クロロホロムのラット及びマウスを用いた
吸 入 に よ る が ん 原 性 試 験 報 告 書

APPENDIX

(B1-1～D)

13Week 試験 NO.0097 ; 0098

APPENDIXES (CONTINUED)

A P P E N D I X E S (CONTINUED)

A P P E N D I X E S (CONTINUED)

APPENDIXES (CONTINUED)

APPENDIX B 1-1

CLINICAL OBSERVATION : SUMMARY, RAT : MALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1 13

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : MALE

Clinical sign	Group Name	Administration Week-day												
		0-0	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
		1	1	1	1	1	1	1	1	1	1	1	1	1	1
LOSS OF HAIR	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100 ppm	0	0	0	0	0	0	0	1	1	1	1	0	0	0
	200 ppm	0	0	0	0	0	0	1	1	0	0	0	0	0	0
	400 ppm	0	0	0	0	0	0	1	2	2	3	4	1	0	0
SORE OF SOLE	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	200 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	400 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LOOSE STOOL	0 ppm	0	1	2	0	0	0	0	0	0	0	0	0	0	0
	25 ppm	0	0	0	1	0	0	0	0	0	0	0	0	0	1
	50 ppm	0	0	0	1	0	0	0	0	0	0	0	0	0	1
	100 ppm	0	0	0	1	0	0	0	0	0	0	2	0	0	0
	200 ppm	0	2	0	0	1	0	0	0	0	0	0	0	0	0
	400 ppm	0	1	0	0	0	0	0	0	0	0	0	0	0	0

APPENDIX B 1-2

CLINICAL OBSERVATION : SUMMARY, RAT : FEMALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1 13

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : FEMALE

Clinical sign	Group Name	Administration Week-day 0-0	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
		1	1	1	1	1	1	1	1	1	1	1	1	1	1
LOSS OF HAIR	0 ppm	0	0	0	0	1	1	0	0	0	0	0	0	0	0
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	0	0	0	0	0	1	1	0	0	3	2	1	1
	100 ppm	0	0	1	1	1	1	2	2	0	1	3	3	3	2
	200 ppm	0	0	0	0	1	1	6	7	7	6	5	5	5	2
	400 ppm	0	0	0	0	1	0	6	6	6	6	5	3	1	1
SOILED PERI GENITALIA	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	400 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LACRYMATION	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	0	0	0	2	0	0	0	0	0	0	0	0	0
	400 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GUM	0 ppm	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	400 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0

APPENDIX B 1-3

CLINICAL OBSERVATION : SUMMARY, MOSUE : MALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1 13

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : MALE

Clinical sign	Group Name	Administration Week-day 0-0 1	1-7 1	2-7 1	3-7 1	4-7 1	5-7 1	6-7 1	7-7 1	8-7 1	9-7 1	10-7 1	11-7 1	12-7 1	13-7 1
DEATH	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12 ppm	0	2	2	2	2	2	2	2	2	2	2	2	2	2
	25 ppm	0	7	7	7	7	7	7	7	7	7	7	7	7	7
	50 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	100 ppm	0	8	8	8	8	8	8	8	8	8	8	8	8	8
	200 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
MORIBUND SACRIFICE	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25 ppm	0	2	2	2	2	2	2	2	2	2	2	2	2	2
	50 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	100 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
HUNCHBACK POSITION	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	100 ppm	0	2	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
PILOERECTION	0 ppm	0	0	1	1	1	0	0	1	1	3	3	3	3	4
	12 ppm	0	1	1	1	1	0	1	1	1	1	1	1	1	1
	25 ppm	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	100 ppm	0	2	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
LOSS OF HAIR	0 ppm	0	0	0	0	0	0	1	4	4	4	4	3	2	2
	12 ppm	0	2	2	2	2	3	3	4	4	5	5	5	6	6
	25 ppm	0	0	0	0	0	1	1	1	1	1	1	1	1	1
	50 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	100 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1 13

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : MALE

Clinical sign	Group Name	Administration Week-day 0-0	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
		1	1	1	1	1	1	1	1	1	1	1	1	1	1
SOILED PERI GENITALIA	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12 ppm	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	100 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
DEFECT OF TEETH	0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12 ppm	0	0	0	0	0	0	1	0	0	0	0	0	0	0
	25 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	100 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200 ppm	0	-	-	-	-	-	-	-	-	-	-	-	-	-

APPENDIX B 1-4

CLINICAL OBSERVATION : SUMMARY, MOSUE: FEMALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1 13

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : FEMALE

Clinical sign	Group Name		Administration Week-day 0-0	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
			1	1	1	1	1	1	1	1	1	1	1	1	1	1
HUNCHBACK POSITION	0	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200	ppm	0	1	0	0	0	0	0	0	0	0	0	0	0	0
PILOERECTION	0	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	25	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100	ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	200	ppm	0	1	0	0	0	0	0	0	0	0	0	0	0	0
LOSS OF HAIR	0	ppm	0	0	0	0	1	1	1	1	5	5	5	7	7	7
	12	ppm	0	0	0	0	1	4	4	5	4	4	4	4	4	5
	25	ppm	0	1	1	1	2	3	3	5	5	5	5	6	7	7
	50	ppm	0	0	1	2	2	3	4	4	5	5	6	6	6	6
	100	ppm	0	1	2	2	2	2	2	2	2	2	2	2	2	2
	200	ppm	0	1	1	1	1	2	2	2	2	2	4	5	4	4

APPENDIX B 2-1

BODY WEIGHT CHANGES :SUMMARY, RAT : MALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
0 ppm	126± 4	157± 4	187± 7	213± 6	236± 7	256± 6	272± 6
25 ppm	126± 4	149± 5*	178± 8	201± 11	223± 13	243± 13	256± 14
50 ppm	126± 4	144± 4**	171± 5**	193± 7*	215± 10**	236± 12*	247± 11**
100 ppm	126± 4	145± 5**	172± 9**	193± 12*	211± 15**	232± 16**	245± 18**
200 ppm	126± 4	137± 5**	158± 8**	179± 8**	196± 11**	221± 13**	231± 13**
400 ppm	126± 4	132± 9**	149± 13**	164± 18**	177± 19**	206± 19**	212± 19**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
0 ppm	286± 6	302± 8	315± 10	324± 10	333± 11	340± 13	348± 15
25 ppm	270± 15*	282± 17*	296± 17*	306± 16*	316± 18	324± 20	331± 20
50 ppm	261± 12**	272± 14**	286± 15**	296± 15**	306± 16**	313± 16**	319± 15**
100 ppm	256± 17**	268± 16**	279± 16**	288± 16**	298± 16**	304± 17**	310± 17**
200 ppm	240± 12**	247± 13**	254± 14**	262± 14**	271± 14**	275± 12**	279± 13**
400 ppm	212± 17**	215± 17**	223± 16**	227± 17**	234± 18**	235± 17**	240± 19**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 2-2

BODY WEIGHT CHANGES : SUMMARY, RAT : FEMALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
0 ppm	103± 4	117± 5	131± 7	144± 8	153± 8	164± 8	170± 8
25 ppm	103± 4	112± 4	123± 4*	134± 6*	143± 7*	155± 8*	158± 8*
50 ppm	103± 4	111± 5*	120± 4**	129± 5**	137± 4**	149± 4**	153± 4**
100 ppm	103± 4	108± 4**	120± 5**	130± 6**	140± 7**	150± 8**	156± 8**
200 ppm	103± 4	103± 5**	109± 7**	120± 8**	129± 9**	146± 11**	148± 11**
400 ppm	103± 3	99± 5**	105± 8**	115± 8**	121± 9**	138± 10**	135± 10**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
0 ppm	176± 8	180± 9	186± 10	190± 11	195± 12	200± 11	202± 11
25 ppm	165± 7*	170± 7	176± 10	183± 11	185± 12	190± 11	192± 14
50 ppm	158± 5**	162± 5**	168± 5**	170± 6**	173± 7**	175± 7**	176± 11**
100 ppm	161± 7**	167± 8*	172± 9**	174± 9**	178± 8**	180± 8**	183± 8**
200 ppm	154± 13**	158± 15**	162± 14**	165± 14**	169± 14**	173± 15**	176± 15**
400 ppm	140± 11**	143± 10**	145± 11**	148± 11**	152± 10**	155± 11**	155± 10**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 2-3

BODY WEIGHT CHANGES :SUMMARY, MOSUE : MALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group	Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
0	ppm	23.4± 0.9	24.7± 1.0	25.1± 1.6	26.2± 1.2	27.3± 1.1	27.9± 1.5	28.9± 1.7
12	ppm	23.4± 0.9	22.6± 0.8**	24.2± 0.8	25.7± 1.0	26.8± 1.0	26.6± 1.0	27.6± 1.0
25	ppm	23.4± 1.0	18.9± 0.0 ?	23.7± 0.0 ?	25.4± 0.0 ?	26.0± 0.0 ?	26.1± 0.0 ?	26.9± 0.0 ?
50	ppm	23.4± 1.0	-	-	-	-	-	-
100	ppm	23.4± 0.8	17.6± 0.5 ?	22.8± 1.2 ?	23.8± 1.1 ?	25.5± 1.1 ?	25.2± 1.1 ?	26.6± 0.8 ?
200	ppm	23.4± 0.8	-	-	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
0 ppm	29.9± 1.6	30.7± 1.9	31.0± 2.0	32.0± 2.2	33.1± 2.2	34.2± 2.5	35.2± 2.5
12 ppm	27.8± 1.3**	28.2± 1.3**	28.5± 1.4**	29.2± 1.5**	29.4± 1.7**	30.3± 1.7**	31.2± 1.8**
25 ppm	27.8± 0.0 ?	27.9± 0.0 ?	28.2± 0.0 ?	29.2± 0.0 ?	29.7± 0.0 ?	30.5± 0.0 ?	31.0± 0.0 ?
50 ppm	-	-	-	-	-	-	-
100 ppm	26.9± 1.0 ?	27.5± 1.5 ?	27.1± 0.8 ?	27.5± 0.8 ?	28.2± 1.3 ?	28.2± 1.6 ?	29.8± 1.6 ?
200 ppm	-	-	-	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

APPENDIX B 2-4

BODY WEIGHT CHANGES : SUMMARY, MOSUE: FEMALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
0 ppm	18.8± 0.8	19.3± 1.0	20.3± 0.9	20.5± 1.1	21.7± 1.2	22.0± 1.2	22.4± 0.9
12 ppm	18.8± 0.8	19.5± 0.9	20.3± 0.8	20.7± 0.8	22.3± 0.8	22.3± 0.9	22.6± 0.8
25 ppm	18.7± 0.8	19.6± 1.2	20.1± 0.8	21.4± 1.2	22.1± 0.7	22.4± 1.1	23.3± 0.9
50 ppm	18.7± 0.8	19.1± 1.1	19.9± 0.8	20.7± 0.9	21.7± 1.2	21.7± 1.0	22.5± 0.8
100 ppm	18.7± 0.8	18.5± 0.7	19.7± 0.7	20.5± 0.7	22.1± 0.8	21.6± 0.7	22.4± 0.6
200 ppm	18.7± 0.8	17.2± 1.3**	18.9± 1.2**	20.4± 1.1	22.7± 1.2	22.3± 0.8	23.2± 0.8

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
0 ppm	22.7± 1.1	23.2± 1.1	23.6± 0.8	23.5± 0.8	24.3± 1.1	24.2± 1.1	25.1± 1.3
12 ppm	23.4± 1.0	23.8± 0.5	24.1± 0.7	24.4± 0.8	24.3± 0.7	24.8± 1.1	25.0± 0.5
25 ppm	23.6± 0.9	24.4± 1.4	24.8± 1.1*	24.5± 1.0*	25.1± 1.1	25.4± 0.9*	26.1± 1.4
50 ppm	23.1± 1.1	23.8± 1.0	23.9± 1.3	24.0± 1.0	24.6± 1.3	24.8± 1.0	25.0± 1.4
100 ppm	23.1± 0.7	23.2± 0.7	24.0± 0.5	24.3± 0.7	24.7± 0.4	24.4± 0.9	25.4± 0.6
200 ppm	23.7± 0.8	24.1± 0.7	24.5± 0.7	25.1± 1.1**	25.1± 0.7	25.7± 1.0**	26.0± 0.9

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 3-1

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : MALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

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)
0 ppm	15.2± 0.9	17.4± 1.6	18.1± 1.9	18.4± 1.5	18.3± 1.3	17.2± 0.5	17.6± 0.8
25 ppm	13.6± 0.7**	15.9± 0.9	16.6± 1.8	16.8± 1.8	17.8± 1.6	17.1± 1.4	17.0± 1.1
50 ppm	12.9± 0.7**	15.1± 0.8**	16.1± 1.4	17.2± 1.7	18.3± 1.7	16.8± 1.2	16.8± 0.7
100 ppm	12.6± 0.5**	15.6± 1.0	16.2± 1.5	16.6± 1.6	17.8± 1.9	16.7± 1.5	16.4± 1.3
200 ppm	12.1± 1.0**	14.8± 1.4**	16.7± 1.8	18.4± 1.7	18.0± 1.8	17.6± 1.5	18.6± 1.4
400 ppm	11.9± 1.3**	16.7± 3.4	19.2± 3.9	20.6± 2.4	20.2± 2.3	21.7± 3.7**	25.1± 5.9**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

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)
0 ppm	17.8± 0.8	17.4± 0.8	17.3± 0.7	16.6± 0.8	16.4± 1.0	16.7± 1.3
25 ppm	16.6± 1.2	17.6± 0.7	17.3± 0.9	16.9± 1.1	17.2± 1.4	17.2± 1.0
50 ppm	17.2± 1.3	17.5± 1.2	18.7± 1.9	17.5± 1.6	17.6± 1.8	18.3± 1.3
100 ppm	17.2± 1.3	17.4± 1.5	17.7± 1.8	17.3± 1.4	17.1± 1.7	17.7± 1.5
200 ppm	19.4± 1.7	19.9± 2.0*	20.6± 2.1**	20.8± 2.6**	21.2± 2.9**	21.3± 3.5**
400 ppm	24.0± 5.1*	24.6± 4.6**	25.9± 7.4**	23.7± 5.3**	23.6± 6.5**	24.0± 5.9**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 3-2

