14.7± 1.6**	14.1± 1.2	13.5± 1.3	
5000 բբա	13.3± 1.3**	13.6± 1.3**	13.3± 1.2**	12.7± 1.0**	11.9± 0.9**	12.1± 1.0*	
10000 ppm	13.0± 1.0**	12.9± 1.0**	12.6± 0.8**	11.4± 0.7**	11.8± 0.4**	11.3± 0.9**	
20000 ppm	11.8± 1.2**	11.8± 0.8**	12.0± 1.3**	· 11.0± 1.1**	10.6± 1.0**	12.8± 4.2**	
40000 ppm	10.4± 1.3**	10.1± 1.3**	10.0± 1.7**	9.8± 1.7**	10.1± 1.8**	9.6± 1.6**	
Significant differend	ce; *: P ≤ 0.05	⇔: P ≤ 0.01		Test of Dunnett			

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## APPENDIX C 2

WATER CONSUMPTION CHANGES: SUMMARY, RAT: FEMALE

WATER CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

STUDY NO. : 0426

ANIMAL : RAT F344/DuCrj

UNIT : g

REPORT TYPE : A1 13

SEX : FEMALE

roup Name	Administration 1-7(4)	week-day(effective) 2-7(4)	3-7 (4)	4-7(4)	5-7 (4)	6-7 (4)	7-7 (4)
					<u> </u>		
Control	16.4 $\pm$ 7.6	15.3± 3.3	15.7± 3.6	17.4 $\pm$ 7.6	15.5 $\pm$ 3.8	15.1± 3.1	15.8± 3.1
2500 ррт	11.7± 0.7	11.5± 1.0	11.5± 0.9	11.2± 0.8	11.2± 1.2	9.9± 1.0	11.3± 1.4
5000 ррт	10.6± 0.6**	10.7± 0.6**	10.6± 1.1**	10.3± 0.5**	9.7± 0.6**	8.9± 0.9*	9.9± 1.6*
10000 ррш	10.4± 0.6**	10.4± 0.5**	10.2± 0.6**	10.3± 0.8**	9.5± 0.8**	7.9± 0.5**	9.0± 0.7**
20000 ppm	9.6± 0.7**	9.8± 0.7**	9.8± 0.6**	9.2± 0.7**	10.8± 4.9**	7.8± 2.3**	8.1± 1.0**
40000 ppm	7.5± 3.4**	10.3± 0.8**	10.7± 2.4**	9.8± 1.9**	8.0± 1.4**	6.8± 1.3**	7.8± 1.6**
Significant differe	ence; *: P ≤ 0.05	** : P ≤ 0.01		Test of Dunnett			

(HAN260)

BAIS 3

PAGE: 3

ANIMAL : RAT F344/DuCrj

UNIT : g

REPORT TYPE : A1 13

WATER CONSUMPTION CHANGES (SUMMARY)

ALL ANIMALS

		week-day(effective)					
	8-7(4)	9-7(4)	10-7 (4)	11-7(4)	12-7 (4)	13-7 (4)	
Control	16.9± 3.8	19.1± 8.6	14.8± 2.7	21.5± 7.9	17.1± 4.7	23,5± 9.9	
2500 ppm	11.7± 2.4	11.0± 1.5	10.8± 1.5	11.5± 2.6	11.0± 1.8	11.8± 4.2	
5000 ррт	9.8± 1.8*	10.2± 3.3	9.8± 2.4	9.4± 1.8*	10.0± 2.9*	9.5± 1.5*	
10000 ррт	8.8± 0.7**	8.5± 0.7**	8.7± 1.3**	8.6± 2.0**	8.5± 0.5**	8.4± 0.7**	
20000 ppm	8.2± 1.4**	7.6± 0.7**	7.9± 0.9**	7.0± 0.9**	7.4± 0.8**	7.0± 0.5**	
40000 ppm	7.6± 1.5**	7.2± 1.3**	6.7± 1.2**	6.6± 0.7**	6.8± 1.1**	7.1± 1.4**	

(HAN260)

## APPENDIX D 1

FOOD CONSUMPTION CHANGES: SUMMARY, RAT: MALE

ANIMAL : RAT F344/DuCrj

UNIT : g

REPORT TYPE : A1 13

SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

PAGE: 1

roup Name	Administration w	eek-day(effective)					
	1-7(7)	2-7(7)	3-7(7)	4-7(7)	5-7(7)	6-7(7)	7-7 (7)
Control	14.2± 0.7	15.7± 0.8	15.8± 0.9	16.5± 0.9	15.8± 0.6	15.4± 0.7	15.9± 1.0
2500 ppm	13.4± 0.9	14.9± 1.2	15.3± 1.4	15.7± 1.1	15.2± 0.9	14.5± 1.1	15.4± 1.3
5000 ррт	12.8± 0.8*	14.2± 1.0*	14.8± 0.7	15.2± 0.6**	14.8± 0.7*	14.3± 0.6*	14.7± 0.7*
10000 ppm	12.7± 0.8**	14.4± 0.9*	14.8± 0.8	14.8± 0.8**	14.3± 0.7**	13.9± 0.7**	14.6± 0.8*
20000 ppm	11.5± 0.8**	13.9± 1.1**	14.3± 1.1*	14.7± 0.9**	14.0± 0.9**	13.3± 0.8**	13.9± 0.8**
40000 ppm	5.8± 1.5**	12.0± 1.4**	13.2± 1.0**	13.9± 1.1**	13.6± 0.8**	12.6± 0.7**	12.7± 0.8**

Significant difference ; \* :  $P \le 0.05$  \*\* :  $P \le 0.01$  Test of Dunnett

(HAN260)

ANIMAL : RAT F344/DuCrj

UNIT : g

REPORT TYPE : A1 13

SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

PAGE: 2

oup Name	Administration 8-7(7)	week-day(effective) 9-7(7)	10-7(7)	11-7(7)	12-7(7)	13-7(7)	
Control	15.5± 0.9	15.1± 0.8	15.2± 0.7	15.2± 0.7	15.0± 0.7	15.7± 0.8	
2500 ppm	14.8± 1.3	14.6± 1.0	14.5± 0.9	14.3± 0.8	13.7± 1.1*	14.3± 1.2*	
5000 թբա	13.9± 0.7**	14.1± 1.0	14.1± 0.7*	13.8± 0.6**	13.1± 0.6**	13.4± 0.9**	
10000 ppm	14.0± 0.9**	14.0± 0.9*	13.7± 1.1**	13.5± 0.9**	13.2± 0.7**	13.4± 1.1**	
20000 ppm	13.1± 0.8**	13.1± 0.9**	13.1± 1.0**	12.7± 0.8**	12.3± 0.7**	13.0± 0.8**	
40000 ppm	12.0± 1.1**	12.2± 0.9**	11.9± 0.7**	12.0± 1.2**	12.1± 1.3**	12.3± 1.3**	
Significant difference	e; *: P ≤ 0.05	** : P ≤ 0.01		Test of Dunnett			

(HAN260)

## APPENDIX D 2

FOOD CONSUMPTION CHANGES: SUMMARY, RAT: FEMALE

ANIMAL : RAT F344/DuCrj

UNIT : g

REPORT TYPE : A1 13

SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)

ALL ANIMALS

PAGE: 3 Group Name Administration week-day(effective)\_ 1-7(7) 2-7(7) 3-7(7) 4-7(7) 5-7(7) 6-7(7) 7-7(7) Control 10.4± 0.5 10.4± 0.5  $10.7 \pm 0.6$  $10.4 \pm 0.7$ 10.7± 0.6 10.1± 0.7  $10.3 \pm 0.9$ 2500 ppm 10.5± 0.5 10.5± 0.4  $10.6 \pm 0.7$  $10.2 \pm 0.5$ 10.4± 0.6 9.7± 0.6 10.0± 0.6 5000 ppm 10.2± 0.6 10.1 $\pm$  0.5  $10.2 \pm 0.6$ 10.1 $\pm$  0.6 9.9生 0.4\* 9.4± 0.5  $9.7 \pm 0.5$ 10000 ppm  $10.1 \pm 0.5$ 10.2± 0.6  $10.1 \pm 0.8$  $9.9 \pm 0.7$ 10.0± 0.8\* 9.2± 0.6\*\*  $9.6 \pm 0.7$ 20000 ppm 9.2± 0.8\* 9.5± 0.5\*\* 9.6± 0.6\*\* 9.5生 0.5\*\* 9.2± 0.6\*\* 9.0± 0.4\*\* 9.0± 0.5\*\* 40000 ppm 5.8± 1.9\*\* 9.6± 0.4\*\* 9.8± 0.9\* 9.5± 0.8\* 9.0± 1.0\*\* 8.6± 0.7\*\* 8.6± 0.7\*\* Significant difference ;  $*: P \leq 0.05$ \*\* :  $P \leq 0.01$ Test of Dunnett

(HAN260)

ANIMAL : RAT F344/DuCrj

UNIT : g

REPORT TYPE : A1 13

SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)

ALL ANIMALS

Group Name Administration week day(effective)\_ 8-7(7) 9-7(7)10-7(7) 11-7(7) 12-7(7)13-7(7)Control  $9.8 \pm 1.0$  $9.6 \pm 0.7$  $9.7 \pm 0.9$  $9.8 \pm 1.0$  $9.5 \pm 0.8$ 9.8± 0.8 2500 ppm 9.5± 0.5 9.2± 0.5  $9.4 \pm 0.4$ 9.4± 0.4  $9.3 \pm 0.7$  $9.5 \pm 0.6$  $9.1\pm 0.5$  $9.1 \pm 0.6$ 9.0± 0.6\*  $9.0 \pm 0.8$  $9.1 \pm 0.6$ 5000 ppm  $9.3 \pm 0.6$ 10000 ppm  $9.1 \pm 0.8$  $9.0 \pm 0.7$  $9.1 \pm 0.8$ 9.0± 0.7\*  $8.9 \pm 0.5$ 8.9± 0.7\* 20000 ppm 8.7± 0.7\*\* 8.5± 0.8\*\* 8.4± 0.8\*\* 8.7± 0.7\*\* 8.4生 0.7\*\* 8.5± 0.6\*\* 40000 ppm 8.5± 1.0\*\* 8.2± 0.9\*\* 8.0± 0.9\*\* 8.2± 0.9\*\* 8.1± 0.6\*\* 8.2± 0.6\*\* Significant difference;  $*: P \leq 0.05$ \*\* : P ≤ 0.01 Test of Dunnett

(HAN260)

BAIS 3

PAGE: 4

## APPENDIX E 1

CHEMICAL INTAKE CHANGES : SUMMARY, RAT : MALE

ANIMAL : RAT F344/DuCrj UNIT : g/kg/day REPORT TYPE : A1 13 CHEMICAL INTAKE CHANGES (SUMMARY)

ALL ANIMALS

SEX : MALE

PAGE: 1

roup Name		weeks)					
	, 1	2	3	4	5	6	7
Control	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000
2500 ррт	0.232± 0.015	0.208± 0.010	0.191± 0.009	0.170± 0.009	0.156± 0.009	0.138± 0.008	0.143± 0.008
5000 բրա	0.429± 0.026	0.400± 0.025	0.368± 0.028	0.325± 0.015	0.290± 0.016	0.248± 0.011	0.256± 0.014
10000 ppm	0.867± 0.027	0.781± 0.022	0.707± 0.029	0.620± 0.034	0.554± 0.016	0.475± 0.014	0.488± 0.028
20000 ppm	1.747± 0.100	1.524± 0.057	1.363± 0.039	1.166± 0.049	1.059± 0.050	0.871± 0.036	0.921± 0.051
40000 ррш	2.200± 1.257	3.294± 0.232	$2.851 \pm 0.209$	2.422± 0.096	2.090± 0.169	1.718± 0.160	1.775± 0.140

(HAN300)

