

シクロヘキセンのラットを用いた
吸入による 2 週間毒性試験報告書

試験番号：0358

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(2-WEEK STUDY)
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APPENDIX A 1

CLINICAL OBSERVATION : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1 2
SEX : MALE

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

PAGE : 1

Clinical sign	Group Name	Administration Week-day				
		1-2	1-4	1-7	2-3	2-7
		1	1	1	1	1
Non Remarkable	control					
	600 ppm					
	1200 ppm					
	2400 ppm					
	4800 ppm					
	9600 ppm					

APPENDIX A 2

CLINICAL OBSERVATION : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1 2
SEX : FEMALE

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

Clinical sign	Group Name	Administration Week-day				
		1-2	1-4	1-7	2-3	2-7
		1	1	1	1	1
Non Remarkable	control					
	600 ppm					
	1200 ppm					
	2400 ppm					
	4800 ppm					
	9600 ppm					

APPENDIX B 1

BODY WEIGHT CHANGES :SUMMARY, RAT : MALE
(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 UNIT : g
 REPORT TYPE : A1 2
 SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
 ALL ANIMALS

PAGE : 1

Group Name	Administration		week-day									
	0-0		1-2		1-4		1-7		2-3		2-7	
control	111±	3	117±	4	120±	5	130±	6	140±	8	155±	9
600ppm	111±	3	115±	4	117±	5	128±	5	136±	5	152±	5
1200ppm	111±	3	116±	4	119±	4	132±	4	142±	6	160±	6
2400ppm	111±	3	112±	4	111±	4*	121±	5*	125±	5**	140±	6**
4800ppm	112±	3	110±	3	106±	4**	116±	4**	113±	8**	128±	8**
9600ppm	111±	4	-		-		-		-		-	
Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$ Test of Dunnett												
(HAN260)											BA1S3	

APPENDIX B 2

BODY WEIGHT CHANGES : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 UNIT : g
 REPORT TYPE : A1 2
 SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
 ALL ANIMALS

PAGE : 2

Group Name	Administration		week-day									
	0-0		1-2		1-4		1-7		2-3		2-7	
control	95±	3	99±	4	101±	4	107±	5	111±	5	117±	5
600ppm	95±	4	98±	3	101±	5	108±	6	111±	7	118±	6
1200ppm	95±	4	98±	3	99±	4	107±	5	110±	5	120±	5
2400ppm	95±	4	94±	4	94±	5	101±	3	102±	3*	110±	4
4800ppm	95±	4	93±	3*	91±	4**	97±	4*	96±	4**	104±	4**
9600ppm	95±	4	-		-		-		-		-	

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

APPENDIX C 1

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : MALE
(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 2
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

PAGE : 1

Group Name	Administration week-day(effective)	
	1-7(6)	2-7(7)
control	13.8± 0.6	13.8± 0.7
600ppm	14.0± 0.7	14.1± 0.3
1200ppm	14.1± 0.9	14.9± 0.8
2400ppm	13.4± 0.9	14.1± 1.4
4800ppm	10.7± 1.7**	11.6± 1.3*
9600ppm	-	-

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

APPENDIX C 2

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : FEMALE
(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 2
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

PAGE : 2

Group Name	Administration week-day(effective)	
	1-7(6)	2-7(7)
control	11.5± 0.3	10.6± 0.5
600ppm	11.7± 0.2	10.8± 0.4
1200ppm	11.2± 0.6	11.1± 0.6
2400ppm	10.5± 0.9	9.8± 0.4
4800ppm	9.7± 0.8*	10.3± 0.6
9600ppm	-	-

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

APPENDIX D 1

HEMATOLOGY : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : MALE

HEMATOLOGY (SUMMARY)
 ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 1

Group Name	NO. of Animals	RED BLOOD CELL 10 ⁶ /μl		HEMOGLOBIN g/dl		HEMATOCRIT %		MCV fl		MCH pg		MCHC g/dl		PLATELET 10 ³ /μl	
control	5	8.39±	0.13	15.6±	0.2	46.4±	0.6	55.3±	0.7	18.5±	0.1	33.6±	0.2	881±	42
600ppm	5	8.54±	0.20	15.8±	0.4	46.6±	1.1	54.6±	0.2	18.5±	0.1	33.9±	0.3	824±	55
1200ppm	5	8.29±	0.15	15.4±	0.3	45.8±	0.9	55.2±	0.5	18.6±	0.1	33.6±	0.2	915±	67
2400ppm	5	8.76±	0.21*	16.1±	0.3	47.5±	1.2	54.3±	0.2**	18.4±	0.1	33.9±	0.3	816±	46
4800ppm	4	8.61±	0.18	15.7±	0.5	46.8±	1.2	54.4±	0.3*	18.2±	0.2**	33.4±	0.3	865±	43
9600ppm	0	-		-		-		-		-		-		-	

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE

HEMATOLOGY (SUMMARY)
ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 2

Group Name	NO. of Animals	RETICULOCYTE ‰		PROTHROMBIN TIME s e c		APTT s e c	
control	5	21±	7	13.4±	0.5	23.8±	3.1
600ppm	5	21±	4	13.3±	0.6	20.9±	1.4
1200ppm	5	28±	6	13.3±	1.1	20.0±	1.9
2400ppm	5	27±	5	13.9±	0.9	21.4±	3.4
4800ppm	4	33±	6*	14.0±	0.1	20.0±	1.4
9600ppm	0	-		-		-	

Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL070)

BAIS3

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : MALE

HEMATOLOGY (SUMMARY)
 ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 3

Group Name	NO. of Animals	WBC 10 ³ /μl		Differential N-BAND		WBC (%) N-SEG		EOSINO		BASO		MONO		LYMPHO		OTHER	
control	5	4.23±	2.54	0±	0	23±	7	1±	1	0±	0	7±	1	67±	9	2±	3
600ppm	5	4.23±	1.19	0±	0	20±	7	1±	1	0±	0	7±	4	70±	9	2±	3
1200ppm	5	5.01±	2.75	0±	0	20±	7	0±	1	0±	0	6±	2	72±	8	1±	1
2400ppm	5	3.70±	0.58	0±	0	23±	9	1±	1	0±	0	7±	1	68±	9	2±	2
4800ppm	4	3.02±	0.47	1±	1	32±	3	1±	1	0±	0	7±	2	58±	2	2±	2
9600ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL070)