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : FEMALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

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)
0 ppm	12.2± 1.0	12.7± 1.1	12.3± 1.0	12.2± 0.7	12.3± 0.9	12.0± 0.9	11.9± 1.0
25 ppm	10.8± 0.7**	11.4± 0.7	11.4± 0.8	11.2± 0.8	12.3± 1.0	11.6± 1.0	11.4± 1.0
50 ppm	10.1± 0.8**	11.3± 0.7*	11.0± 0.8	11.0± 0.4*	12.0± 0.9	11.4± 0.8	11.1± 0.8
100 ppm	10.0± 0.8**	11.4± 1.0	11.6± 1.1	12.0± 0.8	12.2± 0.8	12.6± 1.0	13.1± 1.6
200 ppm	9.7± 0.7**	11.9± 0.9	12.8± 1.6	13.5± 1.3	13.6± 1.8	13.5± 1.7	15.2± 2.1*
400 ppm	9.1± 0.8**	12.7± 1.9	14.8± 2.9	14.7± 2.6	13.9± 1.7	13.6± 2.3	16.0± 2.7**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
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)
0 ppm	11.7± 0.8	12.0± 1.1	12.1± 1.0	11.5± 1.0	11.8± 0.8	11.6± 0.6
25 ppm	12.0± 1.0	12.3± 1.8	12.5± 1.7	11.5± 0.9	12.4± 1.4	12.7± 2.2
50 ppm	11.6± 0.7	12.2± 0.9	12.4± 1.3	11.7± 1.0	12.0± 1.1	12.7± 2.5
100 ppm	13.6± 1.8	14.1± 3.0	13.5± 1.1	13.8± 2.0*	13.6± 1.9	13.9± 1.9
200 ppm	15.3± 2.6**	16.3± 2.0**	16.1± 2.5**	14.8± 2.0**	15.3± 2.8**	16.1± 3.2**
400 ppm	16.8± 3.1**	18.1± 5.0**	17.4± 4.4**	16.5± 3.8**	16.3± 4.4**	15.6± 3.3**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 3-3

FOOD CONSUMPTION CHANGES : SUMMARY, MOSUE : MALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

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)
0 ppm	4.2± 0.3	3.9± 0.3	4.2± 0.3	4.2± 0.2	4.2± 0.3	4.3± 0.3	4.4± 0.4
12 ppm	3.5± 0.4**	4.6± 0.3**	4.3± 0.3	4.7± 0.3**	4.2± 0.3	4.3± 0.2	4.3± 0.1
25 ppm	2.0± 0.0 ?	6.5± 0.0 ?	4.6± 0.0 ?	4.2± 0.0 ?	4.2± 0.0 ?	4.2± 0.0 ?	4.4± 0.0 ?
50 ppm	-	-	-	-	-	-	-
100 ppm	1.7± 1.0 ?	4.7± 0.4 ?	4.9± 1.0 ?	4.6± 0.6 ?	3.9± 0.1 ?	4.7± 0.4 ?	4.7± 0.4 ?
200 ppm	-	-	-	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

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)
0 ppm	4.5± 0.3	4.4± 0.6	4.4± 0.4	4.6± 0.5	4.7± 0.4	4.7± 0.4
12 ppm	4.2± 0.1	4.4± 0.2	4.3± 0.2	4.4± 0.2	4.5± 0.2	4.5± 0.1
25 ppm	4.2± 0.0 ?	4.3± 0.0 ?	4.3± 0.0 ?	4.0± 0.0 ?	4.4± 0.0 ?	4.5± 0.0 ?
50 ppm	-	-	-	-	-	-
100 ppm	4.6± 0.3 ?	4.4± 0.1 ?	4.3± 0.2 ?	4.7± 0.0 ?	4.7± 0.2 ?	4.7± 0.4 ?
200 ppm	-	-	-	-	-	-

Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

APPENDIX B 3-4

FOOD CONSUMPTION CHANGES : SUMMARY, MOSUE : FEMALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

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)
0 ppm	3.1± 0.3	3.2± 0.2	3.6± 0.2	3.8± 0.2	3.8± 0.3	4.1± 0.3	4.2± 0.2
12 ppm	3.2± 0.2	3.3± 0.3	3.6± 0.3	4.0± 0.2	3.9± 0.2	4.1± 0.2	4.3± 0.2
25 ppm	3.1± 0.3	3.4± 0.2	3.9± 0.3	4.0± 0.2	4.1± 0.3	4.4± 0.5	4.6± 0.4*
50 ppm	3.1± 0.5	3.3± 0.2	3.7± 0.3	3.8± 0.4	3.9± 0.4	4.2± 0.4	4.4± 0.3
100 ppm	2.9± 0.4	3.8± 0.5**	4.3± 0.7**	4.2± 0.3**	4.1± 0.4	4.3± 0.3	4.6± 0.5*
200 ppm	3.0± 0.5	4.3± 0.8**	4.3± 0.3**	4.4± 0.3**	4.4± 0.3**	4.8± 0.2**	4.9± 0.3**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
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)
0 ppm	4.1± 0.2	4.2± 0.3	4.2± 0.2	4.4± 0.2	4.4± 0.2	4.3± 0.3
12 ppm	4.3± 0.3	4.5± 0.2	4.4± 0.4	4.4± 0.3	4.6± 0.3	4.6± 0.3
25 ppm	4.7± 0.4**	4.9± 0.5**	4.7± 0.4**	5.1± 0.4**	5.1± 0.5**	5.3± 0.6**
50 ppm	4.4± 0.3	4.5± 0.3	4.4± 0.4	4.6± 0.4	4.6± 0.4	4.9± 0.7
100 ppm	4.6± 0.3*	4.8± 0.4**	4.7± 0.4**	4.9± 0.4**	4.7± 0.4	4.6± 0.5
200 ppm	4.8± 0.3**	4.9± 0.3**	4.8± 0.2**	5.2± 0.4**	5.2± 0.3**	5.1± 0.3**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 4-1

HEMATOLOGY : SUMMARY, RAT : MALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

HEMATOLOGY(1) (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
0	ppm	10	10.14± 0.20	17.4± 0.3	48.6± 1.3	47.8± 0.5	17.2± 0.2	35.9± 0.6	811± 42
25	ppm	10	10.09± 0.39	17.5± 0.6	48.6± 1.9	48.1± 0.4	17.3± 0.3	36.0± 0.6	844± 47
50	ppm	10	9.89± 0.32	17.4± 0.4	48.1± 1.6	48.6± 0.6**	17.6± 0.3**	36.1± 0.8	844± 47
100	ppm	10	9.72± 0.40	17.4± 0.5	47.3± 2.1	48.6± 0.4**	17.9± 0.3**	36.7± 0.7	863± 34*
200	ppm	10	9.96± 0.34	17.5± 0.5	48.0± 1.5	48.1± 0.5	17.6± 0.3**	36.5± 0.8	908± 49**
400	ppm	9	10.17± 0.55	17.1± 0.9	48.1± 2.6	47.2± 0.5	16.9± 0.2	35.7± 0.6	907± 35**

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

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

HEMATOLOGY(2) (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) N-BAND		N-SEG		EOSINO		BASO		MONO		LYMPHO		OTHER	
0	ppm	10	5.64±	1.90	0±	0	21±	4	2±	1	0±	0	2±	2	75±	5	0±	0
25	ppm	10	5.85±	2.37	0±	0	21±	8	1±	1	0±	0	3±	2	76±	9	0±	0
50	ppm	10	6.51±	2.90	0±	0	18±	4	2±	1	0±	0	3±	1	77±	5	0±	0
100	ppm	10	6.25±	2.62	0±	0	17±	5	1±	1	0±	0	3±	1	79±	5	0±	0
200	ppm	10	5.86±	1.88	0±	0	24±	7	1±	1	0±	0	3±	1	72±	7	0±	0
400	ppm	9	4.64±	1.47	0±	0	27±	7	1±	1	0±	0	3±	1	69±	7	0±	0

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

APPENDIX B 4-2

HEMATOLOGY : SUMMARY, RAT : FEMALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

HEMATOLOGY(1) (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
0 ppm	10	9.23± 0.22	17.3± 0.3	47.3± 1.5	51.1± 0.5	18.7± 0.3	36.6± 0.7	845± 52
25 ppm	10	9.12± 0.43	17.2± 0.8	46.8± 2.1	51.3± 0.5	18.9± 0.2	36.7± 0.6	862± 61
50 ppm	10	9.15± 0.23	17.4± 0.2	46.8± 1.2	51.1± 0.4	19.0± 0.3*	37.2± 0.7	873± 34
100 ppm	10	9.22± 0.22	17.4± 0.4	46.9± 1.0	50.7± 0.5	18.8± 0.2	37.1± 0.5	885± 44
200 ppm	10	9.57± 0.38	17.3± 0.7	47.1± 1.5	49.2± 0.5**	18.1± 0.2**	36.8± 0.6	948± 45**
400 ppm	10	9.88± 0.66	17.0± 1.1	47.7± 3.5	48.2± 0.5**	17.2± 0.2**	35.6± 0.6**	948± 60**

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

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

HEMATOLOGY(2) (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$	Differential WBC (%) N-BAND	N-SEG	EOSINO	BASO	MONO	LYMPHO	OTHER
0 ppm	10	3.42± 1.25	0± 0	20± 7	1± 1	0± 0	2± 1	77± 7	0± 0
25 ppm	10	3.42± 1.24	0± 0	19± 6	1± 1	0± 0	2± 2	78± 7	0± 0
50 ppm	10	3.39± 0.76	0± 0	21± 5	1± 1	0± 0	2± 2	75± 5	0± 0
100 ppm	10	3.96± 1.33	0± 0	15± 5	1± 1	0± 0	2± 1	81± 5	0± 0
200 ppm	10	4.28± 1.81	0± 0	21± 10	2± 1	0± 0	2± 2	75± 10	0± 0
400 ppm	10	2.96± 1.01	0± 0	24± 9	1± 1	0± 0	3± 2	73± 9	0± 0

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

APPENDIX B 4-3

HEMATOLOGY : SUMMARY, MOSUE : MALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

HEMATOLOGY(1) (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
0	ppm	10	11.49± 0.31	16.5± 0.4	49.7± 1.2	43.2± 0.5	14.4± 0.1	33.2± 0.3	1416± 126
12	ppm	8	11.44± 0.30	16.6± 0.6	49.8± 1.4	43.5± 0.3	14.5± 0.1	33.2± 0.3	1477± 76
25	ppm	1	11.09± 0.00 ?	15.9± 0.0 ?	48.4± 0.0 ?	43.7± 0.0 ?	14.4± 0.0 ?	32.9± 0.0 ?	1515± 0 ?
50	ppm	0	-	-	-	-	-	-	-
100	ppm	2	11.28± 0.40 ?	16.5± 0.3 ?	49.4± 1.1 ?	43.8± 0.6 ?	14.7± 0.2 ?	33.4± 0.1 ?	1542± 81 ?
200	ppm	0	-	-	-	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

HEMATOLOGY(2) (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) N-BAND		N-SEG		EOSINO		BASO		MONO		LYMPHO		OTHER	
0	ppm	10	1.51±	0.65	0±	0	19±	6	1±	1	0±	0	2±	1	78±	6	0±	0
12	ppm	8	1.34±	0.62	0±	1	16±	4	1±	1	0±	0	1±	1	82±	4	0±	0
25	ppm	1	0.70±	0.00 ?	0±	0 ?	7±	0 ?	1±	0 ?	0±	0 ?	1±	0 ?	91±	0 ?	0±	0 ?
50	ppm	0	-		-		-		-		-		-		-		-	
100	ppm	2	1.15±	1.06 ?	0±	0 ?	10±	4 ?	2±	1 ?	0±	0 ?	1±	1 ?	88±	4 ?	1±	1 ?
200	ppm	0	-		-		-		-		-		-		-		-	

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

APPENDIX B 4-4

HEMATOLOGY : SUMMARY, MOSUE : FEMALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

HEMATOLOGY(1) (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
0 ppm	10	11.50± 0.31	16.8± 0.4	50.1± 1.3	43.5± 0.6	14.7± 0.2	33.6± 0.2	1348± 45
12 ppm	9	11.56± 0.21	16.9± 0.1	50.5± 0.7	43.6± 0.5	14.7± 0.2	33.6± 0.4	1308± 71
25 ppm	9	11.56± 0.28	17.1± 0.4	50.9± 1.4	44.0± 0.5	14.8± 0.2	33.7± 0.4	1390± 82
50 ppm	10	11.67± 0.57	17.2± 0.6	50.7± 2.0	43.5± 2.5	14.7± 0.9*	33.9± 0.3	1489± 128*
100 ppm	10	11.86± 0.31	17.4± 0.7*	51.7± 2.1	43.6± 2.5	14.7± 0.9	33.7± 0.2	1608± 104**
200 ppm	10	11.33± 0.52	16.7± 0.4	49.8± 1.7	44.0± 2.4**	14.7± 0.8*	33.5± 0.3	1598± 164**

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

HEMATOLOGY(2) (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	WBC $10^3/\mu\ell$	Differential WBC (%) N-BAND	N-SEG	EOSINO	BASO	MONO	LYMPHO	OTHER
0	ppm	10	1.17± 0.59	0± 0	19± 4	0± 1	0± 0	1± 1	80± 4	0± 0
12	ppm	9	1.00± 0.76	0± 0	23± 7	0± 1	0± 0	1± 1	76± 8	0± 0
25	ppm	9	0.92± 0.56	0± 0	21± 5	1± 1	0± 0	1± 1	77± 6	0± 0
50	ppm	10	1.04± 0.97	0± 0	17± 7	0± 0	0± 0	1± 1	82± 7	0± 0
100	ppm	10	0.80± 0.48	0± 0	19± 6	0± 0	0± 0	1± 1	80± 6	0± 0
200	ppm	10	1.07± 0.67	0± 0	16± 6	0± 0	0± 0	1± 1	83± 6	0± 0

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

APPENDIX B 5-1

BIOCHEMISTRY : SUMMARY, RAT : MALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

