p-ニトロアニソールのラットを用いた経口投与による
１３ 週 間 毒 性 試 験（混 餌 試 験 ）報 告 書

試験番号：０３６９

APPENDIX

APPENDIXES

APPENDIXES (CONTINUED)

APPENDIX A 1

CLINICAL OBSERVATION : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1 13

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : MALE

Clinical sign	Group Name	Administration Week-day 1-7	2-7	3-7	4-7	5-7	6-7	7-7	8-7	9-7	10-7	11-7	12-7	13-7
COLORED	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	0	0	0	0	0	0	0	7	9	9	9	9	9
	2500 ppm	1	1	7	10	10	10	10	10	10	10	10	10	10
	5000 ppm	9	10	10	10	10	10	10	10	10	10	10	10	10
	8000 ppm	9	9	9	10	10	10	10	10	10	10	10	10	10
	10000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
SOILED PERI GENITALIA	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	5000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	8000 ppm	0	0	1	1	1	1	2	2	2	2	2	4	4
	10000 ppm	0	0	3	3	2	2	3	2	2	2	2	5	6
YELLOW URINE	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	2500 ppm	9	10	10	10	10	10	10	10	10	10	10	10	10
	5000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	8000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	10000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10

APPENDIX A 2

CLINICAL OBSERVATION : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1 13

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : FEMALE

Clinical sign	Group Name	Administration Week-day 1-7	2-7	3-7	4-7	5-7	6-7	7-7	8-7	9-7	10-7	11-7	12-7	13-7
HUNCHBACK POSITION	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	5000 ppm	0	0	0	0	0	0	0	0	0	0	0	1	1
	8000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	1	1
COLORED	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	9	9	9	9	9	10	9	9	9	9	9	10	10
	2500 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	5000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	8000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	10000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
SOILED PERI GENITALIA	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	0	0	0	0	0	0	0	0	0	0	0	1	1
	2500 ppm	0	0	2	0	0	0	0	0	0	0	0	0	0
	5000 ppm	0	0	1	1	1	1	4	5	4	4	4	4	4
	8000 ppm	7	7	7	7	7	7	7	7	7	7	7	8	8
	10000 ppm	8	8	10	10	9	9	8	8	8	8	8	8	8
EYE OPACITY	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	5000 ppm	0	0	0	0	0	0	0	0	1	1	1	1	1
	8000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
CATARACT	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	2500 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	5000 ppm	0	0	0	0	0	0	0	0	1	1	1	1	1
	8000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
	10000 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0
YELLOW URINE	Control	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	2500 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	5000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	8000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10
	10000 ppm	10	10	10	10	10	10	10	10	10	10	10	10	10

APPENDIX B 1

BODY WEIGHT CHANGES : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 0	1	2	3	4	5	6
Control	126± 4	155± 6	182± 9	203± 11	224± 11	239± 12	251± 13
1250 ppm	126± 4	155± 4	180± 2	202± 6	219± 6	236± 7	248± 6
2500 ppm	126± 3	153± 6	178± 7	198± 11	216± 11	230± 12	246± 13
5000 ppm	126± 3	148± 7	173± 11	194± 13	212± 15	226± 15*	240± 15
8000 ppm	126± 3	137± 2**	161± 4**	180± 6**	197± 7**	211± 9**	222± 10**
10000 ppm	126± 4	127± 5**	143± 5**	159± 7**	174± 5**	186± 7**	197± 7**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 7	8	9	10	11	12	13
Control	264± 13	276± 13	286± 13	295± 14	303± 14	309± 15	315± 15
1250 ppm	260± 8	273± 7	281± 8	290± 9	298± 10	306± 10	312± 11
2500 ppm	260± 13	269± 14	280± 15	289± 13	298± 14	306± 15	314± 14
5000 ppm	249± 17*	258± 16**	269± 19	279± 19*	288± 16*	294± 17	301± 19
8000 ppm	234± 11**	242± 11**	250± 12**	256± 13**	263± 14**	269± 14**	276± 15**
10000 ppm	205± 6**	214± 7**	222± 7**	230± 6**	237± 8**	243± 9**	249± 10**

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

APPENDIX B 2

BODY WEIGHT CHANGES : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 0	1	2	3	4	5	6
Control	100± 3	112± 5	123± 5	130± 4	138± 6	144± 5	149± 5
1250 ppm	100± 3	111± 4	118± 5	125± 5	130± 6	136± 7	140± 7*
2500 ppm	100± 3	107± 5	115± 6*	119± 6**	125± 7**	130± 8**	134± 7**
5000 ppm	100± 3	104± 6**	111± 8**	115± 7**	120± 8**	124± 8**	129± 8**
8000 ppm	100± 3	96± 5**	105± 5**	112± 7**	118± 8**	122± 8**	126± 7**
10000 ppm	100± 3	94± 5**	102± 7**	111± 8**	118± 7**	124± 9**	129± 10**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 7	8	9	10	11	12	13
Control	154± 5	157± 6	163± 5	166± 5	171± 5	172± 7	175± 5
1250 ppm	142± 7**	143± 9**	146± 8**	152± 7**	152± 8**	157± 8**	159± 8**
2500 ppm	138± 8**	139± 8**	142± 8**	145± 9**	149± 8**	152± 8**	154± 8**
5000 ppm	131± 8**	133± 8**	135± 9**	138± 7**	140± 10**	142± 10**	144± 11**
8000 ppm	130± 8**	133± 8**	133± 7**	137± 8**	139± 7**	144± 8**	146± 10**
10000 ppm	132± 9**	135± 9**	137± 10**	139± 10**	141± 11**	145± 11**	147± 10**