BAIS3

APPENDIX D 2

HEMATOLOGY : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : FEMALE

HEMATOLOGY (SUMMARY)
 ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 4

Group Name	NO. of Animals	RED BLOOD CELL 10 ⁶ /μl	HEMOGLOBIN g/dl	HEMATOCRIT %	MCV fl	MCH pg	MCHC g/dl	PLATELET 10 ³ /μl
control	5	8.67± 0.25	16.4± 0.5	47.5± 1.5	54.8± 0.3	18.9± 0.1	34.4± 0.3	814± 39
600ppm	5	8.82± 0.37	16.7± 0.6	47.8± 1.9	54.2± 0.4	18.9± 0.3	34.9± 0.3	795± 82
1200ppm	5	8.81± 0.16	16.6± 0.2	47.7± 0.7	54.1± 0.2	18.8± 0.1	34.7± 0.2	861± 56
2400ppm	5	9.07± 0.15	16.8± 0.4	48.7± 0.7	53.7± 0.1**	18.5± 0.1**	34.4± 0.3	756± 66
4800ppm	5	8.65± 0.35	16.0± 0.6	46.6± 1.4	53.8± 0.7*	18.5± 0.2**	34.3± 0.2	811± 61
9600ppm	0	-	-	-	-	-	-	-

Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL070)

BAIS3

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE

HEMATOLOGY (SUMMARY)
ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 5

Group Name	NO. of Animals	RETICULOCYTE ‰		PROTHROMBIN TIME s e c		APTT s e c	
control	5	13±	5	12.8±	0.6	18.6±	1.0
600ppm	5	16±	4	13.3±	0.4	18.9±	0.6
1200ppm	5	17±	4	13.7±	0.3	23.2±	10.0
2400ppm	5	14±	7	13.8±	0.2	18.8±	0.7
4800ppm	5	30±	6**	14.1±	0.1**	21.1±	1.8
9600ppm	0	-		-		-	

Significant difference : * : $P \leq 0.05$

** : $P \leq 0.01$

Test of Dunnett

(HCL070)

BAIS3

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : FEMALE

HEMATOLOGY (SUMMARY)
 ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 6

Group Name	NO. of Animals	WBC 10 ³ /μl		Differential N-BAND		WBC (%) N-SEG		EOSINO		BASO		MONO		LYMPHO		OTHER	
control	5	2.94±	0.67	0±	0	18±	5	1±	1	0±	0	5±	3	74±	5	1±	2
600ppm	5	3.42±	0.80	0±	1	18±	3	1±	1	0±	0	6±	3	72±	3	1±	2
1200ppm	5	3.44±	0.63	0±	0	20±	7	1±	1	0±	0	6±	3	72±	6	2±	2
2400ppm	5	3.62±	1.31	0±	0	20±	7	1±	1	0±	0	5±	2	73±	7	1±	1
4800ppm	5	3.01±	0.80	0±	0	23±	5	1±	1	0±	0	9±	2	65±	5	1±	1
9600ppm	0	-		-		-		-		-		-		-		-	

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL070)

BAIS3

APPENDIX E 1

BIOCHEMISTRY : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : MALE

BIOCHEMISTRY (SUMMARY)
 ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 1

Group Name	NO. of Animals	TOTAL PROTEIN g/dl		ALBUMIN g/dl		A/G RATIO		T-BILIRUBIN mg/dl		GLUCOSE mg/dl		T-CHOLESTEROL mg/dl		TRIGLYCERIDE mg/dl	
control	5	5.5±	0.1	3.6±	0.1	1.8±	0.1	0.11±	0.01	151±	9	49±	4	41±	20
600ppm	5	5.7±	0.1	3.6±	0.1	1.8±	0.1	0.11±	0.01	131±	3	44±	3	25±	12
1200ppm	5	5.6±	0.2	3.5±	0.2	1.8±	0.1	0.11±	0.01	148±	6	48±	7	27±	5
2400ppm	5	5.7±	0.1	3.7±	0.2	1.9±	0.2	0.12±	0.01	136±	18	44±	4	21±	5
4800ppm	4	5.9±	0.2*	3.8±	0.1	1.9±	0.1	0.13±	0.02*	141±	35	57±	3	14±	2**
9600ppm	0	-		-		-		-		-		-		-	

Significant difference ; * : $P \leq 0.05$

** : $P \leq 0.01$

Test of Dunnett

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : MALE

BIOCHEMISTRY (SUMMARY)
 ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 2

Group Name	NO. of Animals	PHOSPHOLIPID mg/dl		GOT IU/l		GPT IU/l		LDH IU/l		ALP IU/l		G-GTP IU/l		CPK IU/l	
control	5	92±	7	71±	3	36±	4	250±	106	712±	76	1±	1	211±	37
600ppm	5	82±	6	70±	2	37±	2	212±	73	730±	21	1±	1	204±	31
1200ppm	5	81±	13	67±	5	32±	3	215±	89	706±	28	1±	1	204±	38
2400ppm	5	80±	10	71±	4	36±	2	258±	63	662±	42	1±	1	209±	31
4800ppm	4	95±	6	67±	2	31±	1*	285±	130	693±	62	2±	1	231±	47
9600ppm	0	-		-		-		-		-		-		-	

Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL074)

BAIS3

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : MALE

BIOCHEMISTRY (SUMMARY)
 ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 3

Group Name	NO. of Animals	UREA NITROGEN mg/dl		CREATININE mg/dl		SODIUM mEq/l		POTASSIUM mEq/l		CHLORIDE mEq/l		CALCIUM mg/dl		INORGANIC PHOSPHORUS mg/dl	
control	5	15.8±	1.5	0.5±	0.1	142±	2	3.8±	0.1	105±	1	10.2±	0.1	8.3±	0.4
600ppm	5	15.2±	1.8	0.5±	0.1	142±	2	3.9±	0.1	104±	1	10.0±	0.3	8.5±	0.7
1200ppm	5	14.6±	0.7	0.4±	0.1	142±	2	3.9±	0.2	104±	2	10.2±	0.2	8.6±	0.7
2400ppm	5	14.1±	1.8	0.4±	0.1	143±	2	3.8±	0.3	105±	2	10.2±	0.2	8.3±	0.8
4800ppm	4	12.2±	2.9	0.4±	0.1	142±	1	4.2±	0.1**	106±	2	10.3±	0.3	8.3±	0.3
9600ppm	0	-		-		-		-		-		-		-	