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
0 ppm	10	6.7± 0.1	3.8± 0.1	1.3± 0.1	0.17± 0.02	176± 9	54± 3	92± 13
25 ppm	10	6.8± 0.1	3.9± 0.1	1.3± 0.1	0.17± 0.02	172± 12	55± 4	77± 13*
50 ppm	10	6.8± 0.1	3.9± 0.1	1.3± 0.0	0.17± 0.02	163± 11*	57± 5	69± 13**
100 ppm	10	7.0± 0.2*	4.0± 0.1**	1.4± 0.1**	0.18± 0.02	159± 10**	68± 10**	57± 9**
200 ppm	10	7.0± 0.2**	4.1± 0.1**	1.4± 0.0**	0.19± 0.03	141± 13**	63± 8*	43± 8**
400 ppm	10	6.9± 0.3	4.0± 0.1**	1.4± 0.0**	0.20± 0.04	117± 9**	63± 6**	41± 8**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	PHOSPHOLIPID mg/dl		GOT IU/l		GPT IU/l		LDH IU/l		ALP IU/l		LAP IU/l		G-GTP IU/l	
0	ppm	10	105±	6	75±	16	25±	4	122±	33	299±	16	56±	1	0±	0
25	ppm	10	104±	6	68±	7	22±	3	112±	20	282±	20	56±	1	0±	0
50	ppm	10	104±	10	70±	13	23±	4	118±	36	276±	15	55±	1	0±	0
100	ppm	10	116±	16	76±	31	24±	7	126±	47	271±	23	56±	2	0±	0
200	ppm	10	105±	14	64±	5	25±	8	114±	26	324±	19	64±	8	1±	1
400	ppm	10	105±	8	75±	16	38±	21	160±	102	371±	44*	75±	16**	4±	2**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	CPK IU/ℓ		UREA NITROGEN mg/dℓ		CREATININE mg/dℓ		SODIUM mEq/ℓ		POTASSIUM mEq/ℓ		CHLORIDE mEq/ℓ		CALCIUM mg/dℓ	
0	ppm	10	72±	8	17.8±	1.5	0.5±	0.1	141±	1	3.7±	0.2	105±	1	10.2±	0.2
25	ppm	10	78±	4	18.6±	1.0	0.5±	0.0	142±	1	3.7±	0.2	105±	1	10.2±	0.2
50	ppm	10	80±	5	17.9±	2.4	0.5±	0.0	142±	2	3.8±	0.2	105±	1	10.2±	0.1
100	ppm	10	77±	4	18.3±	1.9	0.5±	0.1	142±	1	3.7±	0.3	105±	1	10.4±	0.2
200	ppm	10	79±	9	17.8±	2.1	0.5±	0.1	142±	1	3.7±	0.2	103±	2	10.6±	0.3**
400	ppm	10	87±	22	16.2±	1.5	0.5±	0.1	141±	1	3.8±	0.3	102±	2**	10.4±	0.2

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	INORGANIC PHOSPHORUS mg/dl
0	ppm	10	5.0± 0.6
25	ppm	10	5.2± 0.6
50	ppm	10	5.7± 0.7
100	ppm	10	5.6± 0.6
200	ppm	10	6.4± 1.1**
400	ppm	10	7.3± 1.1**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 5-2

BIOCHEMISTRY : SUMMARY, RAT : FEMALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

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
0 ppm	10	6.5± 0.1	3.8± 0.1	1.4± 0.1	0.19± 0.02	138± 5	72± 5	41± 5
25 ppm	10	6.4± 0.2	3.6± 0.1**	1.3± 0.1	0.20± 0.07	133± 11	79± 7	41± 7
50 ppm	10	6.4± 0.2	3.6± 0.1**	1.3± 0.1	0.19± 0.02	126± 12	80± 6*	41± 5
100 ppm	10	6.4± 0.1	3.7± 0.1	1.4± 0.1	0.20± 0.03	125± 10	78± 6	40± 5
200 ppm	10	6.7± 0.1*	3.9± 0.1	1.4± 0.1	0.20± 0.03	121± 15**	71± 4	37± 5
400 ppm	10	6.6± 0.2	3.9± 0.1	1.4± 0.1	0.20± 0.03	109± 9**	63± 12	42± 10

Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	PHOSPHOLIPID mg/dℓ		GOT IU/ℓ		GPT IU/ℓ		LDH IU/ℓ		ALP IU/ℓ		LAP IU/ℓ		G-GTP IU/ℓ	
0	ppm	10	137±	9	74±	22	25±	10	121±	34	209±	21	57±	2	1±	1
25	ppm	10	148±	11	71±	25	30±	23	124±	67	209±	19	58±	3	1±	1
50	ppm	10	144±	7	68±	8	24±	6	113±	26	218±	19	60±	2	2±	1
100	ppm	10	141±	10	61±	4	19±	2	120±	41	223±	24	63±	5	2±	1
200	ppm	10	125±	6*	67±	8	21±	6	117±	32	274±	42**	70±	11*	5±	3**
400	ppm	10	111±	13**	69±	13	23±	9	171±	125	344±	67**	78±	20**	11±	8**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	CPK IU/ℓ		UREA NITROGEN mg/dℓ		CREATININE mg/dℓ		SODIUM mEq/ℓ		POTASSIUM mEq/ℓ		CHLORIDE mEq/ℓ		CALCIUM mg/dℓ	
0	ppm	10	71±	9	18.1±	1.9	0.5±	0.0	141±	2	3.5±	0.2	108±	2	9.9±	0.2
25	ppm	10	75±	14	18.9±	3.0	0.5±	0.0	142±	1	3.7±	0.5	107±	1	10.0±	0.3
50	ppm	10	72±	9	19.3±	1.3	0.5±	0.0	141±	1	3.5±	0.2	107±	1	10.0±	0.2
100	ppm	10	69±	11	18.0±	2.4	0.5±	0.0	141±	1	3.6±	0.1	106±	1	10.2±	0.3
200	ppm	10	74±	12	19.0±	2.0	0.5±	0.1	141±	1	3.5±	0.2	105±	2*	10.2±	0.3
400	ppm	10	85±	31	18.7±	2.1	0.5±	0.1	141±	2	3.5±	0.4	103±	3**	10.2±	0.2

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

Group	Name	NO. of Animals	INORGANIC PHOSPHORUS mg/dℓ	
0	ppm	10	4.3±	1.3
25	ppm	10	5.0±	1.0
50	ppm	10	5.0±	1.1
100	ppm	10	5.5±	1.5
200	ppm	10	6.3±	1.4**
400	ppm	10	6.9±	1.1**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 5-3

BIOCHEMISTRY : SUMMARY, MOSUE : MALE

(13Week　STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

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
0	ppm	10	5.4± 0.1	3.0± 0.0	1.3± 0.1	0.48± 0.08	196± 45	80± 5	71± 9
12	ppm	8	5.3± 0.2	2.9± 0.1	1.2± 0.0	0.40± 0.15	172± 45	87± 12	65± 15
25	ppm	1	5.2± 0.0 ?	2.9± 0.0 ?	1.3± 0.0 ?	0.35± 0.00 ?	206± 0 ?	96± 0 ?	67± 0 ?
50	ppm	0	-	-	-	-	-	-	-
100	ppm	2	5.6± 0.1 ?	3.2± 0.0 ?	1.4± 0.1 ?	0.33± 0.03 ?	192± 58 ?	80± 19 ?	36± 8 ?
200	ppm	0	-	-	-	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	GOT IU/ℓ	GPT IU/ℓ	LDH IU/ℓ	ALP IU/ℓ	CPK IU/ℓ	UREA NITROGEN mg/dℓ	SODIUM mEq/ℓ
0	ppm	10	45± 7	10± 2	359± 94	184± 7	56± 14	32.6± 4.9	150± 2
12	ppm	8	41± 5	11± 1	290± 78	192± 14	56± 24	29.2± 2.3	149± 2
25	ppm	1	40± 0 ?	12± 0 ?	278± 0 ?	190± 0 ?	101± 0 ?	28.9± 0.0 ?	148± 0 ?
50	ppm	0	-	-	-	-	-	-	-
100	ppm	2	52± 13 ?	12± 1 ?	360± 112 ?	264± 23 ?	122± 45 ?	34.7± 2.7 ?	151± 2 ?
200	ppm	0	-	-	-	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	POTASSIUM mEq/ℓ	CHLORIDE mEq/ℓ	CALCIUM mg/dℓ	INORGANIC PHOSPHORUS mg/dℓ
0	ppm	10	5.0± 0.3	120± 2	8.7± 0.3	7.4± 1.2
12	ppm	8	5.2± 0.6	120± 2	8.8± 0.3	7.4± 2.0
25	ppm	1	5.3± 0.0 ?	122± 0 ?	8.7± 0.0 ?	5.7± 0.0 ?
50	ppm	0	-	-	-	-
100	ppm	2	4.9± 0.3 ?	122± 4 ?	9.0± 0.1 ?	7.6± 0.5 ?
200	ppm	0	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

APPENDIX B 5-4

BIOCHEMISTRY : SUMMARY, MOSUE : FEMALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

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
0 ppm	10	5.4± 0.2	3.2± 0.1	1.5± 0.1	0.45± 0.09	152± 15	66± 5	43± 4
12 ppm	9	5.4± 0.1	3.2± 0.1	1.4± 0.1	0.40± 0.10	160± 16	65± 7	41± 7
25 ppm	10	5.4± 0.2	3.2± 0.1	1.4± 0.1	0.44± 0.12	186± 21*	65± 9	38± 9
50 ppm	10	5.5± 0.2	3.3± 0.1	1.5± 0.1	0.36± 0.08	186± 31*	68± 9	29± 7**
100 ppm	10	5.7± 0.2**	3.5± 0.1**	1.5± 0.1	0.40± 0.08	176± 42	63± 7	26± 6**
200 ppm	10	5.8± 0.2**	3.5± 0.1**	1.5± 0.0	0.38± 0.08	172± 39	69± 11	37± 12

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	GOT IU/ℓ	GPT IU/ℓ	LDH IU/ℓ	ALP IU/ℓ	CPK IU/ℓ	UREA NITROGEN mg/dℓ	SODIUM mEq/ℓ
0	ppm	10	58± 15	14± 5	348± 81	327± 30	57± 22	24.3± 1.7	150± 2
12	ppm	9	66± 21	14± 4	340± 131	350± 34	79± 42	25.2± 2.9	149± 2
25	ppm	10	161± 330	48± 113	538± 708	316± 36	85± 69	25.4± 3.0	148± 2
50	ppm	10	60± 16	14± 4	297± 66	333± 35	72± 38	29.3± 3.3**	148± 2
100	ppm	10	86± 25	17± 3	425± 155	349± 53	130± 85	33.5± 3.2**	149± 2
200	ppm	10	113± 24**	39± 9**	451± 150	375± 48*	123± 103	28.7± 4.1*	149± 2

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

BIOCHEMISTRY (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	POTASSIUM mEq/ℓ		CHLORIDE mEq/ℓ		CALCIUM mg/dℓ		INORGANIC PHOSPHORUS mg/dℓ	
0	ppm	10	4.6±	0.4	121±	2	8.6±	0.3	6.2±	0.8
12	ppm	9	4.6±	0.4	121±	1	8.5±	0.2	6.3±	0.7
25	ppm	10	4.6±	0.4	120±	2	8.7±	0.3	6.4±	1.1
50	ppm	10	4.4±	0.4	120±	2	8.6±	0.3	5.7±	1.0
100	ppm	10	4.4±	0.4	121±	2	8.7±	0.3	6.2±	0.6
200	ppm	10	4.3±	0.3	120±	2	8.8±	0.2	6.2±	0.6

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 6-1

URINALYSIS : SUMMARY, RAT : MALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
SAMPLING DATE : 013-7
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group	Name	NO. of Animals	pH 5.0	6.0	6.5	7.0	7.5	8.0	8.5	CHI	Protein −	±	+	2+	3+	4+	CHI	Glucose −	±	+	2+	3+	4+	CHI	Ketone body −	±	+	2+	3+	4+	CHI	Bilirubin −	+	2+	3+	CHI
0	ppm	10	0	0	1	1	3	5	0		0	1	8	1	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	
25	ppm	10	0	0	1	2	5	2	0		0	3	4	3	0	0		10	0	0	0	0	0		9	0	1	0	0	0		10	0	0	0	
50	ppm	10	0	0	1	0	6	3	0		0	2	5	3	0	0		10	0	0	0	0	0		6	0	4	0	0	0	*	10	0	0	0	
100	ppm	10	0	0	3	1	6	0	0		0	0	6	4	0	0		10	0	0	0	0	0		9	0	1	0	0	0		10	0	0	0	
200	ppm	10	0	0	2	3	5	0	0		0	0	8	2	0	0		7	3	0	0	0	0		8	0	2	0	0	0		10	0	0	0	
400	ppm	10	0	0	3	3	4	0	0		0	0	3	3	4	0	*	2	2	3	2	1	0	**	5	0	5	0	0	0	**	10	0	0	0	

Significent difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

STUDY NO. : 0097
ANIMAL : RAT F344
SAMPLING DATE : 013-7
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group	Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
0	ppm	10	9	1	0	0	0		10	0	0	0	0	
25	ppm	10	8	2	0	0	0		10	0	0	0	0	
50	ppm	10	3	7	0	0	0	**	10	0	0	0	0	
100	ppm	10	3	7	0	0	0	**	10	0	0	0	0	
200	ppm	10	0	10	0	0	0	**	10	0	0	0	0	
400	ppm	10	1	9	0	0	0	**	10	0	0	0	0	