ANIMAL : RAT F344/DuCrj UNIT : g/kg/day

CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS

REPORT TYPE : A1 13

SEX : MALE

8 9 10 11 12 13  Control 0.000± 0.000 0.000± 0.000 0.000± 0.000 0.000± 0.000 0.000± 0.000 0.000± 0.000  2500 ppm 0.132± 0.006 0.124± 0.004 0.121± 0.003 0.122± 0.013 0.114± 0.007 0.109± 0.006  5000 ppm 0.243± 0.023 0.241± 0.022 0.230± 0.018 0.217± 0.012 0.200± 0.011 0.202± 0.014  10000 ppm 0.476± 0.032 0.458± 0.027 0.440± 0.025 0.396± 0.026 0.398± 0.015 0.378± 0.026  20000 ppm 0.881± 0.071 0.862± 0.042 0.856± 0.069 0.780± 0.062 0.746± 0.057 0.884± 0.273  40000 ppm 1.703± 0.158 1.619± 0.191 1.583± 0.243 1.529± 0.202 1.526± 0.212 1.438± 0.141	roup Name	Administratio	n (weeks)					
2500 ppm 0.132± 0.006 0.124± 0.004 0.121± 0.003 0.122± 0.013 0.114± 0.007 0.109± 0.006  5000 ppm 0.243± 0.023 0.241± 0.022 0.230± 0.018 0.217± 0.012 0.200± 0.011 0.202± 0.014  10000 ppm 0.476± 0.032 0.458± 0.027 0.440± 0.025 0.396± 0.026 0.398± 0.015 0.378± 0.026  20000 ppm 0.881± 0.071 0.862± 0.042 0.856± 0.069 0.780± 0.062 0.746± 0.057 0.884± 0.273		8	9	10	11	12	13	
2500 ppm 0.132± 0.006 0.124± 0.004 0.121± 0.003 0.122± 0.013 0.114± 0.007 0.109± 0.006  5000 ppm 0.243± 0.023 0.241± 0.022 0.230± 0.018 0.217± 0.012 0.200± 0.011 0.202± 0.014  10000 ppm 0.476± 0.032 0.458± 0.027 0.440± 0.025 0.396± 0.026 0.398± 0.015 0.378± 0.026  20000 ppm 0.881± 0.071 0.862± 0.042 0.856± 0.069 0.780± 0.062 0.746± 0.057 0.884± 0.273								
5000 ppm 0.243± 0.023 0.241± 0.022 0.230± 0.018 0.217± 0.012 0.200± 0.011 0.202± 0.014  10000 ppm 0.476± 0.032 0.458± 0.027 0.440± 0.025 0.396± 0.026 0.398± 0.015 0.378± 0.026  20000 ppm 0.881± 0.071 0.862± 0.042 0.856± 0.069 0.780± 0.062 0.746± 0.057 0.884± 0.273	Control	0.000± 0.000	$0.000 \pm 0.000$	$0.000 \pm 0.000$	0.000± 0.000	0.000± 0.000	0.000± 0.000	
5000 ррш 0. 243± 0. 023 0. 241± 0. 022 0. 230± 0. 018 0. 217± 0. 012 0. 200± 0. 011 0. 202± 0. 014  10000 ррш 0. 476± 0. 032 0. 458± 0. 027 0. 440± 0. 025 0. 396± 0. 026 0. 398± 0. 015 0. 378± 0. 026  20000 ррш 0. 881± 0. 071 0. 862± 0. 042 0. 856± 0. 069 0. 780± 0. 062 0. 746± 0. 057 0. 884± 0. 273	2500 ppm	0.132± 0.006	0.124± 0.004	0.121± 0.003	0.122± 0.013	0.114± 0.007	0.109± 0.006	
10000 ppm 0.476± 0.032 0.458± 0.027 0.440± 0.025 0.396± 0.026 0.398± 0.015 0.378± 0.026 20000 ppm 0.881± 0.071 0.862± 0.042 0.856± 0.069 0.780± 0.062 0.746± 0.057 0.884± 0.273								
20000 ppm 0.881 ± 0.071 0.862 ± 0.042 0.856 ± 0.069 0.780 ± 0.062 0.746 ± 0.057 0.884 ± 0.273	5000 ppm	$0.243 \pm 0.023$	$0.241 \pm 0.022$	$0.230 \pm 0.018$	$0.217 \pm 0.012$	$0.200 \pm 0.011$	$0.202 \pm 0.014$	
20000 ppm 0.881± 0.071 0.862± 0.042 0.856± 0.069 0.780± 0.062 0.746± 0.057 0.884± 0.273	10000 ppm	0.476± 0.032	0.458± 0.027	0.440± 0.025	0.396± 0.026	0.398± 0.015	0.378± 0.026	
	Toolo pp.ii	V. 1.0 = V. 0.00	00 200 == 00 3 <b>0</b>					
40000 ppm 1.703 ± 0.158 1.619 ± 0.191 1.583 ± 0.243 1.529 ± 0.202 1.526 ± 0.212 1.438 ± 0.141	20000 ppm	0.881± 0.071	0.862± 0.042	0.856± 0.069	0.780± 0.062	0.746± 0.057	0.884± 0.273	
40000 ppm 1.705 1.019 1.019 1.019 1.019 1.000 1.019 1.000 1.	40000	1 703 + 0 150	1 610+ 0 101	1 502 - 0 242	1 520+ 0 202	1 526+ 0 212	1 438+ 0 141	
	40000 phis	1.103 ± 0.130	1.019 1.0191	1.000 ± 0.240	1.029 - 0.202	1.020 = 0.212	1. 100 2 0. 141	

(HAN300)

BAIS 3

PAGE: 2

## APPENDIX E 2

CHEMICAL INTAKE CHANGES: SUMMARY, RAT: FEMALE

ANIMAL : RAT F344/DuCrj UNIT : g/kg/day REPORT TYPE : A1 13 CHEMICAL INTAKE CHANGES (SUMMARY)

ALL ANIMALS

SEX : FEMALE

PAGE: 3

roup Name	Administration						
	1	2	3	4	5	6	7
Control	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000
2500 ppm	0.253± 0.011	0.227± 0.017	0.211± 0.012	0.196± 0.009	0.188± 0.020	0.165± 0.014	0.181± 0.020
5000 ррт	0.463± 0.019	0.425± 0.014	0.395± 0.036	0.363± 0.015	0.329± 0.019	0.297± 0.026	0.317± 0.046
10000 ppm	0.926± 0.066	$0.839 \pm 0.052$	0.773± 0.049	0.735± 0.049	0.645± 0.045	0.540± 0.028	0.576± 0.038
20000 ppm	1.748± 0.089	1.616± 0.083	1.503± 0.084	1.342± 0.073	1.519± 0.641	1.099± 0.297	1.103± 0.126
40000 ррш	3.115± 1.064	3.616± 0.371	3.343± 0.776	2.882± 0.527	2.307± 0.288	1.937± 0.270	2. 154± 0. 428

(HAN300)

ANIMAL : RAT F344/DuCrj UNIT : g/kg/day

REPORT TYPE : A1 13

CHEMICAL INTAKE CHANGES (SUMMARY)

ALL ANIMALS

SEX : FEMALE							PAGE: 4
Group Name	Administration	(weeks)					
	8	9	10	11	12	. 13	
Control	0.000± 0.000	$0.000 \pm 0.000$	0.000± 0.000	$0.000\pm 0.000$	$0.000 \pm 0.000$	0.000± 0.000	
2500 ppm	0.183± 0.036	0.169± 0.025	0.163± 0.023	0.171± 0.038	0.162± 0.024	0.172± 0.057	
mqq 0003	$0.308 \pm 0.054$	$0.314\pm 0.096$	$0.297 \pm 0.068$	$0.283 \pm 0.048$	0.296± 0.079	0.281± 0.038	
10000 ppm	0.554± 0.038	0.526± 0.038	0.526± 0.073	0.520± 0.106	0.502± 0.029	0.495± 0.042	
20000 ppm	1. 101± 0. 236	0.989± 0.091	1.011± 0.102	$0.891 \pm 0.098$	$0.927 \pm 0.071$	0.885± 0.083	
40000 ppm	2.054± 0.375	1.918± 0.298	1.732± 0.164	1.733± 0.123	1.721± 0.188	1.782± 0.275	

(IIAN300)

## APPENDIX F 1

HEMATOLOGY: SUMMARY, RAT: MALE

SEX : MALE

HEMATOLOGY (SUMMARY) ALL ANIMALS ( 14\)

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1

REPORT TYPE : A1

PAGE: 1

roup Name	NO. of Animals	RED BLC 1 O⁵∕u	OOD CELL	HEMOGLO g/dl	BIN	HEMATOC %	RIT	MCV f &		MCH pg		MCHC g/dl		PLATELET 1 0³/µl	
Control	10	9.47±	0. 12	16.1±	0.2	47.2±	0.7	49.9±	0.5	17.0±	0.2	34.1±	0.3	715±	55
2500 ppm	10	9.43±	0.26	16.1±	0.4	47.4±	1.3	50.2±	0.5	17.1±	0.2	34.0±	0.4	682±	29
5000 ppm	9	9.21±	0.36	15.8±	0.6	46.6±	1. 9	50.6±	0.7*	17.2±	0. 2	34.0±	0.4	696±	59
10000 ppm	10	9.27±	0. 25	15.9±	0.4	46.8±	1.3	50.4±	0.6	17.1±	0.2	33.9±	0.3	696±	47
20000 ррт	10	9. 13±	0. 19**	15.6±	0.3**	45.9±	1. 0	50.3±	0.3	17.1±	0.2	34.0±	0.4	706±	55
40000 ppm	9	9.15±	0.16**	15.9±	0.3	46.5±	0.7	50.9±	0.4**	17.4±	0.1**	34.2±	0.3	668±	65

(IJCL070)

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1

REPORT TYPE : A1

HEMATOLOGY (SUMMARY) ALL ANIMALS ( 14W)

SEX : MALE PAGE: 2 Group Name NO. of RETICULOCYTE PROTHROMBIN TIME APTT Animals % s e c s e c Control 10  $2.0\pm 0.2$ 17.2± 2.2  $26.5 \pm 2.1$ 2500 ppm 10  $1.9 \pm$ 0.2 17.6± 2.7 27.5± 2.7 5000 ppm 9  $2.0 \pm$ 0.2 17.3± 26.5 $\pm$  3.3 1.9 10000 ppm 10  $1.8 \pm$ 0.2  $15.0 \pm$ 0.4\*\* 22.4± 2.0\*\* 20000 ррт 10  $2.0 \pm$ 0.2 15.0 $\pm$ 0.5\*\*  $21.3 \pm$ 2.1\*\* 40000 ppm  $2.1 \pm 0.2$ 15.5 $\pm$  0.5 22.2± 3.0\*\* Significant difference;  $*: P \leq 0.05$ \*\* : P ≤ 0.01 Test of Dunnett

(HCL070)

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1

HEMATOLOGY (SUMMARY) ALL ANIMALS ( 14W)

: MALE	REPURT	TYPE : A1													PAGE	: 3
up Name	NO. of Animals	1 O³∕µℓ	Dif N-BAND	rferentia)	N-SEG	.)	EOSINO		BASO		MONO		LYMPIIO		OTHER	<u></u>
Control	10	4.72± 1.28	3±	1	21±	4	1±	1	0±	0	2±	1	73±	5	0±	0
2500 ppm	10	4.67± 1.19	2±	1	19±	2	1±	1	0±	0	2±	1	76±	4	0±	0
5000 ppm	9	5.24± 2.21	2±	1	17±	3	2±	1	0土	0	2±	1	78±	4	0±	0
10000 ppm	10	4.53± 1.58	2±	1	21±	5	1±	1	0±	0	2±	1	74±	5	0±	0
20000 թթա	10	3.81± 1.17	2±	1	20±	4	1±	1	0生	0	3±	2	74±	4	0±	0
40000 ppm	9	4.47± 1.03	2±	I	21±	3	Ι±	ı	0±	0	2±	1	73±	4	0±	0