Significant difference : * : $P \leq 0.05$

** : $P \leq 0.01$

Test of Dunnett

APPENDIX E 2

BIOCHEMISTRY : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : FEMALE

REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
 ALL ANIMALS (3W)

PAGE : 4

Group Name	NO. of Animals	TOTAL PROTEIN g/dl		ALBUMIN g/dl		A/G RATIO		T-BILIRUBIN mg/dl		GLUCOSE mg/dl		T-CHOLESTEROL mg/dl		TRIGLYCERIDE mg/dl	
control	5	5.6±	0.2	3.5±	0.1	1.7±	0.1	0.15±	0.03	131±	11	60±	5	16±	2
600ppm	5	5.6±	0.2	3.6±	0.1	1.8±	0.1	0.13±	0.01	126±	11	61±	7	15±	2
1200ppm	5	5.6±	0.1	3.6±	0.1	1.7±	0.1	0.13±	0.01	126±	14	63±	6	17±	4
2400ppm	5	5.5±	0.2	3.5±	0.1	1.8±	0.1	0.14±	0.02	123±	12	67±	7	22±	5*
4800ppm	5	5.8±	0.1	3.7±	0.0	1.8±	0.1	0.14±	0.01	127±	31	58±	5	16±	3
9600ppm	0	-		-		-		-		-		-		-	

Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : FEMALE

REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
 ALL ANIMALS (3W)

PAGE : 5

Group Name	NO. of Animals	PHOSPHOLIPID mg/dl		GOT IU/l		GPT IU/l		LDH IU/l		ALP IU/l		G-GTP IU/l		CPK IU/l	
control	5	110±	6	69±	4	29±	2	373±	112	540±	35	1±	1	220±	43
600ppm	5	111±	10	70±	6	32±	4	300±	61	573±	31	1±	1	212±	43
1200ppm	5	121±	11	70±	3	33±	2	311±	119	560±	28	1±	0	223±	44
2400ppm	5	131±	12*	70±	4	33±	4	379±	255	515±	38	2±	1*	196±	76
4800ppm	5	116±	10	67±	4	32±	3	377±	152	540±	22	2±	1**	222±	57
9600ppm	0	-		-		-		-		-		-		-	

Significant difference ; * : $P \leq 0.05$

** : $P \leq 0.01$

Test of Dunnett

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 MEASURE. TIME : 1
 SEX : FEMALE

BIOCHEMISTRY (SUMMARY)
 ALL ANIMALS (3W)

REPORT TYPE : A1

PAGE : 6

Group Name	NO. of Animals	UREA NITROGEN mg/dl		CREATININE mg/dl		SODIUM mEq/l		POTASSIUM mEq/l		CHLORIDE mEq/l		CALCIUM mg/dl		INORGANIC PHOSPHORUS mg/dl	
control	5	17.6±	1.7	0.5±	0.0	141±	3	3.7±	0.1	107±	3	10.0±	0.2	7.4±	0.7
600ppm	5	16.8±	1.8	0.5±	0.0	141±	1	3.6±	0.1	107±	1	10.0±	0.3	7.6±	0.3
1200ppm	5	17.3±	1.4	0.5±	0.0	142±	2	3.6±	0.1	106±	2	10.0±	0.3	7.4±	0.7
2400ppm	5	14.1±	1.2**	0.4±	0.1	141±	2	3.7±	0.3	107±	1	9.9±	0.2	7.4±	0.9
4800ppm	5	11.8±	1.8**	0.5±	0.0	140±	1	3.9±	0.2	106±	2	10.1±	0.2	8.5±	0.7
9600ppm	0	-		-		-		-		-		-		-	

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL074)

BAIS3

APPENDIX F 1

GROSS FINDINGS : SUMMARY, RAT : MALE

DEAD AND MORIBUND ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 3W)

PAGE : 1

Organ	Findings	Group Name NO. of Animals	control 0 (%)	600ppm 0 (%)	1200ppm 0 (%)	2400ppm 0 (%)
lung	voluminus		- (-)	- (-)	- (-)	- (-)
liver	herniation		- (-)	- (-)	- (-)	- (-)

(IPT080)

BAIS3

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 3W)

PAGE : 2

Organ	Findings	Group Name	4800ppm	9600ppm
		NO. of Animals	1 (%)	5 (%)
Lung	voluminous		0 (0)	4 (80)
Liver	herniation		0 (0)	1 (20)

(HPT080)

BAIS3

APPENDIX F 2

GROSS FINDINGS : SUMMARY, RAT : MALE : SACRIFICED ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuGrj
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (3W)

PAGE : 1

Organ_____	Findings_____	Group Name	control	600ppm	1200ppm	2400ppm
		NO. of Animals	5 (%)	5 (%)	5 (%)	5 (%)
liver	herniation		0 (0)	0 (0)	0 (0)	0 (0)

(HPT080)

BAIS 3

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (3W)

PAGE : 2

Organ_____	Findings_____	Group Name	4800ppm	9600ppm
		NO. of Animals	4 (%)	0 (%)
Liver	herniation		1 (25)	- (-)

(HPT080)

BAIS3

APPENDIX F 3

GROSS FINDINGS : SUMMARY, RAT : FEMALE

DEAD AND MORIBUND ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuGrj
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 3W)

PAGE : 3

Organ	Findings	Group Name	control	600ppm	1200ppm	2400ppm
		NO. of Animals	0 (%)	0 (%)	0 (%)	0 (%)
lung	voluminous		- (-)	- (-)	- (-)	- (-)

(HPT080)

BAIS 3

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 3W)

PAGE : 4

Organ	Findings	Group Name	4800ppm	9600ppm
		NO. of Animals	0 (%)	5 (%)

Lung	voluminous		- (-)	4 (80)
------	------------	--	--------	---------

(HPT080)

BAIS 3

APPENDIX F 4

GROSS FINDINGS : SUMMARY, RAT : FEMALE : SACRIFICED ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (0- 3w)