Significent difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

APPENDIX B 6-2

URINALYSIS : SUMMARY, RAT : FEMALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
SAMPLING DATE : 013-7
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group	Name	NO. of Animals	pH 5.0	6.0	6.5	7.0	7.5	8.0	8.5	CHI	Protein −	±	+	2+	3+	4+	CHI	Glucose −	±	+	2+	3+	4+	CHI	Ketone body −	±	+	2+	3+	4+	CHI	Bilirubin −	+	2+	3+	CHI
0	ppm	10	0	0	0	0	3	7	0		1	8	0	1	0	0		10	0	0	0	0	0		8	0	2	0	0	0		10	0	0	0	
25	ppm	10	0	0	2	2	3	3	0		6	4	0	0	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	
50	ppm	10	0	1	4	2	2	1	0	*	3	4	3	0	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	
100	ppm	10	0	1	2	4	3	0	0	**	2	6	2	0	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	
200	ppm	10	0	4	1	1	2	2	0		0	7	2	0	1	0		9	0	0	0	1	0		10	0	0	0	0	0		10	0	0	0	
400	ppm	10	0	4	3	2	1	0	0	**	0	5	4	1	0	0		0	1	2	5	2	0	**	9	0	1	0	0	0		10	0	0	0	

Significent difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

STUDY NO. : 0097 URINALYSIS
ANIMAL : RAT F344
SAMPLING DATE : 013-7
SEX : FEMALE REPORT TYPE : A1

Group Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
0 ppm	10	10	0	0	0	0		10	0	0	0	0	
25 ppm	10	10	0	0	0	0		10	0	0	0	0	
50 ppm	10	10	0	0	0	0		10	0	0	0	0	
100 ppm	10	10	0	0	0	0		10	0	0	0	0	
200 ppm	10	4	6	0	0	0	**	10	0	0	0	0	
400 ppm	10	3	7	0	0	0	**	10	0	0	0	0	

Significent difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

APPENDIX B 6-3

URINALYSIS : SUMMARY, MOSUE : MALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
SAMPLING DATE : 013-7
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group	Name	NO. of Animals	pH 5.0	6.0	6.5	7.0	7.5	8.0	8.5	CHI	Protein −	±	+	2+	3+	4+	CHI	Glucose −	±	+	2+	3+	4+	CHI	Ketone body −	+	2+	3+	CHI	Occult blood −	±	+	2+	3+	CHI
0	ppm	10	0	0	0	0	2	8	0		0	0	8	2	0	0		10	0	0	0	0	0		2	7	1	0		10	0	0	0	0	
12	ppm	8	0	0	0	2	2	4	0		0	0	0	6	2	0	**	8	0	0	0	0	0		1	7	0	0		8	0	0	0	0	
25	ppm	1	0	0	0	0	0	1	0	?	0	0	1	0	0	0	?	1	0	0	0	0	0	?	0	1	0	0	?	1	0	0	0	0	?
50	ppm	0	-	-	-	-	-	-	-		-	-	-	-	-	-		-	-	-	-	-	-		-	-	-	-		-	-	-	-	-	
100	ppm	2	0	0	0	0	0	2	0	?	0	0	0	2	0	0	?	2	0	0	0	0	0	?	0	1	1	0	?	2	0	0	0	0	?
200	ppm	0	-	-	-	-	-	-	-		-	-	-	-	-	-		-	-	-	-	-	-		-	-	-	-		-	-	-	-	-	

Significent difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
SAMPLING DATE : 013-7
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group	Name	NO. of Animals	Urobilinogen ±	+	2+	3+	4+	CHI
0	ppm	10	10	0	0	0	0	
12	ppm	8	8	0	0	0	0	
25	ppm	1	1	0	0	0	0	?
50	ppm	0	-	-	-	-	-	
100	ppm	2	2	0	0	0	0	?
200	ppm	0	-	-	-	-	-	

Significent difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

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

APPENDIX B 6-4

URINALYSIS : SUMMARY, MOSUE : FEMALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
SAMPLING DATE : 013-7
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group	Name	NO. of Animals	pH 5.0	6.0	6.5	7.0	7.5	8.0	8.5	CHI	Protein −	±	+	2+	3+	4+	CHI	Glucose −	±	+	2+	3+	4+	CHI	Ketone body −	+	2+	3+	CHI	Occult blood −	±	+	2+	3+	CHI
0	ppm	10	0	0	0	1	1	6	2		0	2	6	2	0	0		10	0	0	0	0	0		6	4	0	0		10	0	0	0	0	
12	ppm	10	0	0	1	3	2	2	2		2	2	2	2	2	0		10	0	0	0	0	0		6	4	0	0		9	1	0	0	0	
25	ppm	10	0	0	1	2	1	6	0		0	3	4	3	0	0		10	0	0	0	0	0		5	5	0	0		10	0	0	0	0	
50	ppm	10	0	0	5	2	1	2	0		0	0	7	3	0	0		10	0	0	0	0	0		4	6	0	0		10	0	0	0	0	
100	ppm	10	0	0	0	1	1	8	0		0	0	7	3	0	0		10	0	0	0	0	0		5	5	0	0		10	0	0	0	0	
200	ppm	10	0	0	1	3	4	2	0		0	3	5	1	1	0		10	0	0	0	0	0		3	6	1	0		10	0	0	0	0	

Significent difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
SAMPLING DATE : 013-7
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group	Name	NO. of Animals	Urobilinogen ±	+	2+	3+	4+	CHI
0	ppm	10	10	0	0	0	0	
12	ppm	10	10	0	0	0	0	
25	ppm	10	10	0	0	0	0	
50	ppm	10	10	0	0	0	0	
100	ppm	10	10	0	0	0	0	
200	ppm	10	10	0	0	0	0	

Significent difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

APPENDIX B 7-1

GROSS FINDINGS : SUMMARY, RAT : MALE : SACRIFICED ANIMALS

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name / NO. of Animals	0 ppm 10 (%)	25 ppm 10 (%)	50 ppm 10 (%)	100 ppm 10 (%)
thymus	red zone		2 (20)	3 (30)	1 (10)	0 (0)
liver	herniation		0 (0)	2 (20)	0 (0)	0 (0)
kidney	pale		0 (0)	0 (0)	0 (0)	0 (0)
adipose	nodule		0 (0)	0 (0)	1 (10)	0 (0)

Organ	Findings	Group Name NO. of Animals	200 ppm 10 (%)	400 ppm 10 (%)
thymus	red zone		2 (20)	3 (30)
liver	herniation		0 (0)	0 (0)
kidney	pale		3 (30)	9 (90)
adipose	nodule		0 (0)	0 (0)

APPENDIX B 7-2

GROSS FINDINGS : SUMMARY, RAT : FEMALE : SACRIFICED ANIMALS

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name NO. of Animals	0 ppm 10 (%)	25 ppm 10 (%)	50 ppm 10 (%)	100 ppm 10 (%)
thymus	red zone		1 (10)	0 (0)	0 (0)	1 (10)
spleen	red zone		0 (0)	0 (0)	0 (0)	1 (10)
liver	herniation		2 (20)	1 (10)	0 (0)	0 (0)
kidney	pale		0 (0)	0 (0)	0 (0)	1 (10)
ovary	cyst		0 (0)	0 (0)	0 (0)	0 (0)
uterus	dilated lumen		4 (40)	1 (10)	2 (20)	3 (30)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name NO. of Animals	200 ppm 10 (%)	400 ppm 10 (%)
thymus	red zone		0 (0)	0 (0)
spleen	red zone		0 (0)	0 (0)
liver	herniation		2 (20)	0 (0)
kidney	pale		4 (40)	10 (100)
ovary	cyst		1 (10)	0 (0)
uterus	dilated lumen		1 (10)	0 (0)

APPENDIX B 7-3

GROSS FINDINGS : SUMMARY, MOSUE : MALE :DEAD AND MORIBUND ANIMALS

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 13W)

Organ	Findings	Group Name / NO. of Animals	0 ppm 0 (%)	12 ppm 2 (%)	25 ppm 9 (%)	50 ppm 10 (%)
lung	red		- (-)	1 (50)	5 (56)	4 (40)
spleen	black zone		- (-)	0 (0)	0 (0)	0 (0)
gl stomach	red patch/zone		- (-)	0 (0)	0 (0)	0 (0)
	fluid:red		- (-)	0 (0)	0 (0)	1 (10)
liver	pale		- (-)	2 (100)	8 (89)	9 (90)
kidney	pale		- (-)	0 (0)	1 (11)	0 (0)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 13W)

Organ	Findings	Group Name NO. of Animals	100 ppm 8 (%)	200 ppm 10 (%)
lung	red		5 (63)	8 (80)
spleen	black zone		0 (0)	1 (10)
gl stomach	red patch/zone		2 (25)	2 (20)
	fluid:red		0 (0)	0 (0)
liver	pale		6 (75)	6 (60)
kidney	pale		0 (0)	0 (0)

APPENDIX B 7-4

GROSS FINDINGS : SUMMARY, MOSUE : MALE : SACRIFICED ANIMALS

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	0 ppm	12 ppm	25 ppm	50 ppm
		NO. of Animals	10 (%)	8 (%)	1 (%)	0 (%)
spleen	black zone		2 (20)	0 (0)	0 (0)	- (-)
kidney	hydronephrosis		1 (10)	0 (0)	0 (0)	- (-)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name NO. of Animals	100 ppm 2 (%)	200 ppm 0 (%)
spleen	black zone		1 (50)	- (-)
kidney	hydronephrosis		0 (0)	- (-)

APPENDIX B 7-5

GROSS FINDINGS : SUMMARY, MOSUE : FEMALE : SACRIFICED ANIMALS

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name NO. of Animals	0 ppm 10 (%)	12 ppm 10 (%)	25 ppm 10 (%)	50 ppm 10 (%)
spleen	black zone		1 (10)	2 (20)	3 (30)	2 (20)
liver	white		0 (0)	0 (0)	0 (0)	0 (0)
	white zone		0 (0)	0 (0)	1 (10)	0 (0)
ovary	cyst		0 (0)	1 (10)	0 (0)	0 (0)
uterus	dilated lumen		0 (0)	0 (0)	0 (0)	0 (0)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name NO. of Animals	100 ppm 10 (%)	200 ppm 10 (%)
spleen	black zone		2 (20)	1 (10)
liver	white		0 (0)	9 (90)
	white zone		0 (0)	0 (0)
ovary	cyst		0 (0)	0 (0)
uterus	dilated lumen		1 (10)	3 (30)

APPENDIX B 8-1

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : MALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	Body Weight	THYMUS	ADRENALS	TESTES	HEART	LUNGS
0 ppm	10	327± 13	0.285± 0.025	0.052± 0.004	2.867± 0.157	0.950± 0.107	1.046± 0.089
25 ppm	10	302± 19**	0.234± 0.042**	0.051± 0.004	2.858± 0.098	0.974± 0.056	1.020± 0.063
50 ppm	10	296± 13**	0.235± 0.027**	0.054± 0.006	2.860± 0.076	0.933± 0.064	1.040± 0.084
100 ppm	10	289± 18**	0.217± 0.024**	0.052± 0.004	2.841± 0.088	0.890± 0.052	0.984± 0.074
200 ppm	10	261± 12**	0.210± 0.019**	0.056± 0.008	2.840± 0.120	0.807± 0.084**	0.982± 0.079
400 ppm	10	227± 16**	0.171± 0.020**	0.052± 0.004	2.658± 0.094**	0.753± 0.042**	0.934± 0.083*

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
0	ppm	10	1.880± 0.112	0.567± 0.031	8.113± 0.515	1.886± 0.053
25	ppm	10	1.952± 0.107	0.544± 0.034	7.897± 0.559	1.893± 0.042
50	ppm	10	1.948± 0.113	0.546± 0.031	7.909± 0.412	1.887± 0.057
100	ppm	10	1.927± 0.128	0.536± 0.045	7.937± 0.582	1.872± 0.044
200	ppm	10	1.982± 0.160	0.489± 0.049**	7.344± 0.488**	1.854± 0.015
400	ppm	10	2.023± 0.234	0.442± 0.052**	6.834± 0.593**	1.779± 0.048**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 8-2

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : FEMALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	Body Weight	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
0 ppm	10	187± 11	0.208± 0.013	0.059± 0.005	0.101± 0.009	0.650± 0.040	0.778± 0.043
25 ppm	10	177± 12	0.198± 0.022	0.059± 0.005	0.102± 0.013	0.645± 0.032	0.786± 0.072
50 ppm	10	165± 8**	0.175± 0.014**	0.059± 0.003	0.102± 0.009	0.610± 0.044	0.755± 0.047
100 ppm	10	169± 7**	0.179± 0.011*	0.062± 0.003	0.099± 0.009	0.640± 0.042	0.770± 0.042
200 ppm	10	162± 14**	0.180± 0.029**	0.058± 0.003	0.096± 0.013	0.620± 0.049	0.752± 0.059
400 ppm	10	146± 10**	0.166± 0.017**	0.053± 0.006**	0.087± 0.014*	0.581± 0.033**	0.714± 0.049

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
0	ppm	10	1.219± 0.049	0.393± 0.025	4.418± 0.240	1.774± 0.038
25	ppm	10	1.269± 0.098	0.389± 0.036	4.514± 0.343	1.770± 0.035
50	ppm	10	1.266± 0.058	0.355± 0.020*	4.371± 0.215	1.763± 0.042
100	ppm	10	1.345± 0.094*	0.370± 0.024	4.710± 0.241	1.727± 0.053
200	ppm	10	1.461± 0.159**	0.356± 0.034*	5.228± 0.424**	1.721± 0.043*
400	ppm	10	1.493± 0.179**	0.311± 0.036**	4.908± 0.427**	1.671± 0.035**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 8-3

ORGAN WEIGHT, ABSOLUTE : SUMMARY, MOSUE : MALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	Body Weight	THYMUS	ADRENALS	TESTES	HEART	LUNGS
0 ppm	10	31.5± 2.3	0.037± 0.006	0.009± 0.002	0.219± 0.030	0.161± 0.021	0.163± 0.011
12 ppm	8	27.2± 3.3	0.039± 0.009	0.010± 0.002	0.203± 0.038	0.146± 0.006	0.164± 0.011
25 ppm	1	28.2± 0.0 ?	0.041± 0.000 ?	0.007± 0.000 ?	0.228± 0.000 ?	0.153± 0.000 ?	0.169± 0.000 ?
50 ppm	0	-	-	-	-	-	-
100 ppm	2	26.0± 1.6 ?	0.035± 0.007 ?	0.009± 0.001 ?	0.187± 0.101 ?	0.135± 0.013 ?	0.162± 0.012 ?
200 ppm	0	-	-	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
0	ppm	10	0.466± 0.016	0.052± 0.010	1.235± 0.074	0.448± 0.015
12	ppm	8	0.430± 0.018	0.057± 0.006	1.197± 0.061	0.445± 0.017
25	ppm	1	0.448± 0.000 ?	0.066± 0.000 ?	1.270± 0.000 ?	0.444± 0.000 ?
50	ppm	0	-	-	-	-
100	ppm	2	0.402± 0.022 ?	0.053± 0.013 ?	1.154± 0.153 ?	0.450± 0.009 ?
200	ppm	0	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