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

APPENDIX C 1

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
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)
Control	12.6± 0.7	13.3± 0.9	13.7± 1.0	14.4± 0.9	14.5± 1.0	14.4± 0.9	14.7± 0.6
1250 ppm	12.6± 0.6	13.3± 0.4	14.0± 0.5	14.2± 0.4	14.6± 0.8	14.2± 0.7	14.4± 0.5
2500 ppm	11.8± 0.7*	13.1± 0.5	13.5± 1.0	13.7± 0.9	13.7± 1.3	13.9± 0.8	14.5± 0.6
5000 ppm	10.1± 0.6**	12.9± 1.2	13.3± 1.2	13.7± 1.2	13.8± 1.1	13.8± 1.0	14.0± 1.1
8000 ppm	8.5± 0.5**	11.7± 0.4*	12.6± 0.6*	13.0± 0.6**	13.1± 1.0*	13.3± 1.6	14.1± 1.9
10000 ppm	7.0± 0.6**	9.7± 0.6**	10.8± 0.9**	11.5± 0.7**	11.5± 0.9**	12.0± 0.8**	12.2± 0.7**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
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)
Control	14.5± 0.8	14.3± 0.8	14.2± 0.9	14.2± 0.8	14.0± 1.1	14.2± 1.2
1250 ppm	14.3± 0.4	14.4± 0.6	14.2± 0.8	14.4± 1.1	14.3± 0.8	14.7± 1.2
2500 ppm	13.9± 0.8	14.4± 0.8	14.2± 0.8	14.3± 0.8	14.2± 0.8	14.4± 0.9
5000 ppm	13.6± 1.0	14.2± 1.3	14.3± 1.3	14.3± 0.8	14.4± 0.9	14.3± 1.3
8000 ppm	13.9± 1.5	13.7± 1.2	13.7± 1.2	13.9± 1.5	14.3± 1.8	14.8± 1.9
10000 ppm	12.4± 0.4**	12.1± 0.5**	12.3± 0.5**	12.4± 0.8**	12.8± 0.7	13.1± 0.8

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

APPENDIX C 2

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
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)
Control	9.8± 0.7	9.8± 0.8	10.0± 0.5	10.2± 0.6	10.3± 0.6	10.0± 0.5	10.2± 0.4
1250 ppm	9.4± 0.5	9.2± 0.7	9.4± 0.7	9.5± 0.9	9.7± 0.8	9.3± 0.8	9.3± 0.9
2500 ppm	8.6± 0.6	8.5± 0.8**	8.8± 0.7**	9.1± 0.8*	9.0± 0.7**	9.3± 0.7	9.5± 0.9
5000 ppm	8.2± 2.5*	8.2± 0.9**	8.2± 0.8**	8.3± 0.9**	8.3± 0.7**	8.3± 0.7**	8.4± 0.9**
8000 ppm	6.2± 1.2**	7.4± 0.6**	7.8± 0.5**	8.1± 0.6**	8.1± 0.7**	8.1± 0.7**	8.1± 0.7**
10000 ppm	7.1± 3.3**	7.4± 0.5**	7.8± 0.6**	8.2± 0.6**	8.0± 0.6**	8.3± 1.1**	8.6± 1.4**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 8-7(7)	9-7(7)	10-7(7)	11-7(7)	12-7(7)	13-7(7)
Control	9.8± 0.7	9.8± 0.8	9.7± 0.8	9.9± 0.7	9.8± 0.7	9.9± 0.7
1250 ppm	8.8± 0.5	9.0± 0.4	9.1± 0.4	9.1± 0.4	9.1± 0.5	9.2± 0.6
2500 ppm	8.8± 0.6	8.8± 0.7	8.8± 0.8	8.8± 0.7	8.8± 0.6	9.1± 1.4
5000 ppm	8.2± 0.6**	8.3± 0.8**	8.1± 0.6**	7.9± 0.6**	7.9± 0.7**	8.1± 0.8**
8000 ppm	8.0± 0.5**	7.7± 0.5**	7.8± 0.5**	7.6± 0.7**	8.0± 0.6**	8.3± 0.6**
10000 ppm	8.7± 1.8**	8.6± 1.8**	8.7± 2.3**	8.8± 2.8**	10.2± 4.7**	9.7± 3.7**

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

APPENDIX D 1

CHEMICAL INTAKE CHANGES : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g/kg/day
REPORT TYPE : A1 13
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 1	2	3	4	5	6	7
Control	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000
1250 ppm	0.102± 0.003	0.092± 0.002	0.087± 0.002	0.081± 0.002	0.077± 0.003	0.072± 0.003	0.069± 0.002
2500 ppm	0.192± 0.005	0.185± 0.006	0.170± 0.004	0.159± 0.005	0.149± 0.007	0.141± 0.003	0.140± 0.004
5000 ppm	0.341± 0.017	0.372± 0.019	0.343± 0.011	0.322± 0.011	0.305± 0.009	0.288± 0.006	0.282± 0.010
8000 ppm	0.494± 0.025	0.580± 0.015	0.562± 0.012	0.528± 0.025	0.497± 0.034	0.479± 0.058	0.483± 0.074
10000 ppm	0.554± 0.035	0.679± 0.027	0.679± 0.041	0.661± 0.030	0.618± 0.033	0.607± 0.029	0.597± 0.022