PAGE : 1

Organ	Findings	Group Name No. of Animals	Control 5 (%)	600ppm 5 (%)	1200ppm 5 (%)	2400ppm 5 (%)	4800ppm 5 (%)	9600ppm 0 (%)
-------	----------	------------------------------	------------------	-----------------	------------------	------------------	------------------	------------------

Non Remarkable

APPENDIX G 1

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (3W)

PAGE : 1

Group Name	NO. of Animals	Body Weight		THYMUS		ADRENALS		TESTES		HEART		LUNGS	
control	5	140±	8	0.290±	0.020	0.052±	0.010	2.242±	0.149	0.575±	0.032	0.679±	0.036
600ppm	5	136±	5	0.269±	0.016	0.045±	0.008	2.240±	0.055	0.569±	0.035	0.662±	0.011
1200ppm	5	143±	4	0.301±	0.011	0.042±	0.003	2.214±	0.177	0.591±	0.037	0.710±	0.054
2400ppm	5	124±	5**	0.217±	0.012**	0.046±	0.005	2.046±	0.156	0.551±	0.018	0.645±	0.029
4800ppm	4	113±	8**	0.138±	0.033**	0.045±	0.004	2.200±	0.164	0.529±	0.046	0.645±	0.031
9600ppm	0	-		-		-		-		-		-	

Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : MALE
 UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
 SURVIVAL ANIMALS (3W)

PAGE : 2

Group Name	NO. of Animals	KIDNEYS		SPLEEN		LIVER		BRAIN	
control	5	1.143±	0.064	0.321±	0.014	4.285±	0.334	1.701±	0.037
600ppm	5	1.169±	0.046	0.308±	0.017	4.175±	0.186	1.662±	0.024
1200ppm	5	1.240±	0.030*	0.345±	0.032	4.575±	0.277	1.706±	0.046
2400ppm	5	1.145±	0.057	0.273±	0.017**	4.049±	0.144	1.652±	0.043
4800ppm	4	1.094±	0.045	0.238±	0.021**	3.941±	0.226	1.581±	0.033**
9600ppm	0	-		-		-		-	

Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

APPENDIX G 2

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : FEMALE
(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (3W)

PAGE : 3

Group Name	NO. of Animals	Body Weight		THYMUS		ADRENALS		OVARIES		HEART		LUNGS	
control	5	104±	4	0.259±	0.019	0.052±	0.005	0.080±	0.010	0.458±	0.022	0.582±	0.030
600ppm	5	105±	5	0.232±	0.020	0.051±	0.003	0.084±	0.015	0.447±	0.019	0.596±	0.047
1200ppm	5	106±	5	0.234±	0.028	0.050±	0.001	0.083±	0.006	0.474±	0.028	0.595±	0.022
2400ppm	5	99±	4	0.217±	0.018*	0.049±	0.006	0.082±	0.012	0.456±	0.027	0.599±	0.040
4800ppm	5	93±	3**	0.154±	0.012**	0.058±	0.004	0.087±	0.007	0.466±	0.027	0.568±	0.014
9600ppm	0	-		-		-		-		-		-	

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL040)

BAIS 3

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (3W)

PAGE : 4

Group Name	NO. of Animals	KIDNEYS		SPLEEN		LIVER		BRAIN	
control	5	0.902±	0.049	0.274±	0.018	3.278±	0.167	1.599±	0.027
600ppm	5	0.914±	0.041	0.259±	0.025	3.242±	0.238	1.596±	0.055
1200ppm	5	0.937±	0.039	0.273±	0.011	3.325±	0.156	1.597±	0.036
2400ppm	5	0.928±	0.036	0.240±	0.016*	3.168±	0.149	1.550±	0.027
4800ppm	5	0.906±	0.035	0.220±	0.016**	3.270±	0.180	1.497±	0.043**
9600ppm	0	-		-		-		-	

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

APPENDIX H 1

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (3W)

PAGE : 1

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	TESTES	HEART	LUNGS
control	5	140± 8	0.208± 0.011	0.037± 0.006	1.606± 0.053	0.412± 0.009	0.487± 0.014
600ppm	5	136± 5	0.197± 0.008	0.033± 0.005	1.646± 0.050	0.418± 0.015	0.486± 0.012
1200ppm	5	143± 4	0.211± 0.010	0.029± 0.003*	1.551± 0.088	0.414± 0.021	0.497± 0.024
2400ppm	5	124± 5**	0.176± 0.012**	0.037± 0.004	1.652± 0.107	0.445± 0.018*	0.521± 0.013*
4800ppm	4	113± 8**	0.121± 0.022**	0.040± 0.004	1.956± 0.051**	0.471± 0.023**	0.575± 0.023**
9600ppm	0	-	-	-	-	-	-

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL042)

BAIS 3

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (3W)

PAGE : 2

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
control	5	0.819± 0.018	0.230± 0.005	3.067± 0.082	1.221± 0.047
600ppm	5	0.859± 0.034	0.226± 0.005	3.065± 0.031	1.222± 0.047
1200ppm	5	0.870± 0.017	0.242± 0.016	3.207± 0.114	1.197± 0.027
2400ppm	5	0.925± 0.010**	0.221± 0.015	3.271± 0.064**	1.335± 0.027**
4800ppm	4	0.975± 0.054**	0.212± 0.016	3.509± 0.143**	1.411± 0.094**
9600ppm	0	-	-	-	-

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

APPENDIX H 2

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : FEMALE
 UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
 SURVIVAL ANIMALS (3W)

PAGE : 3

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
control	5	104± 4	0.249± 0.016	0.050± 0.006	0.077± 0.009	0.440± 0.023	0.559± 0.022
600ppm	5	105± 5	0.221± 0.016*	0.049± 0.004	0.080± 0.013	0.426± 0.022	0.568± 0.020
1200ppm	5	106± 5	0.221± 0.018*	0.048± 0.002	0.079± 0.005	0.449± 0.016	0.564± 0.023
2400ppm	5	99± 4	0.219± 0.021*	0.049± 0.006	0.082± 0.011	0.459± 0.014	0.604± 0.042*
4800ppm	5	93± 3**	0.166± 0.008**	0.062± 0.004**	0.094± 0.007	0.502± 0.028**	0.612± 0.011*
9600ppm	0	-	-	-	-	-	-