APPENDIX B 8-4

ORGAN WEIGHT, ABSOLUTE : SUMMARY, MOSUE : FEMALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	Body Weight	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
0 ppm	10	20.6± 1.0	0.041± 0.005	0.013± 0.002	0.032± 0.006	0.129± 0.012	0.149± 0.007
12 ppm	10	20.4± 0.7	0.038± 0.008	0.013± 0.001	0.031± 0.007	0.128± 0.009	0.154± 0.008
25 ppm	10	21.2± 0.9	0.037± 0.006	0.013± 0.001	0.028± 0.002	0.134± 0.012	0.159± 0.011
50 ppm	10	20.5± 1.2	0.037± 0.007	0.013± 0.002	0.026± 0.004	0.130± 0.006	0.150± 0.010
100 ppm	10	20.1± 0.7	0.035± 0.003	0.013± 0.001	0.023± 0.002**	0.126± 0.008	0.150± 0.009
200 ppm	10	21.5± 1.4	0.041± 0.006	0.013± 0.001	0.024± 0.004**	0.125± 0.008	0.155± 0.014

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
0	ppm	10	0.296± 0.007	0.055± 0.005	0.893± 0.055	0.462± 0.010
12	ppm	10	0.307± 0.015	0.057± 0.008	0.945± 0.056	0.461± 0.012
25	ppm	10	0.316± 0.024	0.059± 0.008	0.960± 0.087	0.459± 0.014
50	ppm	10	0.317± 0.020	0.054± 0.010	0.922± 0.089	0.456± 0.010
100	ppm	10	0.303± 0.022	0.055± 0.007	0.891± 0.077	0.456± 0.013
200	ppm	10	0.337± 0.014**	0.065± 0.010*	1.280± 0.131**	0.454± 0.013

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 9-1

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : MALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	TESTES	HEART	LUNGS
0 ppm	10	327± 13	0.087± 0.006	0.016± 0.001	0.878± 0.038	0.291± 0.031	0.320± 0.022
25 ppm	10	302± 19**	0.077± 0.010*	0.017± 0.001	0.947± 0.048*	0.323± 0.020*	0.338± 0.020
50 ppm	10	296± 13**	0.079± 0.009	0.018± 0.002	0.967± 0.038**	0.315± 0.017	0.351± 0.022*
100 ppm	10	289± 18**	0.075± 0.005**	0.018± 0.002	0.986± 0.065**	0.308± 0.010	0.341± 0.016
200 ppm	10	261± 12**	0.080± 0.007	0.022± 0.003**	1.089± 0.055**	0.309± 0.033	0.376± 0.022**
400 ppm	10	227± 16**	0.075± 0.006**	0.023± 0.003**	1.173± 0.052**	0.332± 0.017**	0.412± 0.028**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
0	ppm	10	0.575± 0.019	0.174± 0.005	2.481± 0.059	0.578± 0.015
25	ppm	10	0.646± 0.024	0.180± 0.006	2.611± 0.084	0.628± 0.034**
50	ppm	10	0.658± 0.026*	0.185± 0.009	2.671± 0.050*	0.638± 0.022**
100	ppm	10	0.667± 0.029*	0.185± 0.008*	2.745± 0.085**	0.649± 0.038**
200	ppm	10	0.760± 0.061**	0.188± 0.014*	2.815± 0.157**	0.711± 0.031**
400	ppm	10	0.891± 0.090**	0.194± 0.017**	3.010± 0.187**	0.786± 0.043**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 9-2

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : FEMALE

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
0 ppm	10	187± 11	0.112± 0.008	0.032± 0.003	0.054± 0.004	0.349± 0.018	0.417± 0.016
25 ppm	10	177± 12	0.112± 0.010	0.033± 0.002	0.058± 0.004	0.365± 0.017	0.444± 0.027
50 ppm	10	165± 8**	0.106± 0.007	0.036± 0.002**	0.062± 0.006	0.370± 0.014*	0.459± 0.014**
100 ppm	10	169± 7**	0.106± 0.007	0.037± 0.003**	0.059± 0.006	0.379± 0.021**	0.456± 0.027**
200 ppm	10	162± 14**	0.111± 0.012	0.036± 0.002**	0.059± 0.006	0.383± 0.018**	0.465± 0.032**
400 ppm	10	146± 10**	0.114± 0.008	0.036± 0.002**	0.060± 0.009	0.399± 0.016**	0.490± 0.016**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
0	ppm	10	0.654± 0.032	0.211± 0.011	2.368± 0.049	0.954± 0.064
25	ppm	10	0.716± 0.033	0.220± 0.013	2.549± 0.109	1.002± 0.053
50	ppm	10	0.770± 0.033*	0.216± 0.007	2.657± 0.075	1.073± 0.041**
100	ppm	10	0.796± 0.069**	0.219± 0.010	2.785± 0.095**	1.022± 0.049
200	ppm	10	0.903± 0.083**	0.220± 0.017	3.231± 0.177**	1.068± 0.082**
400	ppm	10	1.027± 0.121**	0.213± 0.015	3.374± 0.275**	1.150± 0.063**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 9-3

ORGAN WEIGHT, RELATIVE : SUMMARY, MOSUE : MALE

(13Week　STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (13)

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	TESTES	HEART	LUNGS
0 ppm	10	31.5± 2.3	0.118± 0.014	0.029± 0.007	0.700± 0.108	0.514± 0.069	0.520± 0.049
12 ppm	8	27.2± 3.3	0.143± 0.022	0.037± 0.005	0.753± 0.146	0.543± 0.064	0.608± 0.068
25 ppm	1	28.2± 0.0 ?	0.145± 0.000 ?	0.025± 0.000 ?	0.809± 0.000 ?	0.543± 0.000 ?	0.599± 0.000 ?
50 ppm	0	-	-	-	-	-	-
100 ppm	2	26.0± 1.6 ?	0.135± 0.019 ?	0.033± 0.001 ?	0.732± 0.436 ?	0.520± 0.016 ?	0.622± 0.007 ?
200 ppm	0	-	-	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
0	ppm	10	1.485± 0.084	0.166± 0.034	3.927± 0.184	1.430± 0.142
12	ppm	8	1.597± 0.169	0.212± 0.021	4.446± 0.472	1.657± 0.189
25	ppm	1	1.589± 0.000 ?	0.234± 0.000 ?	4.504± 0.000 ?	1.574± 0.000 ?
50	ppm	0	-	-	-	-
100	ppm	2	1.548± 0.012 ?	0.201± 0.040 ?	4.436± 0.313 ?	1.737± 0.144 ?
200	ppm	0	-	-	-	-

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

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

APPENDIX B 9-4

ORGAN WEIGHT, RELATIVE : SUMMARY, MOSUE : FEMALE

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
0	ppm	10	20.6± 1.0	0.196± 0.022	0.064± 0.010	0.154± 0.022	0.623± 0.049	0.725± 0.041
12	ppm	10	20.4± 0.7	0.187± 0.035	0.061± 0.006	0.154± 0.040	0.625± 0.059	0.756± 0.045
25	ppm	10	21.2± 0.9	0.175± 0.027	0.061± 0.005	0.132± 0.014	0.632± 0.042	0.748± 0.034
50	ppm	10	20.5± 1.2	0.181± 0.028	0.062± 0.009	0.126± 0.017	0.633± 0.029	0.734± 0.036
100	ppm	10	20.1± 0.7	0.175± 0.015	0.063± 0.005	0.113± 0.011**	0.629± 0.027	0.745± 0.024
200	ppm	10	21.5± 1.4	0.190± 0.023	0.061± 0.006	0.110± 0.016**	0.581± 0.029	0.721± 0.044

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (13)

Group	Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
0	ppm	10	1.439± 0.073	0.265± 0.018	4.330± 0.121	2.246± 0.106
12	ppm	10	1.503± 0.064	0.280± 0.038	4.627± 0.286	2.259± 0.071
25	ppm	10	1.491± 0.082	0.278± 0.029	4.525± 0.328	2.166± 0.085
50	ppm	10	1.544± 0.066**	0.264± 0.031	4.489± 0.258	2.227± 0.125
100	ppm	10	1.508± 0.074	0.271± 0.028	4.435± 0.322	2.272± 0.081
200	ppm	10	1.570± 0.056**	0.301± 0.032	5.950± 0.519**	2.117± 0.096*

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

APPENDIX B 10-1

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : MALE : SACRIFICED ANIMALS

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	Control				25 ppm				50 ppm				100 ppm			
		No. of Animals	10				10				10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]																		
nasal cavit	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	0 ** (0)	4 (40)	6 (60)	0 (0)	0 ** (0)	9 (90)	1 (10)	0 (0)	0 ** (0)
	eosinophilic change:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	7 (70)	0 (0)	0 (0)	0 ** (0)	10 (100)	0 (0)	0 (0)	0 ** (0)	10 (100)	0 (0)	0 (0)	0 ** (0)
	necrosis:olfactory epithelium		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)
larynx	inflammation		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)
[Circulatory system]																		
heart	granulation		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Digestive system]																		
liver	deposit of ceroid		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)
	collapse:central		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)
	vacuolic change:central		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)
[Urinary system]																		
kidney	vacuolic change:proximal tubule		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)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

Organ	Findings	Group Name	200 ppm				400 ppm			
		No. of Animals	10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]										
nasal cavit	mineralization		7 (70)	3 (30)	0 (0)	0 (0) **	9 (90)	1 (10)	0 (0)	0 (0) **
	eosinophilic change:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	atrophy:olfactory epithelium		9 (90)	0 (0)	0 (0)	0 (0) **	6 (60)	4 (40)	0 (0)	0 (0) **
	necrosis:olfactory epithelium		8 (80)	0 (0)	0 (0)	0 (0) **	10 (100)	0 (0)	0 (0)	0 (0) **
larynx	inflammation		1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Circulatory system]										
heart	granulation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Digestive system]										
liver	deposit of ceroid		0 (0)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	0 (0) **
	collapse:central		10 (100)	0 (0)	0 (0)	0 (0) **	8 (80)	2 (20)	0 (0)	0 (0) **
	vacuolic change:central		1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Urinary system]										
kidney	vacuolic change:proximal tubule		3 (30)	0 (0)	0 (0)	0 (0)	4 (40)	0 (0)	0 (0)	0 (0)

Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	Control				25 ppm				50 ppm				100 ppm			
		No. of Animals	10				10				10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Endocrine system]																		
pituitary	Rathke pouch		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Special sense organs/appandage]																		
nasolacr d	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

Organ	Findings	Group Name	200 ppm				400 ppm			
		No. of Animals	10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Endocrine system]										
pituitary	Rathke pouch		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
[Special sense organs/appandage]										
nasolacr d	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

APPENDIX B 10-2

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : FEMALE : SACRIFICED ANIMALS

(13Week STUDY)

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	Control				25 ppm				50 ppm				100 ppm			
		No. of Animals	10				10				10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]																		
nasal cavit	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	9 (90)	1 (10)	0 (0)	0 (0) **	8 (80)	2 (20)	0 (0)	0 (0) **	8 (80)	1 (10)	1 (10)	0 (0) **
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	0 (0) **	10 (100)	0 (0)	0 (0)	0 (0) **	10 (100)	0 (0)	0 (0)	0 (0) **
	necrosis:olfactory epithelium		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)
[Digestive system]																		
liver	deposit of ceroid		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)
	collapse:central		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (80)	0 (0)	0 (0)	0 (0) **
	vacuolic change:central		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)
[Urinary system]																		
kidney	vacuolic change:proximal tubule		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)	0 (0)
[Reproductive system]																		
ovary	cyst		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)
uterus	dilatation		3 (30)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	3 (30)	0 (0)	0 (0)	0 (0)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

Organ	Findings	Group Name	200 ppm				400 ppm			
		No. of Animals	10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]										
nasal cavit	mineralization		10 (100)	0 (0)	0 (0)	0 ** (0)	8 (80)	2 (20)	0 (0)	0 ** (0)
	atrophy:olfactory epithelium		10 (100)	0 (0)	0 (0)	0 ** (0)	8 (80)	2 (20)	0 (0)	0 ** (0)
	necrosis:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
[Digestive system]										
liver	deposit of ceroid		8 (80)	0 (0)	0 (0)	0 ** (0)	10 (100)	0 (0)	0 (0)	0 ** (0)
	collapse:central		8 (80)	1 (10)	0 (0)	0 ** (0)	8 (80)	1 (10)	0 (0)	0 ** (0)
	vacuolic change:central		2 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Urinary system]										
kidney	vacuolic change:proximal tubule		1 (10)	3 (30)	2 (20)	0 * (0)	2 (20)	2 (20)	1 (10)	0 (0)
[Reproductive system]										
ovary	cyst		1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
uterus	dilatation		1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

STUDY NO. : 0097
ANIMAL : RAT F344
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	Control				25 ppm				50 ppm				100 ppm			
		No. of Animals	10				10				10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Special sense organs/appandage]																		
Harder gl	lymphocytic infiltration		1 (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 (0)	0 (0)	0 (0)

Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

Organ	Findings	Group Name	200 ppm				400 ppm			
		No. of Animals	10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Special sense organs/appandage]										
Harder gl	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

APPENDIX B 10-3

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

MOSUE : MALE : DEAD AND MORIBUND ANIMALS

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
DEAD AND MORIBUND ANIMALS (0- 13W)