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g/kg/day
REPORT TYPE : A1 13
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 8	9	10	11	12	13
Control	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000
1250 ppm	0.066± 0.002	0.064± 0.002	0.061± 0.003	0.061± 0.004	0.058± 0.003	0.059± 0.005
2500 ppm	0.129± 0.003	0.128± 0.005	0.123± 0.004	0.120± 0.005	0.116± 0.003	0.115± 0.005
5000 ppm	0.264± 0.009	0.262± 0.008	0.255± 0.007	0.249± 0.004	0.244± 0.009	0.237± 0.011
8000 ppm	0.461± 0.052	0.437± 0.028	0.429± 0.039	0.423± 0.037	0.427± 0.052	0.428± 0.051
10000 ppm	0.577± 0.015	0.547± 0.014	0.533± 0.013	0.524± 0.024	0.527± 0.023	0.524± 0.025

APPENDIX D 2

CHEMICAL INTAKE CHANGES : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g/kg/day
REPORT TYPE : A1 13
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 1	2	3	4	5	6	7
Control	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000
1250 ppm	0.106± 0.004	0.097± 0.005	0.095± 0.006	0.091± 0.004	0.089± 0.004	0.083± 0.004	0.082± 0.005
2500 ppm	0.201± 0.009	0.186± 0.011	0.185± 0.010	0.181± 0.013	0.174± 0.010	0.172± 0.010	0.173± 0.025
5000 ppm	0.392± 0.127	0.368± 0.020	0.354± 0.019	0.346± 0.024	0.335± 0.014	0.322± 0.016	0.321± 0.020
8000 ppm	0.519± 0.109	0.565± 0.029	0.558± 0.020	0.552± 0.020	0.530± 0.017	0.513± 0.028	0.501± 0.024
10000 ppm	0.744± 0.326	0.721± 0.032	0.707± 0.026	0.694± 0.022	0.646± 0.021	0.641± 0.046	0.652± 0.068

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
UNIT : g/kg/day
REPORT TYPE : A1 13
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 8	9	10	11	12	13
Control	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000	0.000± 0.000
1250 ppm	0.077± 0.004	0.077± 0.002	0.075± 0.003	0.075± 0.002	0.073± 0.002	0.072± 0.003
2500 ppm	0.159± 0.010	0.155± 0.014	0.152± 0.013	0.148± 0.011	0.145± 0.010	0.149± 0.028
5000 ppm	0.307± 0.013	0.306± 0.016	0.293± 0.017	0.282± 0.013	0.278± 0.020	0.280± 0.018
8000 ppm	0.481± 0.019	0.463± 0.022	0.454± 0.022	0.439± 0.028	0.448± 0.023	0.457± 0.023
10000 ppm	0.641± 0.092	0.622± 0.088	0.622± 0.119	0.621± 0.151	0.698± 0.302	0.653± 0.208

APPENDIX E 1

HEMATOLOGY : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (14W)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV fℓ	MCH pg	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	10	9.68± 0.25	16.3± 0.3	47.5± 1.3	49.1± 0.6	16.8± 0.2	34.2± 0.5	708± 77
1250 ppm	10	9.51± 0.19	16.0± 0.4	47.1± 1.2	49.5± 0.7	16.8± 0.2	34.0± 0.4	729± 21
2500 ppm	10	9.07± 0.24**	15.5± 0.4**	45.7± 1.5*	50.4± 0.5**	17.0± 0.2*	33.8± 0.3	791± 28
5000 ppm	10	8.36± 0.16**	14.4± 0.3**	42.6± 1.0**	51.0± 0.8**	17.2± 0.2**	33.7± 0.5	911± 47**
8000 ppm	10	7.98± 0.17**	13.8± 0.4**	41.3± 1.1**	51.7± 0.7**	17.3± 0.2**	33.4± 0.4**	935± 26**
10000 ppm	10	8.06± 0.32**	14.0± 0.5**	41.9± 1.5**	52.0± 0.9**	17.4± 0.2**	33.4± 0.4**	938± 20**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (14W)