(IICL070) BAIS 3

# APPENDIX F 2

HEMATOLOGY : SUMMARY, RAT : FEMALE

ANIMAL : RAT F344/DuCrj

MEASURE, TIME: 1

REPORT TYPE : A1

HEMATOLOGY (SUMMARY) ALL ANIMALS ( 14W)

SEX : FEMALE PAGE: 4 Group Name NO. of RED BLOOD CELL HEMOGLOB1N HEMATOCRIT MCV MCH MCHC PLATELET Animals 105/ul g /dl % f L рg g/dl  $10^{3}/\mu l$ Control  $8.54 \pm 0.28$ 10 15.8± 45.0± 1.5 0.4 52.7 $\pm$ 0.5  $18.5 \pm$ 0.2  $35.1 \pm$ 0.6  $790 \pm$ 52 8.50± 0.18 2500 ppm 10 15.6± 0.3 44.6± 0.8 52.5 $\pm$ 0.5 18.4± 0.2  $35.0 \pm$ 0.5 78 756± 5000 ppm 10 8.42± 0.18 15.6± 0.4 44.5± 1.0  $52.8 \pm$  $18.5 \pm$ 755± 0.4 0.2  $35.0 \pm$ 0.4 61 10000 ppm 10 8.46± 0.11 15.7 $\pm$ 0.2 44.7± 0.6 52.8±  $18.5 \pm$ 0.3 0.1  $35.0 \pm$ 0.4  $753 \pm$ 65 20000 ppm 10  $8.37 \pm 0.28$  $15.4\pm$ 0.6 44.2± 1.3  $52.8 \pm$ 0.5 18.4 $\pm$ 0.2  $34.9 \pm$ 0.5 710± 70 8.42± 0.19 40000 ppm  $15.5\pm 0.3$ 44.3± 0.9 52.6± 1.0  $18.5 \pm 0.3$ 35.1± 0.5  $730 \pm$ 67 Significant difference;  $*: P \leq 0.05$  $**: P \leq 0.01$ Test of Dunnett

(IICL070) BAIS 3

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1

REPORT TYPE : A1

HEMATOLOGY (SUMMARY) ALL ANIMALS ( 14W)

SEX : FEMALE PAGE: 5 Group Name NO. of RETICULOCYTE PROTHROMBIN TIME APTT Animals % s e c s e c Control 10  $2.1\pm 0.2$ 15.0 $\pm$ 0.6 18.4± 1.3 2500 ppm 10  $2.0 \pm$ 0.2  $14.3 \pm$ 17.1± 2.1 0.7\* 5000 ppm 15.5± 0.6 10  $2.0\pm$ 0.2 17.6± 1.6 10000 ppm 10 2.1± 0.2 14.9 $\pm$ 0.8 16.  $4\pm$  2. 7 20000 ppm 10  $2.0 \pm$ 0.2 15.1± 0.5 16.3± 1.6 40000 ppm 9 2.2± 0.4 15.3  $\pm$  0.4 17.6± 2.5 Significant difference;  $*: P \leq 0.05$ \*\*:  $P \leq 0.01$ Test of Dunnett

(HCL070)

BAIS 3

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1 SEX : FEMALE

REPORT TYPE : A1

HEMATOLOGY (SUMMARY) ALL ANIMALS ( 14W)

PAGE: 6 Group Name NO. of WBC Differential WBC (%) Animals 1 03/ul BASO N BAND N-SEG EOSINO MONO LYMPIIO OTHER Control  $1\pm$ 10 3.38± 1.43 1  $20\pm$ 5 1±  $0\pm$  $2\pm$ 1 5 0土  $76 \pm$ 0 2500 ppm  $2.39 \pm 0.88$ 19±  $1\pm$ 10  $2\pm$ 1  $0\pm$ 75±  $0\pm$ 0 5000 ppm 10 2.71± 1.05  $2\pm$ 1 19± 6 1±  $0\pm$  $3\pm$ 1 . 76± 6  $0\pm$ 0 10000 ppm 1± 10  $2.67 \pm 0.88$  $2\pm$ 1 19± 6  $0\pm$  $2\pm$ 2 0± 76± 0 20000 ppm 10 3.03± 0.81  $2\pm$ 1 19± 1± 0±  $2\pm$  $76\pm$ 7 0± 1 1 0 40000 ppm  $2.83 \pm 0.90$  $2\pm$ 1 18± 5  $1\pm$ 1  $0\pm$  $2\pm$ 1  $76\pm$  $0\pm$ 0 Significant difference;  $*: P \leq 0.05$ \*\* :  $P \leq 0.01$ Test of Dunnett

(IICL070)

BAIS 3

# APPENDIX G 1

BIOCHEMISTRY: SUMMARY, RAT: MALE

BIOCHEMISTRY (SUMMARY) ALL ANIMALS ( 14W)

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1 SEX : MALE

REPORT TYPE : A1

oup Name	NO. of Animals	TOTAL P g/dl	ROTEIN	ALBUMIN g∕dl		∧/G RAT	10	T-BILII mg∕dl	RUBIN	GLUCOSE mg/dl	,	T-CHOLES mg/dl	TEROL	TRIGLYCH mg/dl	ERIDE
Control	10	6.4±	0. 1	4.0±	0.1	1.7±	0. 1	0.13±	0.01	208±	18	68±	5	52±	23
2500 ppm	10	6.2±	0. 2	3.9±	0. 1	1.7±	0. 1	0.13±	0.01	215±	20	62±	4*	58±	31
5000 mqq	9	6.2±	0.3	3.9±	0.2	1.6±	0. 1	0.14±	0. 01	223±	26	64±	6	53±	23
10000 ppm	10	6.2±	0.2	3.9±	0. 1	1.7±	0. 1	0.13±	0.01	210±	17	63±	4	51±	25
20000 ppm	10	6.1±	0.1**	3.8±	0.1*	1.7±	0. 1	0.13±	0.01	199土	14	64±	4	49±	18
40000 ppm	9	6.0±	0.1**	3.7±	0.1**	1.7±	0. 1	0.14±	0.02	194±	19	60±	5**	52±	10

(HCL074)

BAIS 3

ANIMAL : RAT F344/DuCrj MEASURE. TIME : 1

SEX : MALE

BIOCHEMISTRY (SUMMARY) ALL ANIMALS ( 14W)

SEX : MALE	REPORT 1	YPE : A1													PAGE: 2
Group Name	NO. of Animals	PHOSPHO mg/dl	LIPID	GOT IU/l		GPT I U/L	!	LDH IU/	<b>e</b>	ALP I U / L		G-GTP IU/l		CPK IU/l	
Control	10	125±	10	81 ±	17	51±	8	249±	101	237±	16	1±	1	112±	19
2500 ppm	10	119±	11	77±	21	51±	10	249±	84	242±	13	2±	1	116±	21
5000 ppm	9	124±	14	75±	24	48±	9	260±	59	229±	20	2±	1	116±	22
10000 ррт	10	118±	7	64±	14	44土	6	229±	41	238±	16	2±	1	107±	11
20000 թթա	10	118±	6	60±	18	41±	10*	221±	66	221±	15	1±	1	101±	18
40000 ppm	9	115±	6	54±	12**	40±	4*	189±	33	255±	29	2±	1	107±	15
Significant	difference;	*: P ≤ 0	. 05	**: P ≤ 0.0	1			Test of Dur	nnett						

(IICL074)

BAIS 3

ANIMAL : RAT F344/DuCrj MEASURE. TIME : 1

SEX : MALE

REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY) ALL ANIMALS ( 14W)

Group Name	NO. of Animals	UREA NI mg∕dl	TROGEN	CREATIN mg/dl	ILNE	SODIUM m Eq / L		POTASSI m Eq / )		CHLORIDE m Eq / L		CALCIUM mg/dl	[	INORGAN mg/dl	IC PHOSPHORU
Control	10	17.7±	1.6	0.6±	0. 1	142±	1	3.3±	0.3	105±	1	10.4生	0.2	5.6±	0. 6
2500 ррш	10	19.4±	2. 1	0.6生	0. 1	141±	1	3.3±	0.3	105±	1	10.3±	0.2	5.3±	0.6
5000 ppm	9	20.1±	1. 1**	0.6±	0.1	140±	2	3.4±	0.4	105±	1	10.3±	0.3	5.6±	0.9
10000 ppm	10	20.5±	0. 9**	0.6±	0. 1	141士	1	3.4±	0.1	105±	1	10.2±	0.2	5.2±	0.6
20000 ррт	10	20.4±	1.6**	0.5±	0.0	141±	1	3.4±	0.2	105±	1	10.1±	0.2	5.3±	0.6
40000 ppm	9	21.2±	1.8**	0.5±	0. 1	140±	1	3.5±	0.2	106±	1	10.1±	0.3	5.3±	0.7

PAGE: 3

BAIS 3

(IICL074)

# APPENDIX G 2

BIOCHEMISTRY: SUMMARY, RAT: FEMALE

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1 SEX : FEMALE

BIOCHEMISTRY (SUMMARY) ALL ANIMALS ( 14W)

oup Name	NO. of Animals	TOTAL P g/dl	ROTEIN	ALBUMIN g∕dl		A/G RAT	10	T-BILI mg∕dl		GLUCOSE mg/dl		T-CHOLES mg/dl	STEROL	TRIGLYCE mg/dl	RLDE
Control	10	6.1±	0.3	3.8±	0.2	1.6±	0. 1	0.16±	0.02	147±	15	69±	11	16±	3
2500 ppm	10	6.0±	0.1	3.7±	0.1	1.6±	0. 1	0.16±	0. 01	157±	17	71±	5	16±	4
5000 ppm	10	5.9±	0.2	3.6±	0.1*	1.6±	0. 1	0.16±	0.01	162±	21	68±	5	16 <sup>-</sup> ±	5
10000 ppm	10	5.8±	0.3**	3.6±	0. 2**	1.6±	0. 1	0.15±	0.01	170±	24	70±	8	17±	5
20000 ррт	10	5.7±	0.2**	3.5±	0.1**	1.6±	0. 1	0.16±	0.01	161±	28	66±	6	18±	4
40000 ppm	9	5.6±	0.2**	3.5±	0.1**	1.6±	0.1	0.15±	0. 02	160±	22	66±	6	18±	6

(IICL074) BAIS 3

ANIMAL : RAT F344/DuCrj

MEASURE. TIME : 1 SEX : FEMALE

REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY) ALL ANIMALS ( 14W)

A - I Did IDD	KDI OKI 1														
oup Name	NO. of Animals	PHOSPHOI mg/dl	JPID	GOT IU/2		GPT IU/l		LDH I U / L		ALP I U / L		G-GTP I U/l		CPK I U / £	
Control	10	141±	14	74±	22	46±	32	294±	87	169±	18	3±	1	119±	22
2500 ppm	10	141±	9	78±	22	41±	16	366±	133	164±	18	2±	1	166±	85
5000 ppm	10	136±	8	64±	6	33±	5	354±	152	167±	13	2±	1	147±	45
10000 ppm	10	139±	13	63±	7	31±	3	316±	147	170±	16	2±	1	134±	44
20000 թթա	10	133±	7	62±	7	32±	4	318±	134	173±	13	2±	1	139±	46
40000 ppm	9	134±	13	61±	9	34±	8	336±	201	203±	15**	3±	1	141±	45

(IICL074)

BAIS 3

BIOCHEMISTRY (SUMMARY) ALL ANIMALS (14W)