Organ	Findings	Group Name	Control				12 ppm				25 ppm				50 ppm			
		No. of Animals	0				2				9				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]																		
nasal cavit	degeneration:olfactory epithelium		- (-)	- (-)	- (-)	- (-)	2 (100)	0 (0)	0 (0)	0 (0)	2 (22)	3 (33)	0 (0)	0 (0)	5 (50)	2 (20)	0 (0)	0 (0)
lung	congestion		- (-)	- (-)	- (-)	- (-)	0 (0)	0 (0)	0 (0)	0 (0)	6 (67)	0 (0)	0 (0)	0 (0)	9 (90)	0 (0)	1 (10)	0 (0)
	hemorrhage		- (-)	- (-)	- (-)	- (-)	0 (0)	0 (0)	0 (0)	0 (0)	3 (33)	0 (0)	0 (0)	0 (0)	3 (30)	1 (10)	0 (0)	0 (0)
	inflammation		- (-)	- (-)	- (-)	- (-)	1 (50)	0 (0)	0 (0)	0 (0)	4 (44)	0 (0)	0 (0)	0 (0)	4 (40)	0 (0)	0 (0)	0 (0)
[Hematopoietic system]																		
lymph node	karyorrhexis		- (-)	- (-)	- (-)	- (-)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	7 (78)	0 (0)	0 (0)	6 (60)	3 (30)	0 (0)	0 (0)
thymus	karyorrhexis		- (-)	- (-)	- (-)	- (-)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	2 (22)	7 (78)	0 (0)	0 (0)	0 (0)	10 (100)
spleen	melanin		- (-)	- (-)	- (-)	- (-)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	atrophy		- (-)	- (-)	- (-)	- (-)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	9 (100)	0 (0)	1 (10)	0 (0)	9 (90)	0 (0)
[Digestive system]																		
stomach	ulcer:forestomach		- (-)	- (-)	- (-)	- (-)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
liver	necrosis:focal		- (-)	- (-)	- (-)	- (-)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)

<1>:Slight <2>:Moderate <3>:Marked <4>:Severe

Organ	Findings	Group Name	100 ppm				200 ppm			
		No. of Animals	8				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]										
nasal cavit	degeneration:olfactory epithelium		2 (25)	4 (50)	0 (0)	0 (0)	1 (10)	8 (80)	0 (0)	0 (0)
lung	congestion		8 (100)	0 (0)	0 (0)	0 (0)	8 (80)	2 (20)	0 (0)	0 (0)
	hemorrhage		1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammation		4 (50)	0 (0)	0 (0)	0 (0)	5 (50)	0 (0)	0 (0)	0 (0)
[Hematopoietic system]										
lymph node	karyorrhexis		2 (25)	6 (75)	0 (0)	0 (0)	8 (80)	2 (20)	0 (0)	0 (0)
thymus	karyorrhexis		0 (0)	0 (0)	1 (13)	7 (88)	0 (0)	0 (0)	0 (0)	10 (100)
spleen	melanin		0 (0)	0 (0)	1 (13)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
	atrophy		0 (0)	0 (0)	7 (88)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)
[Digestive system]										
stomach	ulcer:forestomach		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
liver	necrosis:focal		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

<1>:Slight <2>:Moderate <3>:Marked <4>:Severe

Organ	Findings	Group Name	Control				12 ppm				25 ppm				50 ppm			
		No. of Animals	0				2				9				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Digestive system]																		
liver	swelling:central		- (-)	- (-)	- (-)	- (-)	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	degeneration:proximal tubule		- (-)	- (-)	- (-)	- (-)	0 (0)	1 (50)	1 (50)	0 (0)	3 (33)	6 (67)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)
	tubular necrosis:proximale tubule		- (-)	- (-)	- (-)	- (-)	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)	9 (100)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)
[Reproductive system]																		
testis	germ cell necrosis		- (-)	- (-)	- (-)	- (-)	2 (100)	0 (0)	0 (0)	0 (0)	7 (78)	2 (22)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	0 (0)

<1>:Slight <2>:Moderate <3>:Marked <4>:Severe

Organ	Findings	Group Name	100 ppm				200 ppm			
		No. of Animals	8				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Digestive system]										
liver	swelling:central		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	4 (40)	5 (50)	0 (0)
[Urinary system]										
kidney	degeneration:proximal tubule		5 (63)	3 (38)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)
	tubular necrosis:proximale tubule		0 (0)	0 (0)	6 (75)	2 (25)	0 (0)	0 (0)	10 (100)	0 (0)
[Reproductive system]										
testis	germ cell necrosis		8 (100)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	0 (0)

<1>:Slight <2>:Moderate <3>:Marked <4>:Severe

APPENDIX B 10-4

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

MOSUE : MALE : SACRIFICED ANIMALS

(13Week STUDY)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	Control				12 ppm				25 ppm				50 ppm			
		No. of Animals	10				8				1				0			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]																		
nasal cavit	osseous metaplasia		0 (0)	0 (0)	0 (0)	0 (0)	7 (88)	0 (0)	0 (0)	0 ** (0)	1 (100)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
	eosinophilic change:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
	eosinophilic change:respiratory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
lung	congestion		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	1 (13)	1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
[Hematopoietic system]																		
spleen	melanin		1 (10)	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	basophilic change		0 (0)	0 (0)	0 (0)	0 (0)	8 (100)	0 (0)	0 (0)	0 ** (0)	1 (100)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
	vacuolization of proximal tubule		6 (60)	3 (30)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 ** (0)	0 (0)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
	hydronephrosis		0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)

Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name / No. of Animals	100 ppm 2 <1> (%)	<2> (%)	<3> (%)	<4> (%)		200 ppm 0 <1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]											
nasal cavit	osseous metaplasia		1 (50)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
	eosinophilic change:olfactory epithelium		1 (50)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
	eosinophilic change:respiratory epithelium		1 (50)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
lung	congestion		1 (50)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
[Hematopoietic system]											
spleen	melanin		0 (0)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
[Urinary system]											
kidney	basophilic change		2 (100)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
	vacuolization of proximal tubule		0 (0)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
	hydronephrosis		0 (0)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

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

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	Control				12 ppm				25 ppm					50 ppm			
		No. of Animals	10				8				1					0			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)		<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Urinary system]																			
kidney	mineralization:papilla		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
	tubular necrosis:proximale tubule		0 (0)	0 (0)	0 (0)	0 (0)	5 (63)	0 (0)	0 (0)	0 * (0)	1 (100)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)
[Reproductive system]																			
testis	germ cell necrosis		0 (0)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	?	- (-)	- (-)	- (-)	- (-)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

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

Organ	Findings	Group Name	100 ppm				200 ppm			
		No. of Animals	2				0			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Urinary system]										
kidney	mineralization:papilla		1 (50)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
	tubular necrosis:proximale tubule		1 (50)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)
[Reproductive system]										
testis	germ cell necrosis		2 (100)	0 (0)	0 (0)	0 (0) ?	- (-)	- (-)	- (-)	- (-)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

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

APPENDIX B 10-5

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

MOSUE : FEMALE : SACRIFICED ANIMALS

(13Week STUDY))

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	Control				12 ppm				25 ppm				50 ppm			
		No. of Animals	10				10				10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]																		
nasal cavit	osseous metaplasia		0 (0)	0 (0)	0 (0)	0 (0)	7 (70)	0 (0)	0 (0)	0 ** (0)	10 (100)	0 (0)	0 (0)	0 ** (0)	9 (90)	0 (0)	0 (0)	0 ** (0)
	eosinophilic change:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	7 (70)	0 (0)	0 (0)	0 ** (0)	8 (80)	1 (10)	0 (0)	0 ** (0)	4 (40)	4 (40)	0 (0)	0 ** (0)
	eosinophilic change:respiratory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	8 (80)	0 (0)	0 (0)	0 ** (0)	8 (80)	0 (0)	0 (0)	0 ** (0)	7 (70)	0 (0)	0 (0)	0 ** (0)
lung	thrombus		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)
[Hematopoietic system]																		
spleen	melanin		0 (0)	1 (10)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)	0 (0)	3 (30)	0 (0)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)	0 (0)
[Digestive system]																		
liver	cell atypia		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)
	necrosis:central		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)
	necrosis:focal		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)
	vacuolic change:central		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)
[Urinary system]																		
kidney	basophilic change		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)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

Organ	Findings	Group Name	100 ppm				200 ppm			
		No. of Animals	10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Respiratory system]										
nasal cavit	osseous metaplasia		9 (90)	0 (0)	0 (0)	0 ** (0)	9 (90)	0 (0)	0 (0)	0 ** (0)
	eosinophilic change:olfactory epithelium		5 (50)	4 (40)	0 (0)	0 ** (0)	10 (100)	0 (0)	0 (0)	0 ** (0)
	eosinophilic change:respiratory epithelium		7 (70)	0 (0)	0 (0)	0 ** (0)	8 (80)	0 (0)	0 (0)	0 ** (0)
lung	thrombus		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
[Hematopoietic system]										
spleen	melanin		2 (20)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
[Digestive system]										
liver	cell atypia		10 (100)	0 (0)	0 (0)	0 ** (0)	10 (100)	0 (0)	0 (0)	0 ** (0)
	necrosis:central		0 (0)	0 (0)	0 (0)	0 (0)	2 (20)	8 (80)	0 (0)	0 ** (0)
	necrosis:focal		1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	vacuolic change:central		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (10)	0 (0)	0 (0)
[Urinary system]										
kidney	basophilic change		1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	Control				12 ppm				25 ppm				50 ppm			
		No. of Animals	10				10				10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Urinary system]																		
kidney	mineralization:papilla		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
[Reproductive system]																		
ovary	cyst		0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

STUDY NO. : 0098
ANIMAL : MOUSE BDF1
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (13W)

Organ	Findings	Group Name	100 ppm				200 ppm			
		No. of Animals	10				10			
			<1> (%)	<2> (%)	<3> (%)	<4> (%)	<1> (%)	<2> (%)	<3> (%)	<4> (%)
[Urinary system]										
kidney	mineralization:papilla		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Reproductive system]										
ovary	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square <1>:Slight <2>:Moderate <3>:Marked <4>:Severe

APPENDIX B 11-1

IDENTITY AND PURITY OF CHLOROFORM

PERFORMED AT THE JAPAN BIOASSAY LABORATORY

(13Week STUDY)

IDENTITY AND PURITY OF CHLOROFORM PERFORMED AT THE JAPANBIOASSAY LABORATORY
(THIRTEEN-WEEK STUDY)

Lot no.TLK0986

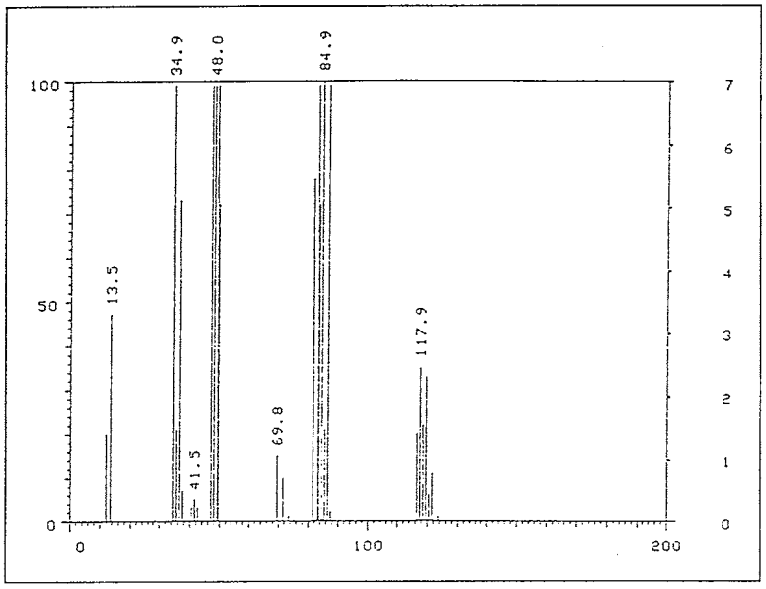
1. Spectral data

(1) Mass Spectrometry

Instrument: Hitachi M-80B

Ionization: EI(Electron Ionization)

Ionization Voltage: 70eV



Mass Spectrum of CHLOROFORM

Result:

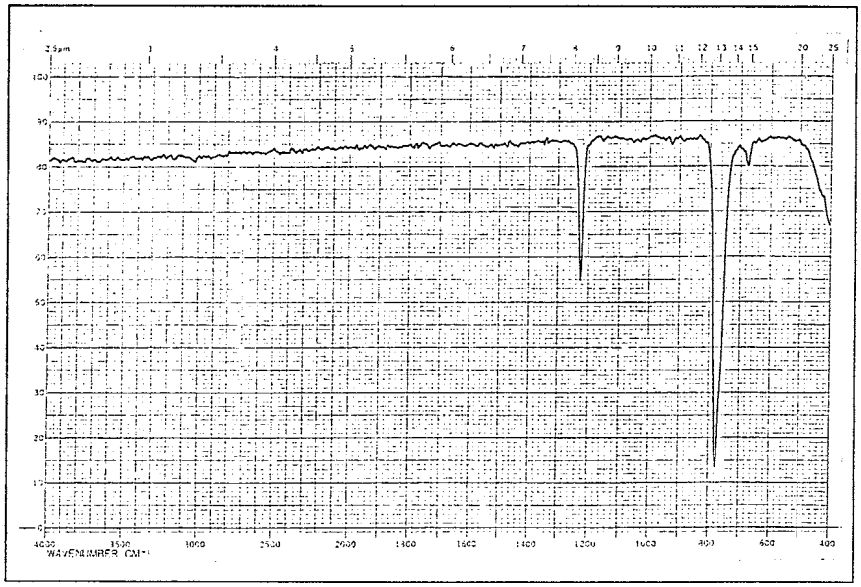
	Molecule Weight
Theoretical Value	117.91(Calculated)
Determined	117.9

(2) Infrared Spectrometry

Instrument : Hitachi 270-30

Cell : KBr(Liquid Cell)

Slit : Medium



Infrared Spectrum of CHLOROFORM

Results	Determines : Wave Number (CM^{-1})	Literature Values
	660～ 700	660～ 700
	720～ 820	720～ 820
	1200～1260	1200～1260 (Sadtler Handbook by Sadtler Research Laboratories, Inc.)