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL042)

BAIS 3

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (3W)

PAGE : 4

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
control	5	0.865± 0.017	0.263± 0.015	3.146± 0.111	1.536± 0.056
600ppm	5	0.871± 0.021	0.246± 0.013	3.085± 0.107	1.522± 0.054
1200ppm	5	0.888± 0.024	0.259± 0.016	3.149± 0.015	1.515± 0.076
2400ppm	5	0.936± 0.038**	0.242± 0.014	3.193± 0.059	1.564± 0.038
4800ppm	5	0.976± 0.013**	0.237± 0.014*	3.522± 0.114**	1.614± 0.045
9600ppm	0	-	-	-	-

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$

Test of Dunnett

(HCL042)

BAIS3

APPENDIX I 1

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : MALE : DEAD AND MORIBUND ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : MALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
 DEAD AND MORIBUND ANIMALS (0- 3W)

PAGE : 1

		Group Name No. of Animals on Study Grade	control 0				600ppm 0				1200ppm 0				2400ppm 0			
Organ	Findings		1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Respiratory system]																		
lung			< 0>				< 0>				< 0>				< 0>			
	congestion		- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
	edema:perivascular		- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
[Hematopoietic system]																		
thymus			< 0>				< 0>				< 0>				< 0>			
	atrophy		- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
spleen			< 0>				< 0>				< 0>				< 0>			
	extramedullary hematopoiesis		- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
[Digestive system]																		
liver			< 0>				< 0>				< 0>				< 0>			
	herniation		- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
 < a > a : Number of animals examined at the site
 b : Number of animals with lesion
 (c) c : b / a * 100

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : MALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
 DEAD AND MORIBUND ANIMALS (0- 3W)

PAGE : 2

		4800ppm				9600ppm				
		1				5				
		No. of Animals on Study				No. of Animals on Study				
		Grade				Grade				
Organ	Findings	1	2	3	4	1	2	3	4	
		(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	
[Respiratory system]										
lung		< 1>				< 5>				
	congestion	0	1	0	0	0	0	0	0	
		(0)	(100)	(0)	(0)	(0)	(0)	(0)	(0)	
	edema:perivascular	1	0	0	0	0	5	0	0	
		(100)	(0)	(0)	(0)	(0)	(100)	(0)	(0)	
[Hematopoietic system]										
thymus		< 1>				< 5>				
	atrophy	1	0	0	0	0	0	0	0	
		(100)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	
		< 1>				< 5>				
spleen	extramedullary hematopoiesis	0	0	0	0	5	0	0	0	
		(0)	(0)	(0)	(0)	(100)	(0)	(0)	(0)	
	[Digestive system]									
	liver		< 1>				< 5>			
herniation		0	0	0	0	1	0	0	0	
		(0)	(0)	(0)	(0)	(20)	(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

APPENDIX I 2

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : MALE: SACRIFICED ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0358
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS-(3W)

PAGE : 1

Organ	Findings	control				600ppm				1200ppm				2400ppm			
		No. of Animals on Study				5				5				5			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
		(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																	
liver	herniation	< 5>				< 5>				< 5>				< 5>			
		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)	(0)	(0)
[Endocrine system]																	
thyroid	ultimibranhial body remanet	< 5>				< 5>				< 5>				< 5>			
		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
[Reproductive system]																	
prostate	inflammation	< 5>				< 5>				< 5>				< 5>			
		2	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
		(40)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
[Nervous system]																	
brain	degeneration:granular cell	< 5>				< 5>				< 5>				< 5>			
		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)	(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 : * : $P \leq 0.05$ ** : $P \leq 0.01$ Test of Chi Square

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : MALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
 SACRIFICED ANIMALS (3W)

PAGE : 2

		Group Name				9600ppm			
		No. of Animals on Study				0			
		Grade							
Organ	Findings	1	2	3	4	1	2	3	4
		(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]									
liver		< 4>				< 0>			
	herniation	1	0	0	0	-	-	-	-
		(25)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
[Endocrine system]									
thyroid		< 4>				< 0>			
	ultimibranchial body remanet	0	0	0	0	-	-	-	-
		(0)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
[Reproductive system]									
prostate		< 4>				< 0>			
	inflammation	0	0	0	0	-	-	-	-
		(0)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
[Nervous system]									
brain		< 4>				< 0>			
	degeneration:granular cell	0	4	0	0 *	-	-	-	-
		(0)	(100)	(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 ; * : $P \leq 0.05$ ** : $P \leq 0.01$ Test of Chi Square

APPENDIX I 3

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : FEMALE : DEAD AND MORIBUND ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : FEMALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
 DEAD AND MORIBUND ANIMALS (0- 3W)

PAGE : 3

		Group Name	control				600ppm				1200ppm				2400ppm			
		No. of Animals on Study	0				0				0				0			
Organ	Findings	Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
Lung			< 0>				< 0>				< 0>				< 0>			
	edema:perivascular		(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
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																	
(HPT150)																		
BAIS																		

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : FEMALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
 DEAD AND MORIBUND ANIMALS (0- 3W)

PAGE : 4

Organ	Findings	4800ppm				9600ppm				
		No. of Animals on Study				No. of Animals on Study				
		0				5				
		Grade	1	2	3	4	Grade	1	2	3
		(%)	(%)	(%)	(%)		(%)	(%)	(%)	(%)

[Respiratory system]

Lung	edema:perivascular	< 0>				< 5>			
		-	-	-	-	0	5	0	0
		(-)	(-)	(-)	(-)	(0)	(100)	(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

(HPT150)

BAIS3

APPENDIX I 4

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : FEMALE : SACRIFICED ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : FEMALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
 SACRIFICED ANIMALS (3W)

PAGE : 3

Organ	Findings	Group Name No. of Animals on Study Grade	control 5				600ppm 5				1200ppm 5				2400ppm 5			
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
nasal cavity	atrophy:olfactory epithelium		< 5>				< 5>				< 5>				< 5>			
			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)	(0)	(0)
[Endocrine system]																		
pituitary	Rathke pouch		< 5>				< 5>				< 5>				< 5>			
			0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
thyroid	ultimibranchial body remanet		< 5>				< 5>				< 5>				< 5>			
			0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(20)	(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
 b : Number of animals with lesion
 (c) c : b / a * 100
 Significant difference : * : P ≤ 0.05 ** : P ≤ 0.01 Test of Chi Square