ANIMAL : RAT F344/DuCrj MEASURE. TIME : 1

SEX : FEMALE

REPORT TYPE : A1

PAGE: 6

Group Name	NO. of Animals	UREA NI mg∕dl	TROGEN	CREATIN mg/dl	INE	SODIUM m Eq / L		POTASSIU mEq/l		chloride m Eq / l		CALCIUW mg∕dl		INORGAN mg∕dl	IC PHOSPHORU
Control	10	20.0±	1.8	0.6±	0.1	139±	1	3.6±	0.3	108±	2	9.9±	0. 2	5.2±	0.8
2500 ppm	10	20.2±	1. 4	0.6±	0.1	139±	2	3.6±	0.1	107±	1	9.9±	0.3	4.9±	1. 0
5000 ppm	10	22.1±	1.3*	0.6±	0.1	139±	1	3.6±	0.2	107±	1	9.7±	0.4	4.9±	1.2
10000 ppm	10	21.6±	1.5	0.6±	. 0. 1	139±	1	3.5±	0.3	107±	1	9.7±	0.3	5.0±	0.5
20000 ррт	10	22.1±	2. 3*	0.6±	0.1	139±	1	3.6±	0.4	107±	1	9.7±	0.3	5.1±	0. 5
40000 ppm	9	22.3±	1.5*	0.6±	1.0	139±	1	3.6±	0.3	106±	i	9.7±	0.2	5.5±	0.6
Significant	difference;	*: P ≤ (	). 05	**: P ≤ 0.0	)1			Test of Dun	nett						

(IICL074) BAIS 3

# APPENDIX H 1

URINALYSIS : SUMMARY, RAT : MALE

URINALYSIS

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1

SEX : MALE

REPORT TYPE : A1

PAGE: 1

oup Name	NO. of	На								Protei	n				Gluce	se_			Ket	one	body				Bi	lirub	in	
•	Animals	5. (	6.	6.5	7.0	7.5	8.0	8.5	CHI	- ±	+	2+ 3	4+	CIII	- ±	: 1	2+ 3+	4+ CHI		± -	- 24	3+	41	CIII	_	+ 2	3+	CIII
Control	10	0	0	0	0	0	5	5		0 0	9	1	0 0		10	) 0	0 0	), 0	6	2	1 1	0	0		10	0	0 0	
2500 բբա	10	0	0	0	1	0	5	4		0 0	6	4	0 0		10	0	0 (	0	1	7	2 0	0	0		10	0	0 0	
5000 ppm	10	0	0	0	0	1	6	3		0 0	6	4	0 0		10	0	0 (	0	0	3	6 1	0	0	*	10	0	0 0	
10000 ppm	10	0	0	0	0	5	3	2	*	0 0	1	9	0 0	**	10	0 0	0 (	0 0	0	5	3 2	0	0	*	10	0	0 0	
20000 ppm	10	0	0	0	0	4	4	2		0 0	2	8	0 0	**	10	0 0	0 0	0 0	0	4	3 3	0	0	*	10	0	0 0	
40000 ppm	10	0	0	0	2	5	0	3	**	0 0	3	7	0 0	**	10	0 0	0 (	0 0	1	4	3 1	. 1	0		10	0	0 0	

BAIS 3

(IICL101)

URINALYSIS

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1

SEX : MALE		TYPE : AI			PAGE: 2
Group Name	NO. of Animals	Occult blood - ± - 2+ 3+ CIII	Urobilinogen ± + 2+ 3+ 4+ CHI		
Control	10	10 0 0 0 0	10 0 0 0 0		
2500 բբա	10	10 0 0 0 0	10 0 0 0 0		
5000 ppm	10	9 1 0 0 0	10 0 0 0 0		
10000 ppm	10	10 0 0 0 0	10 0 0 0 0		
20000 ppm	10	10 0 0 0 0	10 0 0 0 0		
40000 ppm	10	10 0 0 0 0	10 0 0 0 0		
Significan	t difference	; *: P ≤ 0.05 **		Test of CHI SQUARE	
(IICL101)					BAIS 3

# APPENDIX H 2

URINALYSIS : SUMMARY, RAT : FEMALE

UR1NALYS1S

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1

SEX : FEMALE

REPORT TYPE : A1

PAGE: 3

roup Name	NO. of	pH_							F	rot	ein_					G	Luco	se_			_	Ke	tone	e bo	dy			-	Bi	liru	ıbin		
	Animals	5.0	6.0	6.5	7. 0	7. 5	8. 0	8.5 CIII		- ±	<u>-</u> -ŀ	- 2	1 3	41	CIII	-	· ±	+	2+	31	4+ CIII		±	+	24	3+ 4	4	CHI		- -	24	3+	CHI
Control	10	0	0	0	0	0	6	4		0	3 7	7	0 (	0 0		1:	0 0	0	0	0	0	4	6	0	0	0	0		10	0	0	0	
2500 բբա	10	0	0	0	0	0	8	2						0 0		1	0 0	0	0	0	0	3	7	0	0	0	0		10	0	0	0	
5000 ppm	10	0	0	0	0	2	4	4		0	0 (	6	4	0 0	*	1	0 0	0	0	0	0	0	10	0	0	0	0	*	10	0	0	0	
10000 ppm	10	0	0	1	0	1	5	3		0	0 .	4	6	0 0	**	1	0.0	0	0	0	0	0	10	0	. 0	0	0	*	10	0	0	0	
20000 ррт	10	0	0	0	0	4	4	2		0	0 -	4	6	0 0	**	1	0 (	0	0	0	0	0	9	1	0	0	0		10	0	0	0	
40000 ppm	9	0	0	0	1	1	6	1		0	0	2	7	0 0	**		9 (	0	0	0	0	0	6	3	0	0	0	*	g	0	0	0	

(IICL101) BAIS 3

UR1NALYS1S

ANIMAL : RAT F344/DuCrj

MEASURE. TIME: 1

SEX : FEMALE

REPORT TYPE : A1

Group Name	NO. of Animals	Occult blood - ± + 2+ 3+ CHI	Urobilinogen ± + 2: 3: 4: CNI		
Control	10	10 0 0 0	10 0 0 0 0		
2500 թթա	10	10 0 0 0 0	10 0 0 0 0		
5000 ppm	10	10 0 0 0 0	10 0 0 0 0		
10000 ppm	10	10 0 0 0 0	10 0 0 0 0		
20000 ppm	10	10 0 0 0 0	10 0 0 0 0		
40000 ppm	9	9 0 0 0 0	9 0 0 0 0		
Significan	t difference	; *: P ≤ 0.05 **	$P \leq 0.01$ Test of C	CHI SQUARE	
(1101 101)					DATC

BAIS 3

PAGE: 4

(IICL101)

# APPENDIX I 1

GROSS FINDINGS : SUMMARY, RAT : MALE : ALL ANIMALS

ANIMAL : RAT F344/DuCrj

GROSS FINDINGS (SUMMARY) ALL ANIMALS (0- 14W)

REPORT TYPE : A1

SEX : MALE

L ANIMALS (0- 14W)

Organ	Findings	Group Name NO. of Animals	Control 10 (%)	2500 ppm 10 (%)	5000 ppm 10 (%)	10000 ppm 10 (%)
iver	herniation		0 ( 0)	1 (10)	2 ( 20)	0 ( 0)
PT080)						

ANIMAL : RAT F344/DuCrj

GROSS FINDINGS (SUMMARY) ALL ANIMALS (0- 14W)

REPORT TYPE : A1

SEX : MALE

Organ	Findings	Group Name 20000 p NO. of Animals 10 (%)	pm 40000 ppm 10 (%)	
liver	herniation	0 ( 0	0 ( 0)	
(HPT080)				BAIS 3

# APPENDIX I 2

GROSS FINDINGS : SUMMARY, RAT : FEMALE : ALL ANIMALS

ANIMAL : RAT F344/DuCrj

GROSS FINDINGS (SUMMARY)

REPORT TYPE : A1 ·

SEX : FEMALE

ALL ANIMALS (0- 14W)

liver hern	niation	1 (10)	0 ( 0)	3 (30)	2 (20)
vary cyst	t	0 ( 0)	1 (10)	0 ( 0)	0 ( 0)

ANIMAL : RAT F344/DuCrj

GROSS FINDINGS (SUMMARY) ALL ANIMALS (0- 14W).

REPORT TYPE : A1

SEX : FEMALE

Organ	Findings	Group Name NO. of Animals	20000 ppm 10 (%)	40000 ppm 10 (%)	
liver	herniation		2 (20)	4 (40)	
ovary	cyst		0 ( 0)	0 ( 0)	
		,			
(HPT080)					BAIS 3

# APPENDIX I 3

GROSS FINDINGS : SUMMARY, RAT : FEMALE : SACRIFICED ANIMALS

ANIMAL : RAT F344/DuCrj

GROSS FINDINGS (SUMMARY) SACRIFICED ANIMALS ( 14W)

REPORT TYPE : AI

SEX : FEMALE

Organ	Findings	Group Name NO. of Animals	Control 10 (%)	2500 ppm 10 (%)	5000 ppm 10 (%)	10000 ppm 10 (%)
ver	herniation		1 (10)	0 ( 0)	3 (30)	2 (20)
ary	cyst		0 ( 0)	1 (10)	0 ( 0)	0 ( 0)

ANIMAL : RAT F344/DuCrj

GROSS FINDINGS (SUMMARY) SACRIFICED ANIMALS (14W)

REPORT TYPE : A1

SEX : FEMALE

Organ	Findings	Group Name NO. of Animals	20000 ppm 10 (%)	40000 ppm 9 (%)	
liver	herniation		2 (20)	3 (33)	
ovary	cyst		0 ( 0)	0 ( 0)	
(HPT080)					BAIS 3

## APPENDIX I 4

GROSS FINDINGS : SUMMARY, RAT : FEMALE : DEAD AND MORIBUND ANIMALS

ANIMAL : RAT F344/DuCrj

GROSS FINDINGS (SUMMARY)

REPORT TYPE : A1 SEX : FEMALE DEAD AND MORIBUND ANIMALS (0- 14W)

SEX	: FEMALE				PAGE: 2
Organ		Group Name NO. of Animals	20000 ppm 0 (%)	40000 ppm 1 (%)	
liver	herniation		- ( -)	1 (100)	
(HPT080)					BAIS 3

# APPENDIX J 1

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : MALE

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1

REPORT TYPE : A SEX : MALE UNIT: g ORGAN WEIGHT: ABSOLUTE (SUMMARY) SURVIVAL ANIMALS ( 14W)

PAGE: 1

	Animals	Body Weight		TIIYMUS		ADRE	ADRENALS TESTES		ES	HEART			LUNGS	
Control	10	308±	11	0.226±	0.036	0.047±	0.004	3.043±	0. 175	0.949±	0.064	1.061±	0.053	
2500 ppm	10	294±	14	0.220±	0.031	0.050±	0.010	3. 087±	0.146	0.929±	0.060	1.006±	0. 047	
5000 թբա	10	285±	11**	0.210±	0.022	0.048±	0.004	3.029±	0.094	0.885±	0. 036*	1.000±	0.044	
10000 ppm	10	284±	14**	0.210±	0. 032	0.047±	0.004	3.030±	0. 088	0.875±	0.046*	0.990±	0.048*	
20000 ppm	10	274±	14**	0.189±	0.019*	0.046±	0.003	2.975±	0. 158	0.864±	0. 051**	0.979±	0.076**	
40000 ppm	10	256±	19**	0.174±	0.028**	0.044±	0.003	2.919±	0. 107	0.799±	0. 057**	0.936±	0.063**	

(HCL040)

BAIS 3

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1

SEX : MALE UNIT: g ORGAN WEIGHT: ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS ( 14W)

roup Name	NO. of Animals	KIDN	KIDNEYS		EEN	LIVI	ER	BRA	N	-	
Control	10	1.834±	0.064	0.572±	0. 029	7.632±	0. 219	1.920±	0. 037		
2500 ррт	10	1.817±	0. 111	0.540±	0. 041	7. 276±	0.430	1.920±	0.044		
5000 բբա	10	1.803±	0.084	0.530±	0. 034	7.141±	0.383	1.901±	0. 043		
10000 ppm	10	1.837±	0. 116	0.523±	0.032*	6.918±	0.375**	1.908±	0.038		
20000 ppm	10	1.820±	0. 127	0.522±	0.031*	6.794±	0. 497**	1.899±	0. 037		
40000 ppm	10	1.709±	0. 142	0.498±	0.052**	6.158±	0.688**	1.858±	0.058*		