2. Gas Chromatography

Instrument: Hewlett Packard 5890A

Column: Methyl Silicone(0.2mm ϕ ×50m)

Column Temperature: 80°C

Flow Rate: 1 ml/min

Detector: FID(Hydrogen Flame Ionization)

Injection Volume: 1 μl

Results: Major peak and one impurity

Peak No.	Retention Time(min)	Retention Time Relative to Major Peak	Concentration (Percent of Major Peak)
1	2.243	0.86	0.97
2	2.602	1.00	100

3. Conclusions: The result of the mass spectrum agreed with the theoretical value and the infrared spectrum agreed with the literature values. Gas chromtography indicated one impurity with concentration totaling <1% of the major peak.

APPENDIX B 11-2

STABILITY OF CHLOROFORM AT THE JAPAN BIOASSAY LABORATORY

(13Week STUDY)

STABILITY OF CHLOROFORM AT THE JAPAN BIOASSAY LABORATORY(THIRTEEN-WEEK STUDY)

Lot no.TLK0986

1.Sample storage: Chloroform was stored for about 13 weeks at 5°C.

2.Infrared Spectrometry

Instrument : Hitachi 270-30

Cell : KBr(Liquid Cell)

Slit : Medium

Results

	03/09/88	07/04/88
: Wave Number (CM^{-1})		
	660～ 700	660～ 700
	720～ 820	720～ 820
	1200～1260	1200～1260

2.Gas Chromatography

Instrument: Hewlett Packard 5890A

Column: Methyl Silicone(0.2mm ϕ ×50m)

Column Temperature: 80°C

Flow Rate: 1 ml/min

Detector: FID(Hydrogen Flame Ionization)

Injection Volume: 1 μl

Results: Major peak and one impurity

Date	Peak No.	Retention Time(min)	Retention Time Relative to Major Peak	Concentration (Percent of Major Peak)
03/09/88	1	2.243	0.86	0.97
	2	2.602	1.00	100
07/04/88	1	2.238	0.86	0.98
	2	2.593	1.00	100

3. Conclusions: The results of the infrared spectrum agreed with the previous determine of test values.Gas chromtography indicated one impurity with concentration totaling <1% of the major peak.
Consequently,Chloroform was stable as the chemical when stored for about 13 weeks at 5°C.

APPENDIX B 12-1

CONCENTRATION OF CHLOROFORM IN INHALATION CHAMBER

(13Week STUDY)

CONCENTRATION OF CHLOROFORM IN INHALATION CHAMBER
(RAT : THIRTEEN-WEEK STUDY)

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
25ppm	24.9 ± 0.1
50ppm	49.9 ± 0.3
100ppm	99.6 ± 0.4
200ppm	199.4 ± 1.0
400ppm	399.0 ± 1.7

CONCENTRATION OF CHLOROFORM IN INHALATION CHAMBER
(MOUSE : THIRTEEN-WEEK STUDY)

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
12ppm	12.0 ± 0.1
25ppm	25.0 ± 0.1
50ppm	50.1 ± 0.1
100ppm	100.2 ± 0.3
200ppm	200.2 ± 0.5

APPENDIX B 12-2

ENVIRONMENT OF INHALATION CHAMBER

(13Week STUDY)

ENVIRONMENT OF INHALATION CHAMBER IN CHLOROFORM STUDIES

(RAT : THIRTEEN-WEEK STUDY)

Group Name	TEMPERATURE(℃) MEAN ± S.D.	HUMIDITY(%) MEAN ± S.D.	VENTILATION RATE(/min) MEAN ± S.D.	ROOM AIR CHANGE(time/h) MEAN
Control	24.1 ± 0.2	55.3 ± 1.5	210.5 ± 0.6	11.9
25ppm	23.6 ± 0.2	54.7 ± 0.9	209.6 ± 0.4	11.9
50ppm	24.2 ± 0.2	56.9 ± 1.2	210.5 ± 0.5	11.9
100ppm	24.0 ± 0.2	55.0 ± 0.7	212.0 ± 0.3	12.0
200ppm	24.5 ± 0.1	55.1 ± 1.0	209.2 ± 0.7	11.8
400ppm	24.0 ± 0.2	54.0 ± 0.9	210.1 ± 0.4	11.9

ENVIRONMENT OF INHALATION CHAMBER IN CHLOROFORM STUDIES

(MOUSE : THIRTEEN-WEEK STUDY)

Group Name	TEMPERATURE(℃) MEAN ± S.D.	HUMIDITY(%) MEAN ± S.D.	VENTILATION RATE(/min) MEAN ± S.D.	ROOM AIR CHANGE(time/h) MEAN
Control	22.7 ± 0.2	55.5 ± 0.8	105.2 ± 0.4	12.1
12ppm	22.8 ± 0.1	56.2 ± 1.2	105.9 ± 0.3	12.2
25ppm	22.5 ± 0.1	57.7 ± 0.9	105.4 ± 0.3	12.2
50ppm	22.6 ± 0.1	58.1 ± 1.0	106.5 ± 0.2	12.3
100ppm	23.2 ± 0.1	55.8 ± 1.3	104.8 ± 0.3	12.1
200ppm	22.7 ± 0.1	56.6 ± 1.4	105.7 ± 0.3	12.2

APPENDIX C 1

METHODS FOR HEMATOLOGY, BIOCHEMISTRY AND URINALYSIS

METHODS FOR HEMATOLOGY, BIOCHEMISTRY AND URINALYSIS

Item	Method	Unit
Hematology		
Red blood cell (RBC)	Aperture impedance method [1]	$\times 10^6/\mu l$
Hemoglobin (Hgb)	Cyanmethemoglobin method [1]	g/dl
Hematocrit (Hct)	Calculated as RBC×MCV/10 [1]	%
Mean corpuscular volume (MCV)	Aperture impedance method [1]	fl
Mean corpuscular hemoglobin (MCH)	Calculated as Hgb/RBC×10 [1]	pg
Mean corpuscular hemoglobin concentration (MCHC)	Calculated as Hgb/Hct×100 [1]	g/dl
Platelet	Aperture impedance method [1]	$\times 10^3/\mu l$
White blood cell (WBC)	Aperture impedance method [1]	$\times 10^3/\mu l$
Differential WBC	Pattern recognition method [2] (Wright staining)	%
Biochemistry		
Total protein (TP)	Biuret method [3]	g/dl
Albumin (Alb)	BCG method [3]	g/dl
A/G ratio	Calculated as Alb/ (TP−Alb) [3]	
T-bilirubin	Michaelson method [3]	mg/dl
Glucose	Enzymatic method (HK•G-6-PDH) [3]	mg/dl
T-cholesterol	Enzymatic method (CEH•COD•POD) [3]	mg/dl
Triglyceride	Enzymatic method (GK•GPO•POD) [3]	mg/dl
Phospholipid	Enzymatic method (PLD•COD•POD) [3]	mg/dl
Glutamic oxaloacetic transaminase (GOT)	Karmen method [3]	IU/l
Glutamic pyruvic transaminase (GPT)	Karmen method [3]	IU/l
Lactate dehydrogenase (LDH)	Wroblewski-LaDue method [3]	IU/l
Alkaline phosphatase (ALP)	GSCC method [3]	IU/l
Leucine aminopeptidase (LAP)	L-Leucyl-p-nitroanilide substrate method [3]	IU/l
γ-Glutamyl transpeptidase (G-GTP)	L-γ-Glutamyl-p-nitroanilide substrate method [3]	IU/l
Creatine phosphokinase (CPK)	GSCC method [3]	IU/l
Urea nitrogen	Enzymatic method (Urease•GLDH) [3]	mg/dl
Creatinine	Jaffe method [3]	mg/dl
Sodium	Flame photometry [4]	mEq/l
Potassium	Flame photometry [4]	mEq/l
Chloride	Coulometric titration [4]	mEq/l
Calcium	OCPC method [3]	mg/dl
Inorganic phosphorus	Fiske-Subbarow method [3]	mg/dl
Urinalysis		
pH, Protein, Glucose, Ketone body, Bilirubin, Occult blood, Urobilinogen	Urinalysis reagent paper method [5]	

1) Automatic blood cell analyzer (Coulter counter SP : Coulter Electronics Inc.)

2) Automatic blood cell differential analyzer (Hematrak 590 : Geometric Data a Smithkline Company)

3) Automatic analyzer (Hitachi 705 : Hitachi,Ltd.)

4) Flame photometer (Hitachi 750 : Hitachi,Ltd.)

5) Ames reagent strips for urinalysis (Multistix, Uro-Labstix : Miles Sankyo Co.,Ltd.)

APPENDIX C 2

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY

UNITS AND DECIMNAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY

	TEST ITEM	DECIMAL PLACE	UNIT
HEMATOLOGY	Red blood cell	2	$\times 10^6/\mu l$
	Hemoglobin	1	g/dl
	Hematocrit	1	%
	MCV	1	fl
	MCH	1	pg
	MCHC	1	g/dl
	Platelet	0	$\times 10^3/\mu l$
	White blood cell	2	$\times 10^3/\mu l$
	Differntial WBC	0	%
BIOCHEMISTRY	Total protein	1	g/dl
	Albumin	1	g/dl
	A/G ratio	1	
	T-bilirubin	2	mg/dl
	Glucose	0	mg/dl
	T-cholesterol	0	mg/dl
	Triglyceride	0	mg/dl
	Phospholipid	0	mg/dl
	GOT	0	IU/l
	GPT	0	IU/l
	LDH	0	IU/l
	ALP	0	IU/l
	LAP	0	IU/l
	γ-GTP	0	IU/l
	CPK	0	IU/l
	Urea nitrogen	1	mg/dl
	Creatinine	1	mg/dl
	Sodium	0	mEq/l
	Potassium	1	mEq/l
	Chloride	0	mEq/l
	Calcium	1	mg/dl
	Inorganic phosphorus	1	mg/dl

APPENDIX D

TOW-WEEK AND THIRTEEN-WEEK STUDIES

(Study No.4010)

クロロホルムのBDF1マウスを用いた吸入によるがん原性予備試験報告書

（試験番号：４０１０）

平成６年２月２５日

中央労働災害防止協会
日本バイオアッセイ研究センター

クロロホルムのBDF1マウスを用いた吸入によるがん原性予備試験
２８日間試験（試験番号：４０１０）報告書

目　　次

要　旨

Ⅰ．目　的

がん原性試験の投与濃度を決定するために実施した13週間試験の結果、マウスの生死状況に特徴がみられ、雌では全例生存したのに対し、雄では最低投与群においても死亡が認められ、著しい性差を示した。また、雄の死亡はすべて暴露開始ご 1週間以内でみられ、この時期に生存した動物は13週間の投与終了まで生存した。

このように、雄で全例生存する濃度がみいだされなかったこと、それに加えて、当センターの吸入試験システムは、発生装置、暴露チャンバーの構造、規模などの関係から雌雄同濃度、同時暴露が前提になっていることからこの結果からはがん原性試験の濃度決定が困難である。そこで、マウスのがん原性試験の投与方法を検討する目的でさらに予備試験を実施することとした。

本予備試験では、雄の13週間の結果から耐性獲得が示唆されたので、すでに決定している雌の投与濃度を目標に、雄のみを使用し、段階的に濃度を上げて暴露し、動物の死亡がみられないようにクロロホルムに対する耐性が獲得されるかを動物の生死状況を基に判断し、がん原性試験の投与方法を決定することとした。

Ⅱ．試験材料

Ⅱ－1 被験物質

名称　：クロロホルム
構造式：$CHCl_3$
試験に使用したクロロホルムは、和光純薬工業株式会社の製造したもので、純度は99.0%以上、使用ロット番号はPLK0986であった。

Ⅱ－2 試験動物

動物は、日本チャールス・リバー（株）の$Crj:BDF_1$マウス(SPF)の雄を使用した。マウス雄は、48匹を生後4週令で導入し、各1週間の検疫、馴化を経た後、発育順調で一般状態に異常を認めなかった動物から体重値の中央値に近い雄40匹を選別し試験に供した。

Ⅲ．試験方法

Ⅲ－1 投与

Ⅲ－1－1 投与経路、投与方法及び投与期間

投与経路は全身暴露による経気道投与とした。投与は吸入チャンバー内の試験動物に設定濃度のクロロホルムのガスを混合した空気を送り込み、全身暴露することにより行った。

投与期間及び暴露回数はそれぞれ6時間/日、5日/週、10回/4週間とした。

Ⅲ－1－2 投与濃度

4週間の投与期間のうち第1段階の2週間は 5、10、15ppmに設定し、第2段階の2週間は、第1段階で生存した 5ppm及び 10ppm群の10匹の動物を5匹ずつに分けて、それぞれ 30ppm、90ppmに、また 15ppm群で生存した全例を90ppmに濃度を変えて暴露した。

Ⅲ－1－3 被験物質の発生方法と濃度調整

被験物質の発生方法を FIGURE 1 に示した。クロロホルムの入った発生容器を循環水式恒温槽で加熱しながら、清浄空気をバブラーを用いてバブリングして蒸発させた。次にこのクロロホルム蒸気を一定温度に冷却し、更に加熱することにより安定した濃度でラインミキサーに供給した。次に吸入チャンバー内のクロロホルム濃度をガスクロマトグラフにより監視しながら設定値になるように蒸気の供給量を調整した。

Ⅲ－1－4 被験物質の濃度測定

各チャンバー内のクロロホルムの濃度は、自動サンプリング装置付きガスクロマトグラフを用い、暴露開始前から暴露終了後まで15分毎に測定した。測定結果を平均値として TABLE 1 に示した。各群共に設定どうりの結果が得られた。