STUDY NO. : 0358
 ANIMAL : RAT F344/DuCrj
 REPORT TYPE : A1
 SEX : FEMALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
 SACRIFICED ANIMALS (30)

PAGE : 4

		4800ppm				9600ppm			
		No. of Animals on Study				No. of Animals on Study			
		Grade				Grade			
Organ_____	Findings_____	1	2	3	4	1	2	3	4
		(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]									
nasal cavit		< 5>				< 0>			
	atrophy:olfactory epithelium	1	0	0	0	-	-	-	-
		(20)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
[Endocrine system]									
pituitary		< 5>				< 0>			
	Rathke pouch	0	0	0	0	-	-	-	-
		(0)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
thyroid		< 5>				< 0>			
	ultimibranhial body remanet	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
 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

APPENDIX J 1

IDENTITY OF CYCLOHEXENE IN THE 2-WEEK INHALATION STUDY

IDENTITY AND IMPURITY OF CYCLOHEXENE IN THE 2-WEEK INHALATION STUDY

Test Substance : Cyclohexene (Wako Pure Chemical Industries, LTD.)

Lot No. : ACM4092

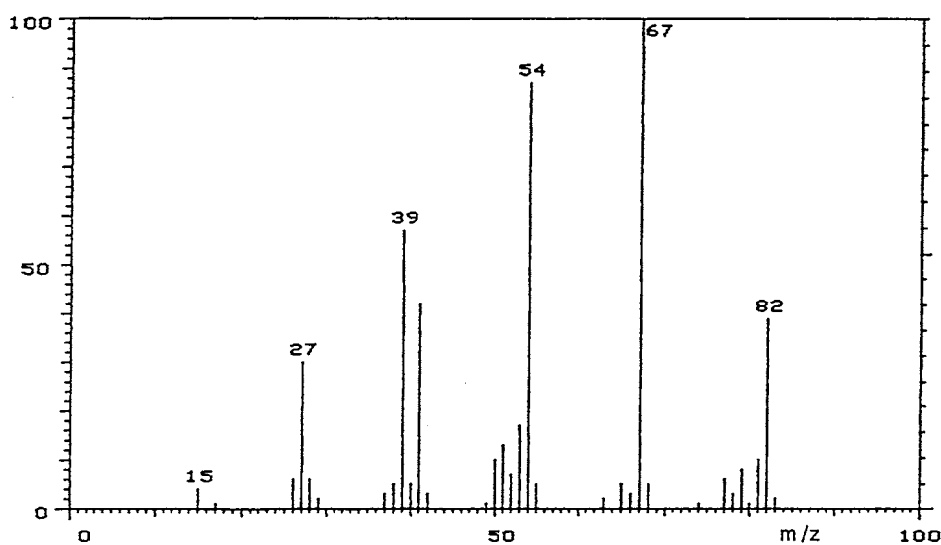
1. Spectral data

Mass Spectrometry

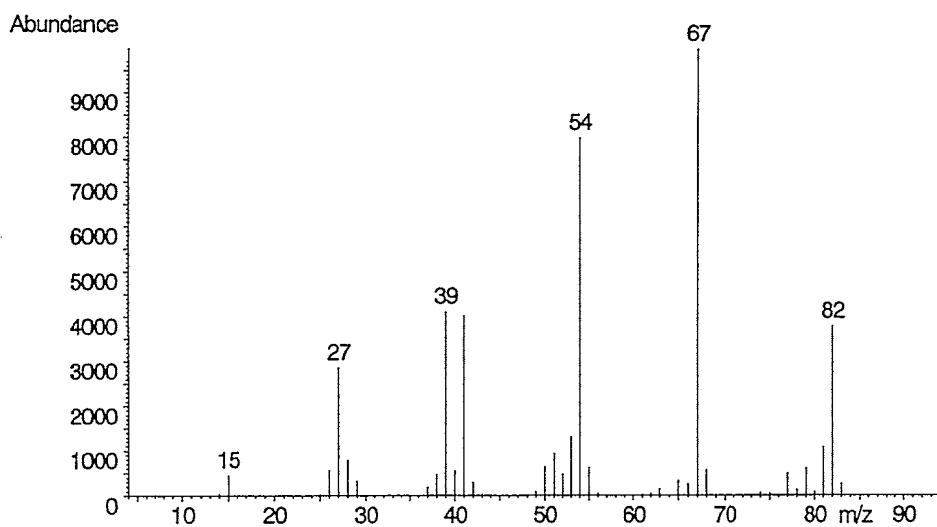
Instrument : Hitachi M-80B Mass Spectrometer

Ionization : EI (Electron Ionization)

Ionization Voltage : 70eV



Mass Spectrum of Test Substance



Mass Spectrum of Literature Data*

Results: The mass spectrum was consistent with literature spectrum.

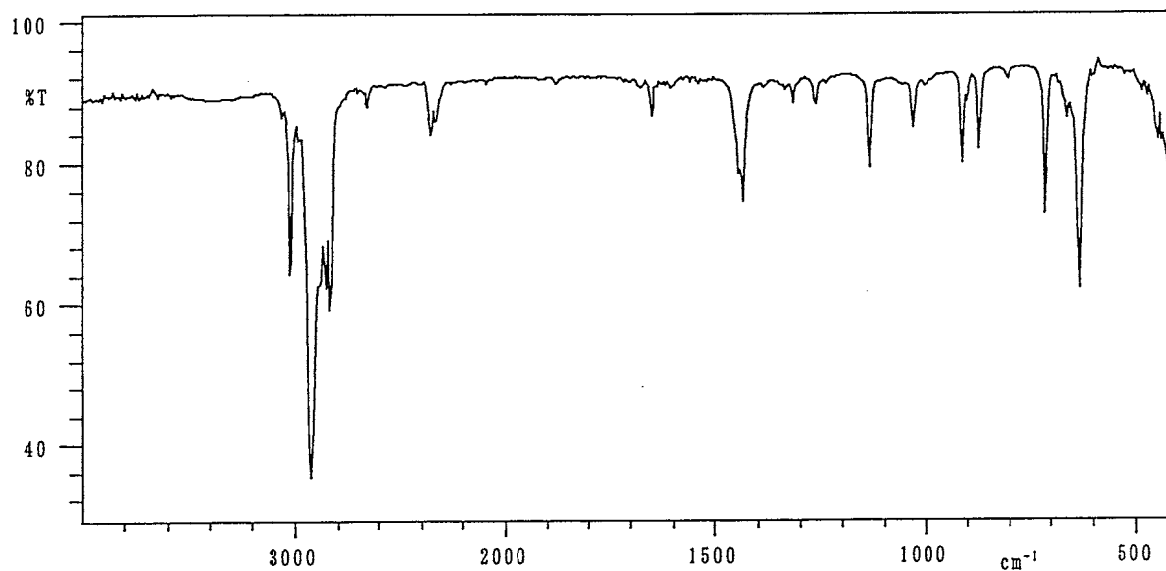
(*Fred W. McLafferty (1994) Wiley registry of mass spectral data, 6th edition.
John Wiley and Sons Inc. (U.S.), Entry Number 2466)