(HCL040)

BAIS 3

# APPENDIX J 2

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : FEMALE

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1 SEX : FEMALE UNIT: g ORGAN WEIGHT: ABSOLUTE (SUMMARY) SURVIVAL ANIMALS ( 14W)

PAGE: 3

Group Name	NO. of Animals	Body W	leight	TIIYM	JS	ADRE	NALS	OVAR	IES	HEAR	<u> </u>	LUNGS	5
Control	10	157±	12	0.168±	0. 028	0.055±	0.005	0.109±	0. 016	0.596±	0.041	0.753±	0.046
2500 ppm	10	160±	10	0.177±	0. 023	0.052±	0.005	0.110±	0.019	0.593±	0. 033	0.753±	0.044
5000 բբա	10	161±	10	0. 162±	0.018	0.052±	0.004	0.105±	0.010	0.576±	0. 031	0.734±	0.037
10000 ppm	10	160±	7	0.166±	0.008	0.049±	0.004**	0.096±	0.012	0.582±	0.032	0.744±	0. 036
20000 ppm	10	153±	11	0.160±	0.018	0.050±	0.004*	0.098±	0.010	0.574±	0.040	0.720±	0. 028
40000 ppm	9	153±	12	0.151±	0.016	0.047±	0.006**	0.094±	0.016	0.561±	0.042	0.715±	0. 041
Significan	t difference;	*: P ≤ 0.	05	** : P ≤ 0.01			Test	of Dunnett					

(HCL040)

BAIS 3

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1 SEX : FEMALE UNIT: g ORGAN WEIGHT: ABSOLUTE (SUMMARY) SURVIVAL ANIMALS ( 14W)

PAGE: 4

roup Name	NO. of Animals	KIDN	VEYS	SPLE	BEN	LIVI	ER	BRAJ	
Control	10	1.087±	0. 069	0.371±	0. 044	3.883±	0. 343	1.747±	0.054
2500 ррт	10	1.160±	0.048	0.396±	0.052	3.844±	0. 285	1.746±	0. 031
5000 руш	10	1.147±	0. 076	0.373±	0. 025	3.737±	0. 194	1.754±	0.047
10000 ppm	10	1.199±	0.056**	0.376±	0.012	3.778±	0. 221	1.786±	0.049
20000 ppm	10	1.168±	0.035*	0.365±	0. 030	3.652±	0. 269	1.751±	0. 038
40000 ppm	9	1.175±	0.083*	0.348±	0. 028	3.553±	0. 270	1.753±	). 060

(HCL040)

BAIS 3

# APPENDIX K 1

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : MALE

(13-WEEK STUDY)

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1 SEX : MALE UNIT: % ORGAN WEIGHT: RELATIVE (SUMMARY)
SURVIVAL ANIMALS (14W)

PAGE: 1

Group Name	NO. of Animals	Body Weight (g)	TIIYMUS	ADRENALS	TESTES	HEART	LUNGS
Control	10	308± 11	0.073± 0.011	0.015± 0.001	0.990± 0.054	0.308± 0.012	0.345± 0.011
2500 ррш	10	294± 14	0.075± 0.008	0.017± 0.004	1.050± 0.032	0.316± 0.016	0.342± 0.011
5000 ррт	10	285± 11**	0.074± 0.006	0.017± 0.001*	1.063± 0.028*	0.311± 0.015	0.351± 0.014
10000 ppm	10	284± 14**	0.074± 0.009	0.016± 0.002	1.067± 0.030*	0.308± 0.013	0.348± 0.009
20000 ppm	10	274± 14**	0.069± 0.006	0.017± 0.001*	1.087± 0.056**	0.316± 0.012	0.357± 0.016
40000 ppm	10	256± 19**	0.068± 0.007	0.017± 0.002**	1.147± 0.081**	0.313± 0.009	0.367± 0.012**

(HCL042)

BAIS 3

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1 SEX : MALE

UNIT: %

ORGAN WEIGHT: RELATIVE (SUMMARY)
SURVIVAL ANIMALS ( 14W)

roup Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN	
Control	10	0.596± 0.013	0.186± 0.005	2.482± 0.069	0.624± 0.019	
2500 ppm	10	0.618± 0.021	0.183± 0.006	2.474± 0.090	0.654± 0.034	
5000 ррш	10	0.633± 0.024**	0.186± 0.009	2.506± 0.103	0.668± 0.020*	
10000 ppm	10	0.646± 0.028**	0.184± 0.004	2. 433± 0. 032	0.673± 0.034**	
20000 ppm	. 10	0.664± 0.024**	0.191± 0.006	2.479± 0.088	0.695± 0.026**	
40000 ppm	10	0.669± 0.026**	0.195± 0.009*	2.405± 0.139	0.730± 0.045**	

(HCL042)

BAIS 3

# APPENDIX K 2

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1 SEX : FEMALE UNIT: % ORGAN WEIGHT: RELATIVE (SUMMARY)
SURVIVAL ANIMALS ( 14W)

PAGE: 3

oup Name	NO. of Animals	Body Weight (g)	TIIYMUS	ADRENALS	OVARIES	HEART	LUNGS
Control	10	157± 12	0.107± 0.013	0.035± 0.003	0.069± 0.007	0.380± 0.021	0.481± 0.025
2500 ppm	10	160± 10	0.111± 0.012 0.032± 0.004 0.069± 0.014 0.370± 0.013		0.470± 0.016		
5000 ppm	10	161± 10	0.100± 0.007	0.100± 0.007		0.456± 0.018	
10000 ppm	10	160± 7	0.103± 0.006	0.030± 0.003**	0.060± 0.008	0.363± 0.013	0.464± 0.018
20000 ppm	10	153± 11	0.104± 0.010	0.033± 0.004	0.064± 0.006	0.375± 0.014	0.471± 0.027
40000 ppm	9	153± 12	0.099± 0.009	0.031± 0.005*	0.061 ± 0.008	0.368± 0.018	0.470± 0.028

(HCL042)

BAIS 3

ANIMAL : RAT F344/DuCrj

REPORT TYPE : AI SEX : FEMALE UNIT: % ORGAN WEIGHT: RELATIVE (SUMMARY)
SURVIVAL ANIMALS (14W)

PAGE: 4

roup Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN	
Control	10	0.695± 0.036	0.237± 0.020	2. 475± 0. 094	1.118± 0.070	
2500 ррт	10	0.725± 0.037	0.247± 0.025	2.398± 0.097	1.093± 0.058	
5000 ррт	10	0.712± 0.031	0.231± 0.012	2.319± 0.076**	1.090± 0.052	
10000 ppm	10	0.748± 0.023*	0.235± 0.010	2.356± 0.112*	1.114± 0.043	
20000 ppm	10	0.764± 0.055**	0.238± 0.013	2.380 ± 0.058	1.146± 0.073	
40000 ppm	9	0.771± 0.043**	0.229± 0.017	2.328± 0.046**	1.152± 0.067	

(HCL042)

BAIS 3

# APPENDIX L 1

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS: SUMMARY

RAT: MALE: ALL ANIMALS

(13-WEEK STUDY)

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)

ALL ANIMALS (0- 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1

SEX : MALE

irgan	Findings	Group Name   Control	5000 ppm 10 1 2 3 4 (%) (%) (%) (%)	10000 ppm 10 1 2 3 4 (%) (%) (%) (%)
Respiratory	system)			
asal cavit	mineralization	<10> 0 0 0 0 0 0 0 0 0 0 0	1 0 0 0 (10) (0) (0) (0)	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)
Hematopoiet	ic system)			
pleen	deposit of hemosiderin	(100) ( 0) ( 0) ( 0	<10> 10 0 0 0 (100) ( 0) ( 0) ( 0)	<10> 10 0 0 0 (100) ( 0) ( 0) ( 0)
Circulatory	system)			
ear t	granulation	<10> 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	2 0 0 0 ( 20) ( 0) ( 0) ( 0)	<10> 4 0 0 0 (40) (0) (0) (0)
Digestive s	ystem)			
iver	herniation	(0)(0)(0)(0	2 0 0 0 ( 20) ( 0) ( 0) ( 0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)
rade (a > b (c)	1: Slight 2: Moderate a: Number of animals examined at the b: Number of animals with lesion c: b / a * 100 difference: *: P ≤ 0.05 **: P			

ANIMAL : RAT F344/DuCrj

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)

ALL ANIMALS (0- 14W)

REPORT TYPE : A1

SEX : MALE

PAGE: 2

Organ		p Name 20000 ppm of Animals on Study 10 le	40000 ppm 10 1 2 3 4 (%) (%) (%) (%)	
{Respiratory	system]			
nasal cavit	mineralization	<10> 0 0 0 0 0 0 0 0 0 0 0	(10) 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	
{Hematopoiet	ic system}			
spleen	deposit of hemosiderin	10 0 0 0 (100) ( 0) ( 0) ( 0)	(10) 10 0 0 0 (100) ( 0) ( 0) ( 0)	
(Circulatory	system)			
lieart	granulation	3 0 0 0 (30) (0) (0) (0)	(10) 1 0 0 0 (10) (0) (0) (0)	
{Digestive s	ystem)			
liver	herniation	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	
Grade < a > b (c) Significant	1: Slight 2: Moderate 3: M a: Number of animals examined at the site b: Number of animals with lesion c: b / a * 100 difference: $*: P \le 0.05$ **: $P \le 0.$			

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1

ALL ANIMALS (0- 14W)

SEX : MALE PAGE: 3 Group Name Control 2500 ppm 5000 ppm 10000 ppm No. of Animals on Study 10 10 10 10 Grade 3 Findings\_ (%) (%) (%) (Digestive system) liver <10> <10> <10> <10> granulation 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) (Urinary system) kidney <10> <10> <10> <10> basophilic change 0 0 0 0 3 0 0 0 3 0 0 0 3 0 0 0 (0)(0)(0)(0) (30) (0) (0) (0) (30) (0) (0) (0) (30) (0) (0) (0) eosinophilic body 0 10 0 0 10 0 0 10 0 0 0 (100) ( 0) ( 0) ( 0) (100) ( 0) ( 0) ( 0) (100) ( 0) ( 0) ( 0) (100) ( 0) ( 0) ( 0) hyaline cast 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 (0)(0)(0)(0) (0)(0)(0)(0) (10) (0) (0) (0) (0)(0)(0)(0) papillary necrosis 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 (0)(0)(0)(0) (0)(0)(0)(0) (10) (0) (0) (0) (0)(0)(0)(0) mineralization:papilla 1 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 (10) (0) (0) (0) (0)(0)(0)(0) (10) (0) (0) (0) (0)(0)(0)(0) {Endocrine system} pituitary <10> <10> <10> <10> Rathke pouch 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 (10) (0) (0) (0) (10) (0) (0) (0) (0)(0)(0)(0) (0)(0)(0)(0) Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe < a > a: Number of animals examined at the site ь b : Number of animals with lesion (c) c:b/a \* 100 Significant difference;  $*: P \leq 0.05$  \*\*:  $P \leq 0.01$  Test of Chi Square

STUDY NO. : 0426 ANIMAL : RAT F344/DuCrj HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)

ALL ANIMALS (0- 14W)

REPORT TYPE : A1

SEX : MALE

Organ	Group No. of Grade Findings	Name 20000 ppm Animals on Study 10  1 2 3 4 (%) (%) (%) (%)	40000 ppm 10 1 2 3 4 (%) (%) (%)		
{Digestive	system)				
liver	granulation	1 0 0 0 ( 10) ( 0) ( 0) ( 0)	<10> 1 0 0 0 (10) (0) (0) (0)		
{Urimary sy	stem)				
kidney	basophilic change	2 0 0 0 ( 20) ( 0) ( 0) ( 0)	<10> 4 0 0 0 (40) (0) (0) (0)		
	eosinophilic body	10 0 0 0 (0) (100)	10 0 0 0 (100) (100) (100)		
	hyaline cast	2 0 0 0 0 (20) (0) (0) (0)	1 0 0 0 0 (10) (10) (10)		
	pepillary necrosis	0 0 0 0 0 (0) (0)	2 0 0 0 0 (20) (0) (0) (0)	. ,	
	mineralization:papilla	1 0 0 0 0 (10) (10) (10)	1 0 0 0 0 (10) (10) (10)		
{Endocrine	system}				
pituitary	Rathke pouch	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	1 0 0 0 ( 10) ( 0) ( 0) ( 0)		
Grade <a>a&gt; b (c) Significan</a>	1: Slight 2: Moderate 3: Mar a: Number of animals examined at the site b: Number of animals with lesion c: b / a * 100 t difference; *: P ≤ 0.05 **: P ≤ 0.01				
(HPT150)					BATSS