Group Name	NO. of Animals	RETICULOCYTE ‰		PROTHROMBIN TIME sec		APTT sec	
Control	10	16±	2	15.7±	1.3	26.0±	1.1
1250 ppm	10	19±	4	15.3±	1.0	26.3±	1.1
2500 ppm	10	25±	6	14.4±	0.9	23.4±	1.5
5000 ppm	10	33±	7**	13.9±	0.5*	23.0±	2.6*
8000 ppm	10	42±	11**	13.4±	0.4**	19.7±	2.4**
10000 ppm	10	53±	13**	13.3±	0.3**	21.8±	0.9**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (14W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$	Differential WBC (%) N-BAND	N-SEG	EOSINO	BASO	MONO	LYMPHO	OTHER
Control	10	5.77± 1.40	0± 1	22± 2	1± 1	0± 0	3± 1	74± 3	0± 0
1250 ppm	10	7.48± 1.46*	0± 0	21± 4	1± 1	0± 0	4± 2	74± 4	0± 0
2500 ppm	10	6.75± 1.09	0± 1	22± 5	1± 1	0± 0	3± 2	73± 5	0± 0
5000 ppm	10	7.75± 1.60*	1± 1	24± 5	1± 1	0± 0	3± 2	71± 5	0± 0
8000 ppm	10	8.65± 1.58**	0± 0	27± 7	1± 1	0± 0	3± 2	69± 7	0± 0
10000 ppm	10	8.08± 1.13**	0± 1	30± 6**	1± 1	0± 0	3± 2	66± 6*	0± 0

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

APPENDIX E 2

HEMATOLOGY : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (14W)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$		HEMOGLOBIN g/dℓ		HEMATOCRIT %		MCV fℓ		MCH pg		MCHC g/dℓ		PLATELET $10^3/\mu\ell$	
Control	10	8.83±	0.24	16.0±	0.5	45.5±	1.5	51.6±	0.6	18.0±	0.2	35.0±	0.5	836±	57
1250 ppm	10	8.58±	0.26	15.4±	0.5	44.0±	1.6	51.3±	0.7	18.0±	0.1	35.1±	0.4	854±	59
2500 ppm	10	8.29±	0.32**	15.1±	0.6**	43.7±	1.9*	52.7±	0.7**	18.2±	0.2	34.6±	0.4*	898±	44
5000 ppm	10	7.46±	0.25**	13.7±	0.5**	40.1±	1.4**	53.8±	0.6**	18.3±	0.3**	34.1±	0.3**	960±	72**
8000 ppm	10	7.47±	0.25**	13.4±	0.4**	39.6±	1.4**	53.0±	0.5**	17.9±	0.3	33.8±	0.3**	941±	61**
10000 ppm	10	7.40±	0.21**	13.1±	0.4**	39.1±	1.4**	52.8±	0.6**	17.7±	0.2**	33.5±	0.3**	992±	45**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (14W)

Group Name	NO. of Animals	RETICULOCYTE ‰		PROTHROMBIN TIME sec		APTT sec	
Control	10	14±	3	13.7±	0.4	19.4±	1.7
1250 ppm	10	18±	4	13.8±	0.4	20.6±	1.2
2500 ppm	10	19±	5	14.2±	0.3*	20.2±	2.0
5000 ppm	10	34±	10**	13.9±	0.4	21.7±	1.1**
8000 ppm	10	41±	12**	13.8±	0.3	21.0±	1.4
10000 ppm	10	49±	14**	13.8±	0.3	21.2±	2.0

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (14W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) N-BAND		N-SEG		EOSINO		BASO		MONO		LYMPHO		OTHER	
Control	10	3.29±	0.76	0±	1	20±	3	2±	1	0±	0	2±	2	75±	3	0±	0
1250 ppm	10	3.44±	0.90	0±	0	20±	5	1±	1	0±	0	3±	2	76±	6	0±	0
2500 ppm	10	4.19±	1.08	0±	0	17±	3	1±	1	0±	0	2±	1	80±	3	0±	0
5000 ppm	10	5.06±	1.04**	0±	0	24±	8	1±	1	0±	0	2±	1	73±	8	0±	0
8000 ppm	10	5.23±	0.70**	0±	1	23±	6	1±	1	0±	0	2±	1	74±	6	0±	0
10000 ppm	10	5.05±	1.07**	0±	0	22±	5	0±	1**	0±	0	2±	2	75±	5	0±	0

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

APPENDIX F 1

BIOCHEMISTRY : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (14W)

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	10	6.1±	0.1	3.8±	0.1	1.7±	0.1	0.13±	0.01	178±	24	67±	4	75±	31
1250 ppm	10	6.3±	0.2	3.9±	0.1	1.6±	0.1*	0.12±	0.01	178±	13	69±	4	65±	23
2500 ppm	10	6.3±	0.2*	4.0±	0.1	1.7±	0.1	0.13±	0.01	180±	10	82±	5	55±	17
5000 ppm	10	7.0±	0.2**	4.4±	0.1**	1.7±	0.1	0.14±	0.01	160±	8	118±	14**	45±	16**
8000 ppm	10	7.4±	0.1**	4.6±	0.1**	1.6±	0.0*	0.15±	0.01**	151±	12*	162±	17**	33±	13**
10000 ppm	10	7.4±	0.2**	4.6±	0.2**	1.6±	0.1*	0.15±	0.01**	140±	11**	166±	17**	38±	19**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (14W)

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	10	118± 11	82± 40	46± 15	169± 71	232± 16	2± 1	95± 11
1250 ppm	10	119± 9	88± 21	48± 8	173± 50	234± 19	2± 1	96± 10
2500 ppm	10	130± 7	57± 9	36± 5	141± 42	209± 11**	2± 1	93± 15
5000 ppm	10	176± 19*	47± 4**	31± 1**	115± 14	194± 16**	4± 1	87± 6
8000 ppm	10	236± 24**	51± 6	36± 4	127± 13	186± 15**	8± 2**	94± 10
10000 ppm	10	245± 33**	54± 9	41± 8	125± 19	177± 18**	11± 3**	98± 14