Infrared Spectrometry

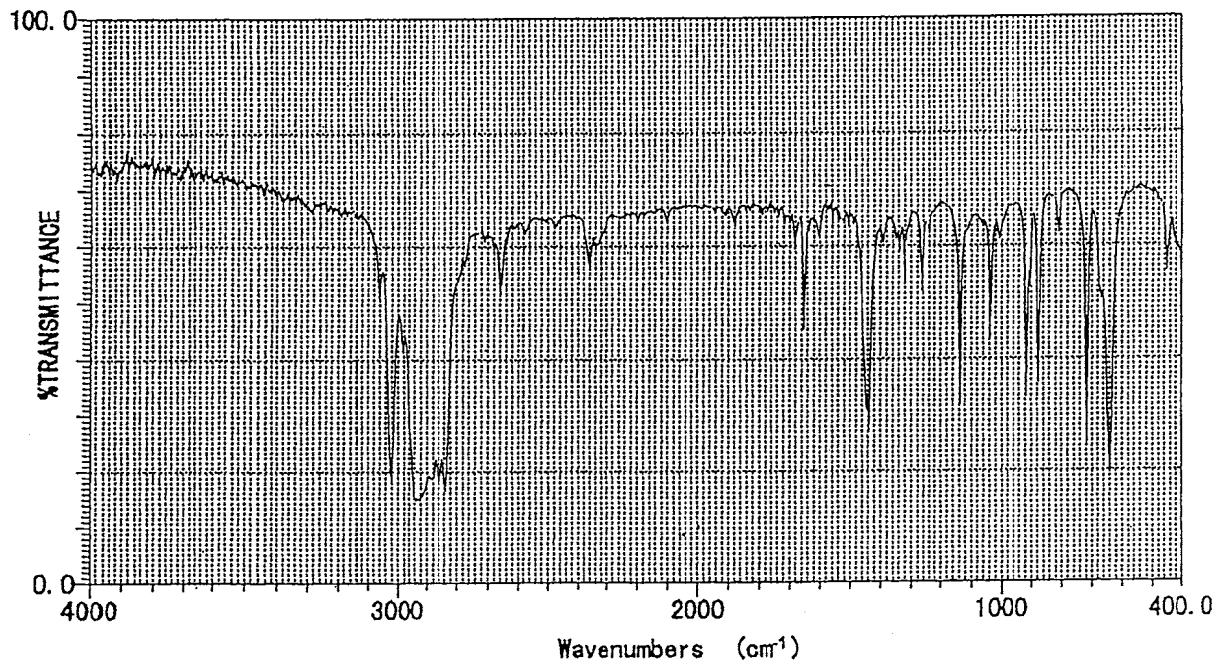
Instrument : Shimadzu FTIR-8200PC Infrared Spectrometer

Cell : KBr Liquid Cell

Resolution : 4 cm^{-1}



Infrared Spectrum of Test Substance



Infrared Spectrum of Literature Data*

Results: The infrared spectrum was consistent with literature spectrum.

(*Performed by the Wako Pure Chemical Industries, LTD.)

2. Impurity

Instrument : Hewlett Packard 6890 Gas Chromatograph
Column : Methyl Silicone (0.53 mm ϕ \times 60 m)
Column Temperature : 60° C
Flow Rate : 15 mL/min
Detector : FID (Flame Ionization Detector)
Injection Volume : 1 μ L

Sample Name	Peak No.	Area (%)	Peak Name
Test Substance	1	0.04	1,3-Cyclodiene
	2	99.87	Cyclohexene
	3	0.09	1,4-Cyclodiene

Results: Gas chromatography indicated one major peak (peak No. 2) and two impurities. It was identified only by comparing its gas chromatograph with that of 1,3-Cyclodiene (peak No. 1) and 1,4-Cyclodiene (peak No. 3) in the Cyclohexene, the amount in the test substance were 0.04% and 0.09%.

3. Conclusions: The test substance was identified as Cyclohexene, by the mass spectrum and the infrared spectrum. Gas chromatography indicated one major peak (peak No. 2) and two impurities. It was identified only by comparing its gas chromatograph with that of 1,3-Cyclodiene and 1,4-Cyclodiene, the amount in the test substance were 0.04% and 0.09%.

APPENDIX J 2

STABILITY OF CYCLOHEXENE IN THE 2-WEEK INHALATION STUDY

STABILITY OF CYCLOHEXENE IN THE 2-WEEK INHALATION STUDY

Test Substance : Cyclohexene (Wako Pure Chemical Industries, LTD.)

Lot No. : ACM4092

1. Sample : This lot was used from 1998.5.26 to 1998.6.8. Test substance was stored in a dark place at room temperature.

2. Gas Chromatography

Instrument : Hewlett Packard 6890 Gas Chromatograph

Column : Methyl silicone (0.53 mm ϕ \times 60 m)

Column Temperature : 60° C

Flow Rate : 15 mL/min

Detector : FID (Flame Ionization Detector)

Injection Volume : 1 μ L

Date (date analyzed)	Peak No.	Retention Time (min)	Area (%)
1998.05.25	1	7.78	0.04
	2	8.91	99.87
	3	9.89	0.09
1998.06.25	1	7.80	0.04
	2	8.92	99.87
	3	9.90	0.09

Results: Gas chromatography indicated one major peak (peak No. 2) and two impurities (peak No. 1, 3 < 0.2% of total area) analyzed at 1998.5.25 and one major peak (peak No. 2) and two impurities (peak No. 1, 3 < 0.2% of total area) analyzed at 1998.6.25. No new trace impurity peak in the test substance analyzed at 1998.6.25 was detected.