ANIMAL : RAT F344/DuCrj

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)

ALL ANIMALS (0 - 14\)

REPORT TYPE : A1
SEX : MALE

PAGE: 5

	No. Grad		2500 ppm 10 1 2 3 4	5000 ppm 10 1 2 3 4	10000 ppm 10 1 2 3 4
)rgan	Findings	(%) (%) (%)	(%) (%) (%) (%)	(%) (%) (%) (%)	(%) (%) (%) (%)
Endocrine sy	vstem)				
hyroid	ultimobranchial body remanet	( 0) ( 0) ( 0) ( 0)	\(\frac{10}{10}\) \(\begin{array}{cccccccccccccccccccccccccccccccccccc	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)
{Keproductive	e system)				
estis	atrophy	( 0) ( 0) ( 0) ( 0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)
rostate	inflammation	<10> 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	<10> 0 0 0 0 0 0 0 0 0 0 0	<10> 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	<pre></pre>
(Special sem	se organs/appendage}				
larder gl	lymphocytic infiltration	2 0 0 0 ( 20) ( 0) ( 0) ( 0)		1 0 0 0 ( 10) ( 0) ( 0) ( 0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)
Grade (a) b (c)	1: Slight 2: Moderate 3: Na : Number of animals examined at the site b: Number of animals with lesion c: b / a * 100	larked 4: Severe			

(HPT150)

BA1S3

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)

ALL ANIMALS (0- 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1

SEX : MALE

Organ		pp Name 20000 ppm of Animals on Study 10 le	40000 ppm 10 1 2 3 4 (%) (%) (%) (%)	
{Endocrine s	ystem}			
thyroid	ultimobranchial body remanet	0 0 0 0 0 ( 0) ( 0) ( 0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	
{Keproductiv	e system)			
testis	atrophy	1 0 0 0 ( 10) ( 0) ( 0) ( 0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	
prostate	inflammation	1 0 0 0 (10) (10) (10) (10)	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	
{Special ser	nse organs/appendage)			
Harder gl	lymphocytic infiltration	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	1 0 0 0 (10) (0) (0) (0)	
Grade (a) b (c) Significant	1: Slight 2: Moderate 3: Number of animals examined at the site b: Number of animals with lesion c: b/a*100 difference; *: P≤0.05 **: P≤0.	darked 4: Severe		-

# APPENDIX L 2

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS: SUMMARY

RAT : FEMALE : ALL ANIMALS

(13-WEEK STUDY)

(HPT150)

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1
SEX : FEMALE

ALL ANIMALS (0- 14W)

rgan	И	roup Name to. of Animals on Study trade	Con 10 2 (%)	3 (%)	<u>4</u> (%)	1 (%)	2500 10 2 (%)	) ppm ) 3 (%)	<u>4</u> (%)	1 (%)	5000 10 2 (%)		<u>4</u> (%)	1 (%		3 (%)	<u>4</u> (%)
Respiratory s	ystem)																
ung	ossecus metaplasia	( 0)	<10 0 ( 0) (	0	0	1 ( 10)	<10 0 ( 0)	0 ( 0) (	0 0)	0 ( 0)	<100 0 0 (	0	0 ( 0)	0 ( 0		0 (	0 0)
Hematopojetic	; system)																
one marrow	granulation	3 ( 30)	<10 0 ( 0)	0	0 ( 0)	2 ( 20)	0 ( 0)	0> ( 0) (		1 ( 10)		0	0 ( 0)	( 0	<10> 0 0) (	, 0 0) (	0
ymph node	lymphadenitis	0 ( 0)	<10 0 ( 0)	0	0	0 ( 0)	<1 0 ( 0)		0 (0)	0 ( 0)	<10 0 ( 0) (	0	0 ( 0)	( (	<10> 0 0) (	) 0 0) (	0 ( 0)
pleen	doposit of homosidorin	10 (100)	(10) ( 0)	0	0 ( 0)	10 (100)	(0)		0	10 (100)	<10 0 ( 0) (	0	0 ( 0)	10 (100		) 0 0) (	0 ( 0)
Circulatory	system)												•				
neart	granulation	1 ( 10)	(1 0 (0)	0	0 ( 0)	0 ( 0)	0	0 ( 0)	0	0 ( 0)	<10 0 ( 0)	0			<100 0 0) (		0
Grade ( a > b ( c )	1: Slight 2: Moderate 3 a: Number of animals examined at the si b: Number of animals with lesion c: b/a * 100	: Marked 4 : Sever te	e														

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)

ALL ANIMALS (0- 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1

SEX : FEMALE

PAGE: 8

Organ		Group Name 20000 ppm  No. of Animals on Study 10  Grade 1 2 3 4  (%) (%) (%) (%) (%)	40000 ppm 10 1 2 3 4 (%) (%) (%) (%)	
{Respiratory s	system)			
Iung	ossecus metaplasia	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<pre></pre>	
{Hematopoieti	c system}			
bone marrow	granulation	(10) 0 0 0 0 (0) (0) (0) (0)	<10> 2	
lymph node	lymphadenitis	(10) ( 0) ( 0) ( 0)	(10) 1 0 0 0 (10) (0) (0) (0)	
spleen	deposit of hemosiderin	10 0 0 0 (100) ( 0) ( 0) ( 0)	\$ 0 0 0 (90) (0) (0) (0)	
{Circulatory	system)			
heart	granulation	0 0 0 0 0 0 ( 0) ( 0) ( 0)	(10) 1 0 0 0 (10) (0) (0) (0)	
Grade <a>&gt; b (c) Significant o</a>	1: Slight 2: Moderate a: Number of animals examined at the b: Number of animals with lesion c: b / a * 100 difference: *: P ≤ 0.05 **: P	·		

(HPT150)

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)

ANIMAL : RAT F344/DuCrj

REPORT TYPE: A1

SEX : FEMALE

ALL ANIMALS (0- 14W)

Group Name 2500 ppm 5000 ppm 10000 ppm Control No. of Animals on Study 10 10 10 10 3 Grade 3 (%) (%) (%) (%) (%) (%) (%) (%) Findings\_ (Digestive system) liver <10> <10> <10> <10> herniation 1 0 0 0 0 0 0 3 0 0 0 2 0 0 0 0 (10) (0) (0) (0) (0)(0)(0)(0) (30) (0) (0) (0) (20) (0) (0) (0) granulation 1 0 0 0 0 0 0 0 0 0 0 0 1 (20) (0) (0) (0) (10) (0) (0) (0) (10) (0) (0) (0) (0)(0)(0)(0) {Urinary system} kidney <10> <10> <10> <10> 0 0 0 0 0 0 0 0 0 infarct 0 0 0 (10) (0) (0) (0) (0)(0)(0)(0) (0)(0)(0)(0) (0)(0)(0)(0) basophilic change (0)(0)(0)(0) (10) (0) (0) (0) (0)(0)(0)(0) (0)(0)(0)(0) hvaline cast (0)(0)(0)(0) (0)(0)(0)(0) (20) (0) (0) (0) (0)(0)(0)(0) papillary necrosis 0 0 0 (0)(0)(0)(0) (0)(0)(0)(0) (0)(0)(0)(0) (0)(0)(0)(0) mineralization:cortico-medullary junction 5 0 0 0 4 0 0 0 0 0 0 0 \* 3 0 0 0 (50) (0) (0) (0) (40) (0) (0) (0) (0)(0)(0)(0) (30) (0) (0) (0) Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe < a > a : Number of animals examined at the site b b: Number of animals with lesion (c) c:b/a \* 100 Significant difference;  $*: P \le 0.05$  \*\*:  $P \le 0.01$  Test of Chi Square

SEX

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)

ALL ANIMALS (0- 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE: A1

: FEMALE

Group Name 20000 ppm 40000 ppm No. of Animals on Study 10 10 3 Findings\_ (%) (Digestive system) liver <10> <10> 0 0 0 4 0 0 0 hernistion (20) (0) (0) (0) (40) (0) (0) (0) 0 0 0 granulation 0 0 (0)(0)(0)(0) (30) (0) (0) (0) {Urinary system} <10> <10> kidney 0 0 0 0 0 0 0 infarct (0)(0)(0).(0) (0)(0)(0)(0) basophilic change 0 0 0 0 (0)(0)(0)(0) (0)(0)(0)(0) 0 0 1 0 0 0 3 0 hyaline cast (30) (0) (0) (0) (10) (0) (0) (0) 5 0 0 0 \* papillary necrosis 2 0 0 0 (20) (0) (0) (0) (50) (0) (0) (0) 2 0 0 0 4 0 0 0 mineralization:cortico-medullary junction (20) (0) (0) (0) (40) (0) (0) (0) Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe (a) a: Number of animals examined at the site b: Number of animals with lesion b (c) c:b/a\*100

Significant difference ; \* : P  $\leq$  0.05 \*\* : P  $\leq$  0.01 Test of Chi Square

ANIMAL : RAT F344/DuCrj

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)

ALL ANIMALS (0 - 14W)

REPORT TYPE : A1

PAGE: 11 SEX : FEMALE

Organ	•	O Name Control  of Animals on Study 10  a 1 2 3 4  (%) (%) (%) (%)	2500 ppm 10 1 2 3 4 (%) (%) (%)	5000 ppm 10 1 2 3 4 (%) (%) (%) (%)	10000 ppm 10 1 2 3 4 (%) (%) (%) (%)
{Urinary sys	tem}				
kidnoy	mineralization:papilla	1 0 0 0 ( 10) ( 0) ( 0) ( 0)	2 0 0 0 ( 20) ( 0) ( 0) ( 0)	<10> 2 0 0 0 ( 20) ( 0) ( 0) ( 0)	<pre></pre>
{Reproductiv	re system)				
ovary	cyst	(10) 0 0 0 0 (0) (0) (0) (0)	1 0 0 0 (10) (0) (0) (0)	(10) 0 0 0 0 (0) (0) (0) (0)	( 0) ( 0) ( 0) ( 0) ( 0) ( 0) ( 0) ( 0)
{Special ser	nse organs/appendage)				
Harder gl	lymphocytic infiltration	(10) 1 0 0 0 (10) (0) (0) (0)	(10) (10) (0) (0)	(10) 1	<10> 2 0 0 0 ( 20) ( 0) ( 0) ( 0)
Grade { a } b ( c ) Significant	1: Slight 2: Moderate 3: Ma a: Number of animals examined at the site b: Number of animals with lesion c: b / a * 100 difference; *: $P \le 0.05$ **: $P \le 0.0$				

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0- 14W)

ANIMAL : RAT F344/DuCri

REPORT TYPE : A1

SEX : FEMALE

Organ	Group Name No. of Ani Grade Findings	20000 ppm mals on Study 10 10 1 2 3 4 (%) (%) (%) (%)	40000 ppm 10 1 2 3 4 (%) (%) (%) (%)	
{Urinary sys	stem}			
kidney	mineralization:papilla	4 0 0 0 (40) (0) (0) (0)	<10> 1 0 0 0 ( 10) ( 0) ( 0) ( 0)	
{Reproducti	ve system)			
ovary	cyst	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	
{Special se	nse organs/appendage)			
Harder gl	lymphocytic infiltration	1 0 0 0 ( 10) ( 0) ( 0) ( 0)	<10> 2 0 0 0 ( 20) ( 0) ( 0) ( 0)	
Grade <a>b</a> <a>c</a> <a>c<!--</td--><td>1: Slight 2: Moderate 3: Marked a: Number of animals examined at the site b: Number of animals with lesion c: b / a * 100 difference: *: P ≤ 0.05 **: P ≤ 0.01</td><td>4 : Severe Test of Chi Square</td><td>-</td><td></td></a>	1: Slight 2: Moderate 3: Marked a: Number of animals examined at the site b: Number of animals with lesion c: b / a * 100 difference: *: P ≤ 0.05 **: P ≤ 0.01	4 : Severe Test of Chi Square	-	
(IIPT150)				BA