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (14W)

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	10	20.3±	6.7	0.5±	0.1	142±	2	3.8±	0.5	105±	3	10.1±	0.2	5.4±	1.1
1250 ppm	10	19.3±	1.2	0.5±	0.1	142±	2	3.8±	0.2	106±	2	10.1±	0.2	5.7±	0.7
2500 ppm	10	20.7±	1.6	0.5±	0.0	141±	2	3.9±	0.3	104±	2	10.2±	0.3	5.7±	0.9
5000 ppm	10	26.1±	1.7**	0.6±	0.1	140±	1	4.1±	0.2	101±	1*	10.9±	0.2**	5.9±	0.4
8000 ppm	10	29.9±	4.3**	0.6±	0.1	139±	1**	4.1±	0.4	99±	2**	11.3±	0.1**	6.0±	0.4
10000 ppm	10	29.5±	4.3**	0.5±	0.0	139±	2**	4.1±	0.4	98±	2**	11.3±	0.2**	6.6±	0.5*

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

APPENDIX F 2

BIOCHEMISTRY : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (14W)

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	10	6.0±	0.1	3.8±	0.1	1.7±	0.1	0.14±	0.01	143±	15	74±	5	18±	5
1250 ppm	10	6.0±	0.1	3.8±	0.1	1.7±	0.1	0.14±	0.01	140±	11	72±	6	16±	2
2500 ppm	10	6.1±	0.2	3.7±	0.1	1.6±	0.1**	0.14±	0.01	144±	14	79±	4	14±	3
5000 ppm	10	6.6±	0.2*	4.1±	0.1	1.6±	0.1**	0.14±	0.01	144±	9	132±	9*	14±	3
8000 ppm	10	7.2±	0.3**	4.5±	0.2**	1.6±	0.1*	0.15±	0.02	137±	10	178±	15**	20±	6
10000 ppm	10	7.5±	0.4**	4.6±	0.3**	1.6±	0.1**	0.16±	0.02	137±	18	205±	24**	24±	11

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (14W)

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	10	139± 9	67± 11	36± 9	154± 40	168± 18	2± 1	109± 55
1250 ppm	10	131± 9	70± 12	39± 15	139± 49	162± 15	2± 1	95± 13
2500 ppm	10	137± 5	64± 4	29± 3	175± 63	161± 10	2± 1	95± 18
5000 ppm	10	199± 13	53± 6*	29± 4	163± 88	129± 7**	3± 1	94± 25
8000 ppm	10	260± 34**	53± 8*	31± 4	165± 53	125± 25**	9± 3**	94± 22
10000 ppm	10	301± 48**	49± 6**	31± 4	191± 139	117± 28**	12± 3**	102± 38

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (14W)

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	10	17.8±	1.6	0.5±	0.1	141±	2	3.8±	0.3	107±	2	9.7±	0.3	4.8±	1.4
1250 ppm	10	19.8±	1.7	0.5±	0.1	140±	1	3.8±	0.2	107±	2	9.7±	0.2	5.3±	1.2
2500 ppm	10	20.4±	1.3	0.5±	0.1	140±	1	4.0±	0.2	107±	2	9.8±	0.2	5.3±	0.8
5000 ppm	10	27.0±	2.9**	0.5±	0.1	139±	2*	4.0±	0.3	104±	2**	10.1±	0.2	5.0±	0.7
8000 ppm	10	29.2±	3.3**	0.5±	0.0	139±	1*	4.0±	0.3	101±	2**	10.9±	0.3**	5.5±	0.5
10000 ppm	10	30.5±	2.8**	0.5±	0.1	138±	1**	4.1±	0.2**	100±	1**	11.1±	0.4**	5.5±	0.6

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

APPENDIX G 1

URINALYSIS : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369 URINALYSIS
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

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
Control	10	0	0	0	0	0	2	8		0	0	5	5	0	0		10	0	0	0	0	0		0	6	4	0	0	0		10	0	0	0	
1250 ppm	10	0	0	0	0	0	4	6		0	0	6	3	1	0		10	0	0	0	0	0		0	7	3	0	0	0		10	0	0	0	
2500 ppm	10	0	0	0	0	1	3	6		0	0	4	6	0	0		10	0	0	0	0	0		2	6	2	0	0	0		10	0	0	0	
5000 ppm	10	0	0	0	0	1	6	3		0	0	7	3	0	0		10	0	0	0	0	0		6	3	1	0	0	0	*	10	0	0	0	
8000 ppm	10	0	0	0	1	5	4	0	**	0	0	5	5	0	0		10	0	0	0	0	0		9	1	0	0	0	0	**	10	0	0	0	
10000 ppm	10	0	0	1	0	4	4	1	*	0	0	0	9	1	0	*	10	0	0	0	0	0		5	5	0	0	0	0	*	10	0	0	0	

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
Control	10	10	0	0	0	0		10	0	0	0	0	
1250 ppm	10	10	0	0	0	0		10	0	0	0	0	
2500 ppm	10	10	0	0	0	0		10	0	0	0	0	
5000 ppm	10	10	0	0	0	0		10	0	0	0	0	
8000 ppm	10	10	0	0	0	0		10	0	0	0	0	
10000 ppm	10	10	0	0	0	0		10	0	0	0	0	