3. Conclusions: The test substance was stable for about 1 month in a dark place at room temperature.

APPENDIX K 1

CONCENTRATION OF GLYCIDL IN THE INHALATION CHAMBER OF THE 2-WEEK INHALATION STUDY

CONCENTRATION OF CYCLOHEXENE IN THE INHALATION CHAMBER OF THE 2-WEEK INHALATION STUDY

Group Name	Concentration(ppm) Mean \pm S.D.
0ppm(Control)	0.0 \pm 0.0
600ppm	594.9 \pm 4.2
1200ppm	1195.3 \pm 22.2
2400ppm	2385.1 \pm 35.1
4800ppm	4783.7 \pm 40.7
9600ppm	7724.8 \pm 0.0

APPENDIX K 2

ENVIRONMENTAL CONDITIONS OF INHALATION CHAMBER IN THE 2-WEEK INHALATION STUDY OF CYCLOHEXENE

ENVIRONMENTAL CONDITIONS OF INHALATION CHAMBER IN THE 2-WEEK INHALATION STUDY OF CYCLOHEXENE

Group Name	Temperature(°C)	Humidity(%)	Ventilation Rate(L/min)	Air Change(time/h)
	Mean \pm S.D.	Mean \pm S.D.	Mean \pm S.D.	Mean
0ppm(Control)	22.1 \pm 0.0	52.4 \pm 0.2	212.2 \pm 0.3	12.0
600ppm	22.1 \pm 0.1	55.3 \pm 0.7	212.3 \pm 0.6	12.0
1200ppm	22.2 \pm 0.1	53.3 \pm 0.7	211.8 \pm 0.5	12.0
2400ppm	21.8 \pm 0.1	50.3 \pm 0.6	212.7 \pm 0.5	12.0
4800ppm	21.9 \pm 0.1	50.7 \pm 1.5	212.7 \pm 0.2	12.0
9600ppm	22.1 \pm 0.0	47.4 \pm 0.0	211.9 \pm 0.0	12.0

APPENDIX L 1

METHODS FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 2-WEEK INHALATION STUDY OF CYCLOHEXENE

METHODS FOR HEMATOLOGY AND BIOCHEMISTRY IN THE
2-WEEK INHALATION STUDY OF CYCLOHEXENE

Item	Method
Hematology	
Red blood cell (RBC)	Light scattering method ¹⁾
Hemoglobin (Hgb)	Cyanmethemoglobin method ¹⁾
Hematocrit (Hct)	Calculated as $RBC \times MCV/10$ ¹⁾
Mean corpuscular volume (MCV)	Light scattering method ¹⁾
Mean corpuscular hemoglobin (MCH)	Calculated as $Hgb/RBC \times 10$ ¹⁾
Mean corpuscular hemoglobin concentration (MCHC)	Calculated as $Hgb/Hct \times 100$ ¹⁾
Platelet	Light scattering method ¹⁾
Reticulocyte	Pattern recognition method ³⁾ (New methyleneblue staining)
Prothrombin time	Quick one stage method ²⁾
Activated partial thromboplastin time (APTT)	Ellagic acid activaterd method ²⁾
White blood cell (WBC)	Light scattering method ¹⁾
Differential WBC	Pattern recognition method ³⁾ (May-Grunwald-Giemsa 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	Enzymatic method (GLK·G-6-PDH) ⁴⁾
T-cholesterol	Enzymatic method (CE·COD·POD) ⁴⁾
Triglyceride	Enzymatic method (LPL·GK·GPO·POD) ⁴⁾
Phospholipid	Enzymatic method (PLD·COD·POD) ⁴⁾
Glutamic oxaloacetic transaminase (GOT)	UV·Rate method ⁴⁾
Glutamic pyruvic transaminase (GPT)	UV·Rate method ⁴⁾
Lactate dehydrogenase (LDH)	UV·Rate method ⁴⁾
Alkaline phosphatase (ALP)	p-Nitrophenylphosphate method ⁴⁾
γ -Glutamyl transpeptidase (γ -GTP)	L- γ -Glutamyl-p-nitroanilide method ⁴⁾
Creatine phosphokinase (CPK)	UV·Rate method ⁴⁾
Urea nitrogen	Enzymatic method (Urease·GLDH) 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 ⁴⁾
Inorganic phosphorus	Enzymatic method (PNP·XOD·POD) ⁴⁾

1) Automatic blood cell analyzer (Technicon H·1 : Technicon Instruments Corporation, USA)

2) Automatic coagulometer (Sysmex CA-5000 : Toa Medical Electronics Co., Ltd., Japan)

3) Automatic blood cell differential analyzer (Hitachi 8200 : Hitachi, Ltd., Japan)

4) Automatic analyzer (Hitachi 7070 : Hitachi, Ltd., Japan)

APPENDIX L 2

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY IN THE
2-WEEK INHALATION STUDY OF CYCLOHEXENE

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY
IN THE 2-WEEK INHALATION STUDY OF CYCLOHEXENE

Item	Unit	Decimal place
Hematology		
Red blood cell (RBC)	$\times 10^6/\mu\text{L}$	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	$\times 10^3/\mu\text{L}$	0
Reticulocyte	%	0
Prothrombin time	sec	1
Activated partial thromboplastin time (APTT)	sec	1
White blood cell (WBC)	$\times 10^3/\mu\text{L}$	2
Differential WBC	%	0
Biochemistry		
Total protein	g/dL	1
Albumin	g/dL	1
A/G ratio	—	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 transaminase (GOT)	IU/L	0
Glutamic pyruvic transaminase (GPT)	IU/L	0
Lactate dehydrogenase (LDH)	IU/L	0
Alkaline phosphatase (ALP)	IU/L	0
γ -Glutamyl transpeptidase (γ -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