# APPENDIX L 3

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS: SUMMARY

RAT : FEMALE : SACRIFICED ANIMALS

(13-WEEK STUDY)

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1

SEX : FEMALE

PAGE: 7

		Group Name Contro No. of Animals on Study 10 Grade 1 2 3		2500 ppm 10 1 2 3 4	5000 ppm 10 _1 2 3 4	10000 ppm 10 1 2 3 4
Organ	Findings	(%) (%) (%)	(%)	(%) (%) (%)	(%) (%) (%)	(%) (%) (%) (%)
{Respiratory	system)					
lung	osseous metaplasia	( 0) ( 0) ( 6		(10) 1 0 0 0 (10) (0) (0) (0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)
{Hematopoieti	ic system)					
bone marrow	granulation	3 0 ( (30) ( 0) (	0 0	<10> 2	1 0 0 0 ( 10) ( 0) ( 0) ( 0)	(0)(0)(0)(0)
lymph node	lymphadenitis	0 0 ( 0) ( 0) (	o o o) ( o)	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	( 0) ( 0) ( 0) ( 0) ( 0)
spleen	deposit of hemosiderin	10 0 (100) ( 0) (	0 0	10 0 0 0 (100) ( 0) ( 0) ( 0)	10 0 0 0 (100) ( 0) ( 0) ( 0)	10 0 0 0 (100) ( 0) ( 0) ( 0)
{Circulatory	system)					
heart	granulation	(10) 1 0 (10) (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)
Grade <a> b (c) Significant</a>	1: Slight 2: Moderate 3 a: Number of animals examined at the s b: Number of animals with lesion c: b / a * 100 difference; *: P ≤ 0.05 **: P ≤				· · · · · · · · · · · · · · · · · · ·	

(HPT150)

BAIS3

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY) SACRIFICED ANIMALS ( 14W)

ANIMAL : KAT F344/DuCrj

REPORT TYPE : A1

SEX : FEMALE

PAGE: 8

Organ	Group Nam No. of An Grade Findings	e 20000 ppm imals on Study 10 1 2 3 4 (%) (%) (%) (%)	40000 ppm 9 1 2 3 4 (%) (%) (%) (%)	
{Respiratory	system)			
lung	osseous metaplasia	<10> 0 0 0 0 0 0 0 0 0 0 0	( 0) ( 0) ( 0) ( 0)	
{Hematopoiet	ic system)			
bone marrow	granulation	0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<pre></pre>	
lymph node	lymphadenitis	(10) 1 0 0 0 ( 10) ( 0) ( 0) ( 0)	( 11) ( 0) ( 0) ( 0)	
spleen	deposit of hemosiderin	10 0 0 0 (100) ( 0) ( 0) ( 0)	9 0 0 0 (100) ( 0) ( 0) ( 0)	
{Circulatory	system)			
heart	granulation	( 0) ( 0) ( 0) ( 0)	<pre></pre>	
Grade <a>&gt; b (c) Significant</a>	I: Slight 2: Moderate 3: Marked a: Number of animals examined at the site b: Number of animals with lesion c: b / a * 100 difference: *: P ≤ 0.05 **: P ≤ 0.01	4 : Severe Test of Chi Square		

(IIPT150)

BAIS3

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1

SEX : FEMALE

Organ	Group Nam No. of An Grade Findings	e Control imals on Study 10 1 2 3 4 (%) (%) (%) (%)	2500 ppm 10 1 2 3 4 (%) (%) (%) (%)	5000 ppm 10 1 2 3 4 (%) (%) (%) (%)	10000 ppm 10 1 2 3 4 (%) (%) (%) (%)
{Digestive	system)				
liver	herniation	1 0 0 0 ( 10) ( 0) ( 0) ( 0)	(10) 0 0 0 0 (0) (0) (0) (0)	3 0 0 0 (30) (0) (0) (0)	2 0 0 0 ( 20) ( 0) ( 0) ( 0)
	granulation	1 0 0 0 (10) (0) (0) (0)	2 0 0 0 0 (20) ( 0) ( 0) ( 0)	1 0 0 0 (10) (0) (0) (0)	0 0 0 0 0 (0)
{Urimary sy	ystem}				
idney	infarct	1 0 0 0 ( 10) ( 0) ( 0) ( 0)	(10) 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<pre></pre>
	basophilic change	0 0 0 0 0 ( 0) ( 0)	1 0 0 0 0 (10) (10) (10)	0 0 0 0 0 (0) (0)	0 0 0 0 0 (0) (0)
	hyaline cast	0 0 0 0 0 ( 0) ( 0)	2 0 0 0 0 (20) ( 0) ( 0) ( 0)	0 0 0 0 0 (0) (0)	0 0 0 0 0
	papillary necrosis	0 0 0 0 0 ( 0)	0 0 0 0 0	0 0 0 0 0 (0) (0)	0 0 0 0 0
	mineralization:cortico-medullary junction	5 0 0 0 (50) ( 0) ( 0) ( 0)	4 0 0 0 (40) (0) (0)	0 0 0 0 *	3 0 0 0 0 (30) ( 0) ( 0)
Grade <a> b (c) Significan</a>	1: Slight 2: Moderate 3: Marked a: Number of animals examined at the site b: Number of animals with lesion c: b / a * 100 at difference; *: P ≤ 0.05 **: P ≤ 0.01	4 : Severe Test of Chi Square			

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1

SEX : FEMALE

Organ	Group No. of Grade Findings	Name 20000 ppm Animals on Study 10 1 2 3 4 (%) (%) (%) (%)	40000 ppm 9 1 2 3 4 (%) (%) (%) (%)		
{Digestive	system)				
liver	herniation	<10> 2 0 0 0 ( 20) ( 0) ( 0) ( 0)	3 0 0 0 (33) (0) (0) (0)		
	granulation	0 0 0 0 0 ( 0) ( 0)	3 0 0 0 0 (33) (0) (0) (0)		
{Urinary sy	stem)				
kidney	infarct	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<pre></pre>		
	basophilic change	0 0 0 0 0 0 ( 0)	0 0 0 0 0 (0)		,
	hyaline cast	3 0 0 0 0 (30) ( 0) ( 0)	1 0 0 0 (11) (0) (0) (0)		
	papillary necrosis	2 0 0 0 0 (20) (0) (0)	5 0 0 0 * (56) (0) (0) (0)	·	
	mineralization cortico-medullary junction	2 0 0 0 0 (20) ( 0) ( 0)	4 0 0 0 0 (44) (0) (0) (0)		
Grade <a>&gt; b (c) Significant</a>	1 : Slight 2 : Moderate 3 : Mar a : Number of animals examined at the site b : Number of animals with lesion c : b / a * 100 t difference; * : P ≤ 0.05 **: P ≤ 0.01				

(IIPT150)

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE : A1

SEX : FEMALE

0rgan		O Name	2500 ppm 10 1 2 3 4 (%) (%) (%) (%)	5000 ppm 10 1 2 3 4 (%) (%) (%) (%)	10000 ppm 10 1 2 3 4 (%) (%) (%) (%)
{Urimary syste	an)				
kidnoy	mineralization:papilla	(10) 1 0 0 0 (10) (0) (0) (0)	2 0 0 0 (20) (0) (0) (0)	<10> 2 0 0 0 ( 20) ( 0) ( 0) ( 0)	<10> 2 1 0 0 ( 20) ( 10) ( 0) ( 0)
{Reproductive	system)			·	
ovary	cyst	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	(10) 1 0 0 0 (10) (0) (0) (0)	<10> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<pre></pre>
{Special sens	e organs/appendage)				
Harder gl	lymphocytic infiltration	1 0 0 0 ( 10) ( 0) ( 0) ( 0)	<pre></pre>	(10) 1 0 0 0 (10) (0) (0) (0)	2 0 0 0 ( 20) ( 0) ( 0) ( 0)
Grade (a) b (c)	1: Slight 2: Moderate 3: Ma a: Number of animals examined at the site b: Number of animals with lesion c: b $/$ a * 100 ifference; * *: $P \le 0.05$ **: $P \le 0.05$				

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)

SACRIFICED ANIMALS ( 14W)

ANIMAL : RAT F344/DuCrj REPORT TYPE: A1

SEX : FEMALE

PAGE: 12 Group Name 20000 ррт 40000 ppm 10 9 No. of Animals on Study (%) Findings\_ (%) (%) (%) (%) (%) (%) (%) {Urinary system} kidney < 9> <10> 1 0 0 0 mineralization:papilla 0 0 0 (40) (0) (0) (0) (11) (0) (0) (0) (Reproductive system) <10> ovary < 9> 0 0 0 0 0 0 0 cyst (0)(0)(0)(0) (0)(0)(0)(0) {Special sense organs/appendage} Harder gl <10> lymphocytic infiltration 1 0 0 0 2 0 0 0 (22) (0) (0) (0) (10) (0) (0) (0) Grade 3 : Marked 1 : Slight 2 : Moderate 4 : Severe < a > a : Number of animals examined at the site ь b : Number of animals with lesion (c) c:b/a\*100 Significant difference;  $*: P \le 0.05$  \*\*:  $P \le 0.01$  Test of Chi Square (IIPT150) BATS3

## APPENDIX L 4

HISTOLOGICAL FINDINGS: NON-NEOPLASTIC LESIONS: SUMMARY

RAT : FEMALE : DEAD AND MORIBUND ANIMALS

(13-WEEK STUDY)

ANIMAL : RAT F344/DuCrj

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) DEAD AND MORIBUND ANIMALS (0- 14W)

REPORT TYPE : A1

SEX : FEMALE

Organ	Findings	Group Name No. of Animals on Study Grade  (7	Control 0 1 2 3 4 %) (%) (%) (%)	2500 ppm 0 1 2 3 4 (%) (%) (%) (%)	5000 ppm 0 1 2 3 4 (%) (%) (%)	10000 ppm 0 1 2 3 4 (%) (%) (%) (%)
{Digestive	system)					
liver			< 0>	< 0>	< 0>	< 0>
	herniation	(	-) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)	( -) ( -) ( -) ( -)
Grade < n > b	1: Slight 2: Moderate a: Number of animals examined at t b: Number of animals with lesion c: b/a * 100	3: Marked 4: Sev he site	ere			

ANIMAL : RAT F344/DuCrj

REPORT TYPE : A1

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

PAGE: 2

DEAD AND MORIBUND ANIMALS (0- 14W)

Group Name 20000 ppm 40000 ppm No. of Animals on Study 1 Grade Organ\_\_ Findings\_\_ (%) (%) (%) (%) (%) (Digestive system) liver < 0> < 1> herniation 1 0 0 0 ( -) ( -) ( -) ( -) (100) ( 0) ( 0) ( 0) 1 : Slight Grade 2 : Moderate 3 : Marked 4 : Severe < a > a: Number of animals examined at the site ь b : Number of animals with lesion (c) c:b/a \* 100 (HPT150) BAIS3

# APPENDIX M 1

IDENTITY OF METHYL ACETOACETATE

IN THE 13-WEEK DRINKING WATER STUDY

#### IDENTITY OF METHYL ACETOACETATE IN THE 13-WEEK DRINKING WATER STUDY

Test Substance : Methyl Acetoacetate (Tokyo Kasei Kogyo Co., Ltd.)