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

APPENDIX G 2

URINALYSIS : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369 URINALYSIS
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

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
Control	10	0	0	0	0	0	8	2		0	0	7	3	0	0		10	0	0	0	0	0		8	2	0	0	0	0		10	0	0	0	
1250 ppm	10	0	0	0	0	0	6	4		0	0	9	1	0	0		10	0	0	0	0	0		9	1	0	0	0	0		10	0	0	0	
2500 ppm	10	0	0	0	0	0	3	7	*	0	1	8	1	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	
5000 ppm	10	0	0	0	0	1	7	2		0	0	3	7	0	0		10	0	0	0	0	0		9	1	0	0	0	0		10	0	0	0	
8000 ppm	10	0	0	0	0	0	9	1		0	0	9	1	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	
10000 ppm	10	0	0	1	2	2	2	3		0	0	8	2	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
Control	10	10	0	0	0	0		10	0	0	0	0	
1250 ppm	10	10	0	0	0	0		10	0	0	0	0	
2500 ppm	10	10	0	0	0	0		10	0	0	0	0	
5000 ppm	10	10	0	0	0	0		10	0	0	0	0	
8000 ppm	10	10	0	0	0	0		10	0	0	0	0	
10000 ppm	10	10	0	0	0	0		10	0	0	0	0	

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

APPENDIX H 1

GROSS FINDINGS : SUMMARY, RAT : MALE ALL ANIMALS

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

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

Organ	Findings	Group Name NO. of Animals	Control 10 (%)	1250 ppm 10 (%)	2500 ppm 10 (%)	5000 ppm 10 (%)
liver	herniation		0 (0)	1 (10)	0 (0)	3 (30)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

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

Organ	Findings	Group Name	8000 ppm	10000 ppm
		NO. of Animals	10 (%)	10 (%)
liver	herniation		0 (0)	3 (30)

APPENDIX H 2

GROSS FINDINGS : SUMMARY, RAT : FEMALE ALL ANIMALS

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

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

Organ	Findings	Group Name / NO. of Animals	Control 10 (%)	1250 ppm 10 (%)	2500 ppm 10 (%)	5000 ppm 10 (%)
liver	herniation		1 (10)	2 (20)	2 (20)	0 (0)
kidney	nodule		0 (0)	0 (0)	0 (0)	1 (10)
pituitary	cyst		0 (0)	0 (0)	0 (0)	0 (0)
ovary	cyst		0 (0)	0 (0)	0 (0)	0 (0)

Organ	Findings	Group Name NO. of Animals	8000 ppm 10 (%)	10000 ppm 10 (%)
liver	herniation		2 (20)	0 (0)
kidney	nodule		0 (0)	0 (0)
pituitary	cyst		0 (0)	1 (10)
ovary	cyst		1 (10)	0 (0)

APPENDIX I 1

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: g

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

Group Name	NO. of Animals	Body Weight	THYMUS	ADRENALS	TESTES	HEART	LUNGS
Control	10	297± 17	0.214± 0.017	0.049± 0.007	2.950± 0.110	0.945± 0.051	1.029± 0.040
1250 ppm	10	294± 10	0.204± 0.023	0.052± 0.006	2.876± 0.154	0.921± 0.033	1.013± 0.047
2500 ppm	10	295± 15	0.205± 0.026	0.052± 0.011	3.061± 0.090	0.913± 0.046	1.026± 0.063
5000 ppm	10	283± 18	0.191± 0.018	0.054± 0.006	3.094± 0.092*	0.917± 0.047	1.036± 0.054
8000 ppm	10	259± 14**	0.184± 0.024*	0.057± 0.010	3.079± 0.092*	0.862± 0.070**	1.014± 0.058
10000 ppm	10	234± 10**	0.171± 0.014**	0.054± 0.006	3.101± 0.084*	0.811± 0.038**	0.947± 0.044**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: g

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

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
Control	10	1.805± 0.113	0.549± 0.036	7.113± 0.399	1.882± 0.044
1250 ppm	10	1.809± 0.061	0.538± 0.029	7.258± 0.490	1.862± 0.047
2500 ppm	10	1.878± 0.094	0.609± 0.089	8.117± 0.601**	1.894± 0.055
5000 ppm	10	2.112± 0.109**	0.715± 0.078**	9.930± 0.849**	1.914± 0.032
8000 ppm	10	2.102± 0.126**	0.757± 0.088**	11.528± 0.841**	1.888± 0.034
10000 ppm	10	2.104± 0.107**	0.732± 0.098**	11.389± 0.712**	1.858± 0.026