Ⅲ－2 動物管理

Ⅲ－2－1 群分け及び個体識別方法

供試動物の各投与群への割当は、体重を指標として群間の体重の偏りを小さくする群分け方法（適正層別方式）により実施した。

試験期間中の動物の個体識別は、検疫･馴化期間に於いては色素塗布し、投与期間に於いては耳パンチにより識別し、又ケージにも全試験期間を通して個体識別番号を付けた。

Ⅲ－2－2 飼育条件

動物は、投与期間中は吸入チャンバー内で飼育した。飼育室の環境条件は温度 21±2℃、湿度 60±10%、明暗サイクル:12時間点灯（8:00～20:00）/12時間消灯（20:00～8:00）、換気回数15～17回/時であった。投与期間中の飼育ケージは、ステンレス製 5連網ケージ（100W×116D×120Hmm）の単飼とし、ケージは 2週間毎に交換した。飼料は、オリエンタル酵母工業（株）製造のＣＲＦ－１固形飼料を飼育全期間を通して自由摂取させた。飲水は全飼育期間を通して市水（秦野市水道局）をフィルター濾過したのち、紫外線滅菌し、自動給水により自由摂取させた。

Ⅲ－3 観察・検査項目

Ⅲ－3－1 動物の一般状態の観察

毎日 1回以上、動物の生死確認及び一般状態の観察を行った。

Ⅲ－3－2 体重測定

投与開始直前、7日、14日、21日、28日に体重の測定を行った。

Ⅳ．試験成績

Ⅳ－1 動物の生死状況

投与期間中、第1段階と第2段階の2段階に投与濃度を変えた暴露でそれぞれの生存動物数を TABLE 2 に示した。

この表から明らかなように第1段階の14日間では、5ppm、10ppm群では全匹生存したが、15ppm群では4匹の死亡がみられた。第2段階の14日間では投与濃度を 5ppmから30ppmへ上げた群では1匹、5ppmから 90ppmへ上げた群では4匹が死亡したが 10ppmから 30ppm、90ppmへ上げた群、また 15ppmから 90ppmへ上げた群ではすべて生存した。

Ⅳ－2 体重推移

各投与群の体重の推移を TABLE 3に示した。

第1段階の暴露での生存動物の体重は、投与初期に投与濃度に対応して増加抑制が示されたが後半には回復傾向がみられた。第2段階の暴露では、第1段階の投与濃度が低いものほど体重増加の抑制がみられた。しかし、第1段階の場合と同様後半には回復の傾向を示した。

Ⅴ．考察及び結論

第1段階の暴露に於ける動物の生死状況に付いてみると、5ppm群、10ppm群では全例生存したが、15ppm群では4/10例の死亡がみられた。また、この死亡はすべて 1週間以内に生じ、この期間生存したものは第1段階の全期間生存した。生存例の体重の推移に付いてみると、全投与群で暴露開始後1週間以内で投与濃度に対応した体重増加の抑制がみられるものの、その後回復傾向を示した。

第2段階の暴露では、投与濃度を 5ppmから 30ppm、90ppmへ上げた群ではそれぞれ1/5、4/5例が死亡したが、10ppm及び 15ppmから 30ppm、90ppmに上げた群ではすべて生存した。生存例の体重の推移に付いてみると、第1段階に投与濃度が低い群ほど第2段階での暴露の影響がみられたが、その後、体重増加は回復傾向を示した。

これらの結果から、BDF_1マウスの雄は 5ppm及び 10ppmの暴露に耐えられること、30ppmまたは 90ppmの暴露に耐えるためには 5ppmの予備暴露のみでは十分な耐性が得られないこと、しかし、投与濃度を徐々に上げることにより雌の最高投与濃度(90ppm)での暴露でも生存し得ることが明らかになった。

以上のことを踏まえてマウスの最終的ながん原性試験における雌マウスで設定可能とされた投与濃度である 5ppm、30ppm及び 90ppmの投与濃度を次のように段階的に設定するように計画した。

先ず、全投与濃度群共に最低投与濃度の 5ppmで2週間暴露し、5ppm群はこのままの設定で暴露を続け、他の群は、次に 10ppmで2週間暴露した後に 30ppmとし、30ppm群はこのままの設定で暴露を続け、さらに最高投与濃度群の 90ppm群は 30ppmで2週間暴露した後、最終の 90ppmの投与濃度に段階的にあげていくこととした。

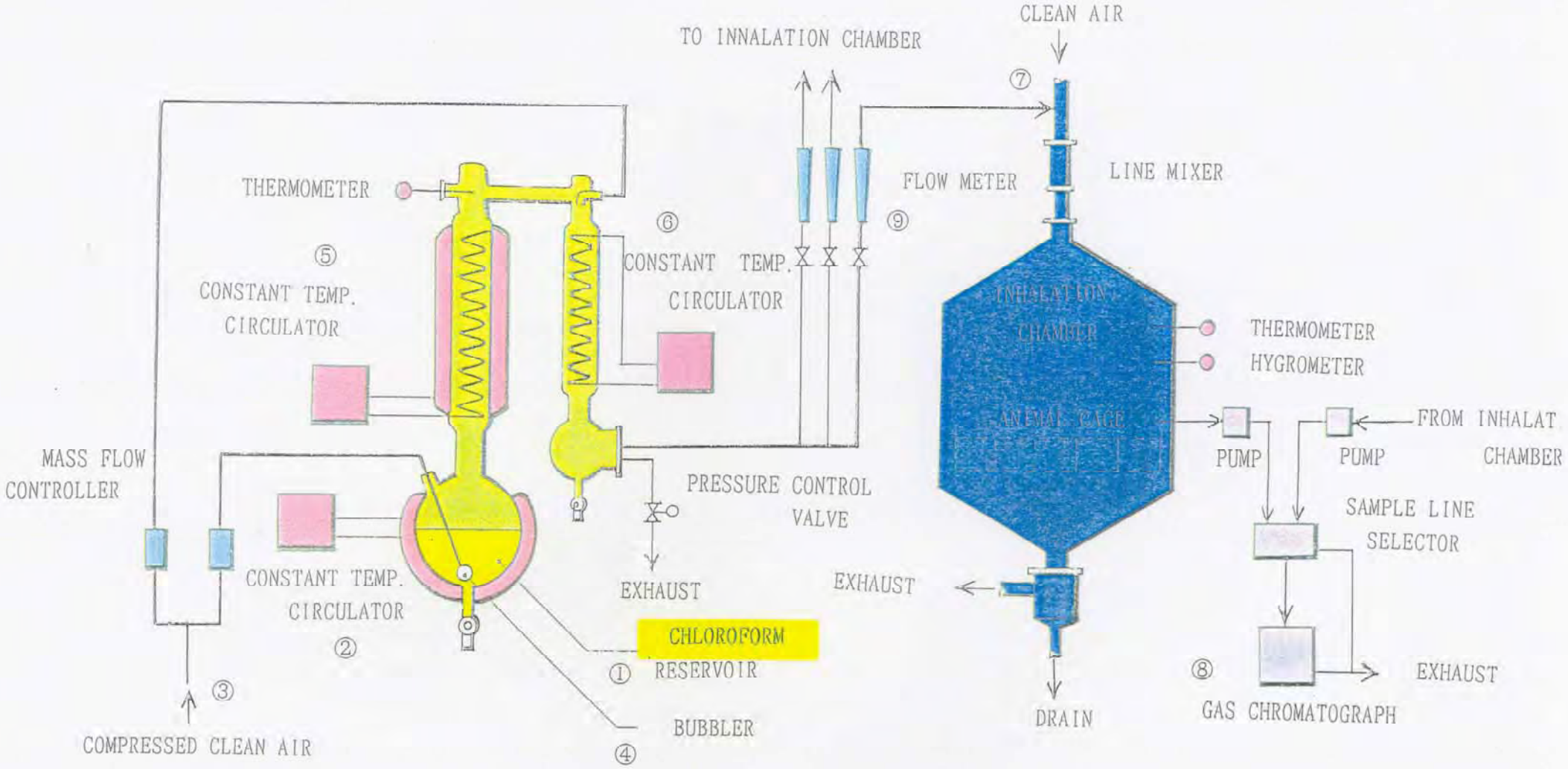


FIGURE 1 CHLOROFORM VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

Figure 2 BODY WEIGHT CHANGES

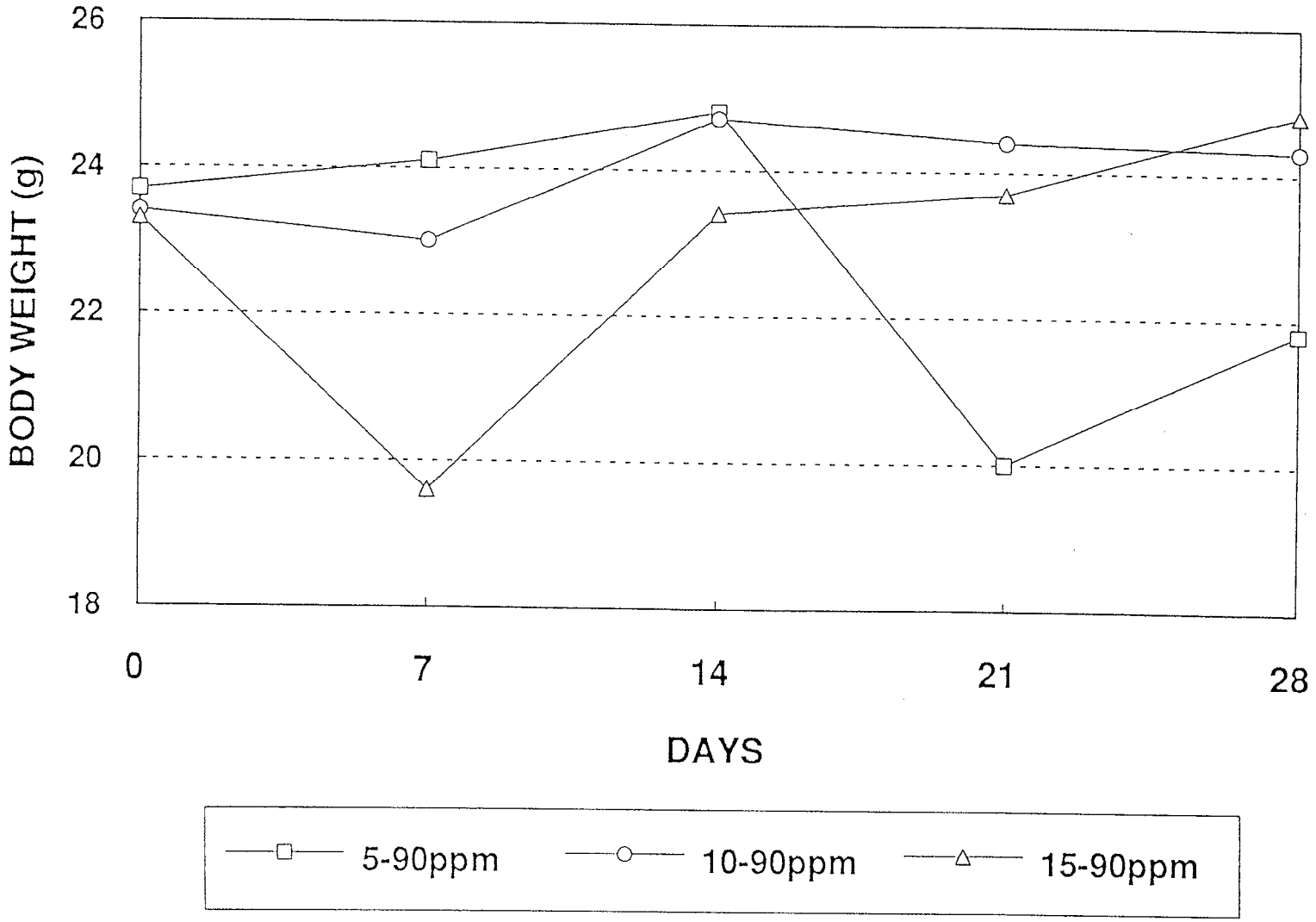


Table 1 CONCENTRATION OF CHLOROFORM IN INHALATION CHAMBER

(28-DAY STUDIES)

FIRST TWO WEEKS		SECOND TWO WEEKS	
TARGET CONC. (ppm)	MEASURMENT(ppm) MEAN ± SD	TARGET CONC. (ppm)	MEASURMENT(ppm) MEAN ± SD
5	5.0 ± 0.0	30	30.0 ± 0.1
		90	90.0 ± 0.2
10	10.0 ± 0.0	30	30.0 ± 0.1
		90	90.0 ± 0.2
15	15.0 ± 0.1	90	90.0 ± 0.2

Table 2 SURVIVAL ANIMAL NUMBERS IN 28-DAY STUDY

FIRST TWO WEEKS		SECOND TWO WEEKS	
DOSE GROUP	NUMBER OF SURVIVAL	DOSE GROUP	NUBMER OF SURVIVAL
5	10/10	30	4/5
		90	1/5
10	10/10	30	5/5
		90	5/5
15	6/10	90	6/6

Number of survival/Number of effective animals

Table 3 BODY WEIGHT CHANGES IN 28-DAY STUDIES

	FIRST TWO WEEKS			SECOND TWO WEEKS	
GROUP NAME	0	7	14	21	28 (DAY)
CONTROL	23.3 ± 1.0(10)	25.0 ± 1.0(10)	25.9 ± 1.1(10)	27.1 ± 1.0(10)	27.9 ± 1.2(10)
5ppm	23.3 ± 0.9(10)	23.9 ± 0.9(10)	24.9 ± 1.0(10)		
5-30ppm	22.9 ± 0.7(5)	23.8 ± 0.7(5)	25.1 ± 0.7(5)	24.2 ± 1.3(4)	23.6 ± 2.8(4)
5-90ppm	23.7 ± 0.9(5)	24.1 ± 1.1(5)	24.8 ± 1.2(5)	20.0 ± 0.0(1)	21.8 ± 0.0(1)
10ppm	23.3 ± 0.9(10)	23.0 ± 1.2(10)	24.7 ± 0.8(10)		
10-30ppm	23.0 ± 0.9(5)	23.0 ± 0.6(5)	24.7 ± 0.8(5)	25.2 ± 0.9(5)	25.6 ± 0.7(5)
10-90ppm	23.4 ± 0.8(5)	23.0 ± 1.7(5)	24.7± 0.8(5)	24.4 ± 1.2(5)	24.3 ± 1.3(5)
15-90ppm	23.3 ± 1.0(10)	19.6 ± 2.7(6)	23.4 ± 1.1(6)	23.7 ± 1.4(6)	24.8 ± 0.8(6)

( ):Number of animals

Mean ± SD