Lot No. : GK01

#### 1. Spectral Data

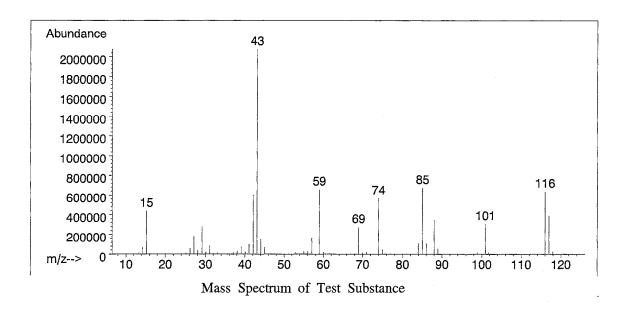
)

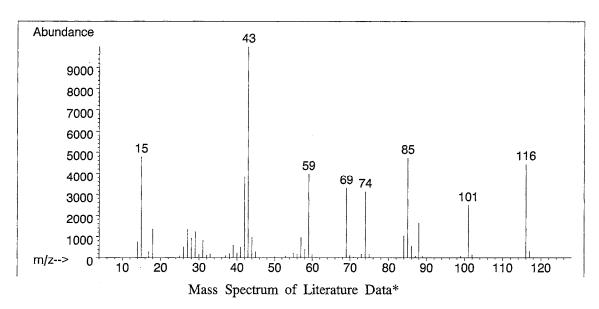
#### Mass Spectrometry

Instrument : Hewlett Packard 5989B Mass Spectrometer

Ionization : EI (Electron Ionization)

Ionization Voltage : 70eV





Results: The mass spectrum was consistent with literature spectrum.

(\*Fred W. McLafferty (1994) Wiley Registry of Mass Spectral Data, 6th edition.

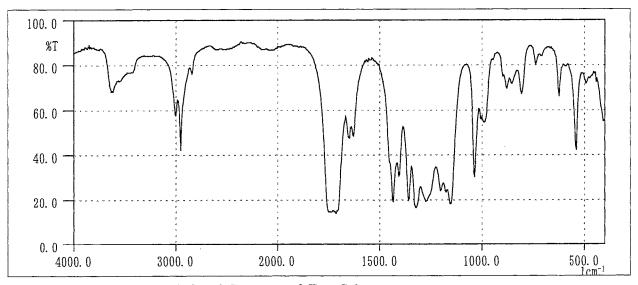
John Wiley and Sons, Inc. (U.S.), Entry Number 12752)

#### Infrared Spectrometry

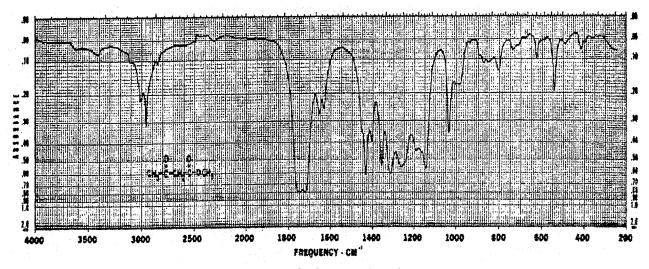
Instrument : Shimadzu FTIR-8200PC Infrared Spectrometer

Cell : KBr Liquid Cell

Resolution : 2 cm<sup>-1</sup>



Infrared Spectrum of Test Substance



Infrared Spectrum of Literature Data\*

Results: The infrared spectrum was consistent with literature spectrum.

(\*William W. Simons (1978) The Sadtler Handbook of Infrared Spectra.

Sadtler Research Laboratories, Inc. (U.K.), p.766)

2. Conclusions: The test substance was identified as methyl acetoacetate, by the mass spectrum and the infrared spectrum.

# APPENDIX M 2

STABILITY OF METHYL ACETOACETATE

IN THE 13-WEEK DRINKING WATER STUDY

#### STABILITY OF METHYL ACETOACETATE IN THE 13-WEEK DRINKING WATER STUDY

Test Substance

: Methyl Acetoacetate (Tokyo Kasei Kogyo Co., Ltd.)

Lot No.

: GK01

1. Sample

: This lot was used from 2001.4.6 to 2000.7.10. Test substance was

stored in a dark place at room temperature.

#### 2. Gas Chromatography

Instrument

: Hewlett Packard 5890A Gas Chromatograph

Column

: INNOWAX (0.2 mm  $\phi$  × 50 m)

Column Temperature

: 100 °C (1 min)  $\rightarrow$  (10 °C/min)  $\rightarrow$  190 °C

Flow Rate

: 1 mL/min

Detector

: FID (Flame Ionization Detector)

Injection Volume

: 1 µL

Date (date analyzed)	Peak No.	Retention Time (min)	Area (%)
2001.03.21	1	6.815	100
2001.07.24	1	6.811	100

Results: Gas chromatography indicated one major peak (peak No.1) analyzed at 2001.03.21 and one major peak (peak No.1) analyzed at 2001.07.24. No new trace impurity peak in the test substance analyzed at 2001.07.24 was detected.

3. Conclusions: The test substance was stable for about 4 months in a dark place at room temperature.

## APPENDIX M 3

# CONCENTRATION OF METHYL ACETOACETATE IN FORMULATED WATER IN THE 13-WEEK DRINKING WATER STUDY

# CONCENTRATION OF METHYL ACETOACETATE IN FORMULATED WATER IN THE 13-WEEK DRINKING WATER STUDY

Target Concentration						
Date Analyzed	2500ª	5000	10000	20000	40000	
2001.04.06	2490 ( 99.6) <sup>b</sup>	5010 (100)	9970 ( 99.7)	19800 ( 99.0)	37400 ( 93.5)	

a ppm b %

%

Analytical Method : The samples were analyzed by gas chromatography.

Instrument : Hewlett Packard 5890A Gas Chromatograph

Column : INNOWAX (0.2 mm  $\phi$  × 50 m)

Column Temperature : 100 °C (1 min)  $\rightarrow$  (10 °C/min)  $\rightarrow$  190 °C

Flow Rate : 1 mL/min

Detector : FID (Flame Ionization Detector)

Injection Volume : 1 μL

## APPENDIX M 4

# STABILITY OF METHYL ACETOACETATE IN FORMULATED WATER IN THE 13-WEEK DRINKING WATER STUDY

# STABILITY OF METHYL ACETOACETATE IN FORMULATED WATER IN THE 13-WEEK DRINKING WATER STUDY

		Target Concentration		
Date Prepared	Date Analyzed	2500 <sup>a</sup>	40000	
2000.10.02	2000.10.02	2590 (100) <sup>b</sup>	39000 (100)	
	2000.10.06°	2510 ( 96.9)	41200 (106)	
	2000.10.12°	2540 ( 98.1)	40300 (103)	

<sup>&</sup>lt;sup>a</sup> ppm

Analytical Method : The samples were analyzed by gas chromatography.

Instrument : Hewlett Packard 5890A Gas Chromatograph

Column : INNOWAX (0.2 mm  $\phi$  × 50 m)

Column Temperature : 100  $^{\circ}$  C (1 min)  $\rightarrow$  (10  $^{\circ}$ C/min)  $\rightarrow$  190  $^{\circ}$  C

Flow Rate : 1 mL/min

Detector : FID (Flame Ionization Detector)

Injection Volume : 1 μL

<sup>&</sup>lt;sup>b</sup> % (Percentage was based on the concentration on date of preparation.)

<sup>&</sup>lt;sup>c</sup> Animal room samples

# APPENDIX N 1

METHODS FOR HEMATOLOGY, BIOCHEMISTRY AND URINALYSIS

IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

# METHODS FOR HEMATOLOGY, BIOCHEMISTRY AND URINALYSIS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Item	Method
Hematology	
Red blood cell (RBC)	Light scattering method 1)
Hemoglobin (Hgb)	Cyanmethemoglobin method 1)
Hematocrit (Hct)	Calculated as RBC×MCV/10 1)
Mean corpuscular volume (MCV)	Light scattering method 1)
Mean corpuscular hemoglobin (MCH)	Calculated as Hgb/RBC×10 1)
Mean corpuscular hemoglobin concentration (MCHC)	Calculated as Hgb/Hct×100 1)
Platelet	Light scattering method 1)
Reticulocyte	Light scattering method 1)
Prothrombin time	Quick one stage method 2)
Activated partial thromboplastin time (APTT)	Ellagic acid activaterd method <sup>2)</sup>
White blood cell (WBC)	Light scattering method 1)
Differential WBC	Pattern recognition method <sup>3)</sup>
Differential Wife	(Wright staining)
Biochemistry	
Total protein (TP)	Biuret method 4)
Albumin (Alb)	BCG method 4)
A/G ratio	Calculated as Alb/(TP – Alb) 4)
T-bilirubin	Alkaline azobilirubin method 4)
Glucose	GlcK·G-6-PDH method 4)
T-cholesterol	CE·COD·POD method 4)
Triglyceride	LPL·GK·GPO·POD method 4)
Phospholipid	PLD·ChOD·POD method 4)
Glutamic oxaloacetic transaminase (GOT)	JSCC method 4)
Glutamic pyruvic transaminase (GPT)	JSCC method 4)
Lactate dehydrogenase (LDH)	SFBC method 4)
Alkaline phosphatase (ALP)	GSCC method <sup>4)</sup>
$\gamma$ -Glutamyl transpeptidase ( $\gamma$ -GTP)	L-γ-Glutamyl-p-nitroanilide method 4)
Creatine phosphokinase (CPK)	JSCC method 4)
Urea nitrogen	Urease · GLDH method 4)
Creatinine	Jaffe method 4)
Sodium	Ion selective electrode method 4)
Potassium	Ion selective electrode method 4)
Chloride	Ion selective electrode method 4)
Calcium	OCPC method <sup>4)</sup>
Inorganic phosphorus	PNP·XOD·POD method 4)
Urinalysis	
pH,Protein,Glucose,Ketone body,Bilirubin,Occult Blood,	Urinalysis reagent paper method 5)
Urobilinogen	

- 1) Automatic blood cell analyzer (ADVIA120: Bayer Corporation)
- 2) Automatic coagulometer (Sysmex CA-5000 : Sysmex Corporation)
- 3) Automatic blood cell differential analyzer (MICROX HEG-120NA: OMRON Corporation)
- 4) Automatic analyzer (Hitachi 7070: Hitachi, Ltd.)
- 5) Ames reagent strips for urinalysis (Multistix: Bayer Corporation)

# APPENDIX O 1

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY

IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

# UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Item	Unit	Decimal place
Hematology		
Red blood cell (RBC)	$ imes 10^6/\mu$ L	2
Hemoglobin	g/dL	1
Hematocrit	%	1
Mean corpuscular volume (MCV)	fL	1
Mean corpuscular hemoglobin (MCH)	pg	1
Mean corpuscular hemoglobin concentration (MCHC)	g/dL	1
Platelet	$\times 10^3/\mu L$	0
Reticulocyte	%	1
Prothrombin time	sec	1
Activated partial thromboplastin time (APTT)	sec	1
White blood cell (WBC)	$\times 10^3/\mu L$	2
Differential WBC	%	0
Biochemistry		
Total protein	g/dL	1
Albumin	g/dL	1
A/G ratio	- g, u.z	1
T-bilirubin	mg/dL	2
Glucose	mg/dL	0
T-cholesterol	mg/dL	0
Triglyceride	mg/dL	0
Phospholipid	mg/dL	0
Glutamic oxaloacetic transminase (GOT)	IU/L	0
Glutamic pyruvic transaminase (GPT)	IU/L	0
Lactate dehydrogenase (LDH)	IU/L	0
Alkaline phosphatase (ALP)	IU/L	0
$\gamma$ -Glutamyl transpeptidase ( $\gamma$ -GTP)	IU/L	0
Creatine phosphokinase (CPK)	IU/L	0
Urea nitrogen	mg/dL	1
Creatinine	mg/dL	1
Sodium	mEq/L	0
Potassium	mEq/L	1
Chloride	mEq/L	0
Calcium	mg/dL	1
Inorganic phosphorus	mg/dL	1