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

APPENDIX I 2

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

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

Group Name	NO. of Animals	Body Weight	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
Control	10	163± 5	0.171± 0.020	0.060± 0.009	0.090± 0.011	0.605± 0.026	0.763± 0.036
1250 ppm	10	147± 8**	0.150± 0.022	0.054± 0.007	0.086± 0.010	0.562± 0.058	0.724± 0.045
2500 ppm	10	143± 8**	0.154± 0.020	0.053± 0.005	0.091± 0.017	0.542± 0.043*	0.714± 0.026*
5000 ppm	10	136± 10**	0.144± 0.012**	0.050± 0.005**	0.086± 0.007	0.534± 0.047**	0.694± 0.032**
8000 ppm	10	137± 10**	0.143± 0.020**	0.049± 0.009**	0.090± 0.023	0.559± 0.051	0.684± 0.041**
10000 ppm	10	139± 8**	0.149± 0.018	0.047± 0.005**	0.089± 0.009	0.571± 0.051	0.681± 0.040**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

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

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
Control	10	1.106± 0.026	0.331± 0.022	3.776± 0.122	1.732± 0.046
1250 ppm	10	1.078± 0.065	0.328± 0.030	3.611± 0.201	1.726± 0.034
2500 ppm	10	1.104± 0.056	0.335± 0.034	3.717± 0.171	1.767± 0.036
5000 ppm	10	1.189± 0.067*	0.380± 0.033*	4.768± 0.338	1.730± 0.040
8000 ppm	10	1.289± 0.086**	0.429± 0.060**	6.083± 0.555**	1.737± 0.045
10000 ppm	10	1.334± 0.056**	0.475± 0.048**	6.977± 0.528**	1.769± 0.057

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

APPENDIX J 1

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: %

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

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	TESTES	HEART	LUNGS
Control	10	297± 17	0.072± 0.007	0.016± 0.002	0.997± 0.071	0.319± 0.014	0.348± 0.016
1250 ppm	10	294± 10	0.069± 0.007	0.018± 0.002	0.978± 0.055	0.314± 0.018	0.345± 0.011
2500 ppm	10	295± 15	0.069± 0.008	0.018± 0.004	1.039± 0.053	0.309± 0.009	0.348± 0.016
5000 ppm	10	283± 18	0.067± 0.005	0.019± 0.003	1.096± 0.073**	0.324± 0.017	0.366± 0.011
8000 ppm	10	259± 14**	0.071± 0.008	0.022± 0.003**	1.192± 0.049**	0.333± 0.019	0.392± 0.012**
10000 ppm	10	234± 10**	0.073± 0.005	0.023± 0.003**	1.327± 0.078**	0.347± 0.012**	0.405± 0.026**

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: %

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

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
Control	10	0.609± 0.025	0.185± 0.013	2.399± 0.077	0.636± 0.040
1250 ppm	10	0.615± 0.013	0.183± 0.010	2.465± 0.088	0.634± 0.025
2500 ppm	10	0.637± 0.015	0.206± 0.022	2.748± 0.095	0.643± 0.034
5000 ppm	10	0.746± 0.022**	0.252± 0.017**	3.501± 0.119**	0.678± 0.041*
8000 ppm	10	0.813± 0.040**	0.292± 0.026**	4.453± 0.148**	0.731± 0.034**
10000 ppm	10	0.899± 0.031**	0.312± 0.036**	4.864± 0.201**	0.795± 0.038**

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

APPENDIX J 2

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

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

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
Control	10	163± 5	0.105± 0.011	0.037± 0.006	0.055± 0.008	0.370± 0.012	0.467± 0.024
1250 ppm	10	147± 8**	0.102± 0.013	0.037± 0.005	0.059± 0.008	0.384± 0.035	0.494± 0.022*
2500 ppm	10	143± 8**	0.108± 0.014	0.037± 0.002	0.064± 0.013	0.380± 0.015	0.502± 0.023**
5000 ppm	10	136± 10**	0.106± 0.007	0.037± 0.003	0.064± 0.008	0.394± 0.024	0.513± 0.024**
8000 ppm	10	137± 10**	0.104± 0.008	0.036± 0.006	0.066± 0.016	0.410± 0.034**	0.502± 0.024**
10000 ppm	10	139± 8**	0.107± 0.011	0.034± 0.004	0.064± 0.007	0.410± 0.019**	0.490± 0.017

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

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

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

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
Control	10	0.677± 0.016	0.203± 0.015	2.312± 0.074	1.061± 0.043
1250 ppm	10	0.737± 0.054	0.224± 0.015	2.464± 0.055	1.181± 0.072**
2500 ppm	10	0.776± 0.032	0.235± 0.020**	2.611± 0.080	1.243± 0.065**
5000 ppm	10	0.880± 0.047**	0.281± 0.017**	3.519± 0.062**	1.283± 0.092**
8000 ppm	10	0.945± 0.052**	0.313± 0.031**	4.450± 0.177**	1.277± 0.094**
10000 ppm	10	0.961± 0.047**	0.342± 0.028**	5.018± 0.280**	1.276± 0.077**

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

APPENDIX K 1

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : MALE : ALL ANIMALS

(13-WEEK STUDY)

Organ	Findings	Group Name	Control				1250 ppm				2500 ppm				5000 ppm			
		No. of Animals on Study	10				10				10				10			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
nasal cavit			<10>				<10>				<10>				<10>			
	respiratory metaplasia:gland		3	1	0	0	3	0	0	0	3	0	0	0	0	0	0	0
			(30)	(10)	(0)	(0)	(30)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
lung			<10>				<10>				<10>				<10>			
	osseous metaplasia		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			<10>				<10>				<10>				<10>			
	deposit of hemosiderin		0	0	0	0	0	0	0	0	3	0	0	0	5	5	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(50)	(50)	(0)	(0)
	engorgement of erythrocyte		0	0	0	0	0	0	0	0	3	0	0	0	9	1	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(90)	(10)	(0)	(0)
[Digestive system]																		
liver			<10>				<10>				<10>				<10>			
	herniation		1	0	0	0	1	0	0	0	0	0	0	0	3	0	0	0
			(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(30)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	8000 ppm				10000 ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]										
nasal cavit			<10>				<10>			
	respiratory metaplasia:gland		3	0	0	0	1	0	0	0
			(30)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
lung			<10>				<10>			
	osseous metaplasia		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
[Hematopoietic system]										
spleen			<10>				<10>			
	deposit of hemosiderin		0	10	0	0 **	0	10	0	0 **
			(0)	(100)	(0)	(0)	(0)	(100)	(0)	(0)
	engorgement of erythrocyte		6	4	0	0 **	0	10	0	0 **
			(60)	(40)	(0)	(0)	(0)	(100)	(0)	(0)
[Digestive system]										
liver			<10>				<10>			
	herniation		0	0	0	0	3	0	0	0
			(0)	(0)	(0)	(0)	(30)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				1250 ppm				2500 ppm				5000 ppm			
		No. of Animals on Study	10				10				10				10			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
liver			<10>				<10>				<10>				<10>			
	granulation		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hepatocellular hypertrophy: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			<10>				<10>				<10>				<10>			
	basophilic change		1	0	0	0	3	0	0	0	3	0	0	0	8	2	0	0 **
			(10)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(80)	(20)	(0)	(0)
	eosinophilic body		4	6	0	0	0	10	0	0	0	10	0	0	0	0	10	0 **
			(40)	(60)	(0)	(0)	(0)	(100)	(0)	(0)	(0)	(100)	(0)	(0)	(0)	(0)	(100)	(0)
	hyaline cast		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)
	papillary necrosis		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization:papilla		2	1	0	0	0	0	0	0	3	0	0	0	2	6	0	0 *
			(20)	(10)	(0)	(0)	(0)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(20)	(60)	(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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	8000 ppm				10000 ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]										
liver			<10>				<10>			
	granulation		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	hepatocellular hypertrophy:central		5	0	0	0 *	8	0	0	0 **
			(50)	(0)	(0)	(0)	(80)	(0)	(0)	(0)
[Urinary system]										
kidney			<10>				<10>			
	basophilic change		10	0	0	0 **	0	10	0	0 **
			(100)	(0)	(0)	(0)	(0)	(100)	(0)	(0)
	eosinophilic body		0	0	10	0 **	0	0	10	0 **
			(0)	(0)	(100)	(0)	(0)	(0)	(100)	(0)
	hyaline cast		5	0	0	0 *	8	0	0	0 **
			(50)	(0)	(0)	(0)	(80)	(0)	(0)	(0)
	papillary necrosis		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	mineralization:papilla		4	5	0	0 *	2	0	0	0
			(40)	(50)	(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
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 10				1250 ppm 10				2500 ppm 10				5000 ppm 10			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Urinary system]																		
kidney		<10>																
	granular cast formation		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) **
	basophilic change: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)	1 (10)	0 (0)	0 (0)	0 (0)
[Endocrine system]																		
pituitary		<10>																
	Rathke pouch		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)
thyroid		<10>																
	ultimibranchial body remanet		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]																		
testis		<10>																
	mineralization		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)

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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	8000 ppm				10000 ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Urinary system]										
kidney			<10>				<10>			
	granular cast formation		7	0	0	0 **	0	0	0	0
			(70)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	basophilic change:atypia		2	0	0	0	1	1	0	0
			(20)	(0)	(0)	(0)	(10)	(10)	(0)	(0)
[Endocrine system]										
pituitary			<10>				<10>			
	Rathke pouch		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
thyroid			<10>				<10>			
	ultimibranchial body remanet		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
[Reproductive system]										
testis			<10>				<10>			
	mineralization		2	0	0	0	0	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 b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				1250 ppm				2500 ppm				5000 ppm			
		No. of Animals on Study	10				10				10				10			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Special sense organs/appendage]																		
Harder gl			<10>				<10>				<10>				<10>			
	degeneration		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	lymphocytic infiltration		1	0	0	0	0	0	0	0	2	0	0	0	2	1	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(20)	(10)	(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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	8000 ppm				10000 ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Special sense organs/appendage]										
Harder gl			<10>				<10>			
	degeneration		10	0	0	0 **	10	0	0	0 **
			(100)	(0)	(0)	(0)	(100)	(0)	(0)	(0)
	lymphocytic infiltration		3	0	0	0	2	0	0	0
			(30)	(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
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

APPENDIX K 2

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : FEMALE : ALL ANIMALS

(13-WEEK STUDY)

Organ	Findings	Group Name	Control				1250 ppm				2500 ppm				5000 ppm			
		No. of Animals on Study	10				10				10				10			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
nasal cavit			<10>				<10>				<10>				<10>			
	inflammation		0	0	0	0	1	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
	respiratory metaplasia: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)
	respiratory metaplasia:gland		4	1	0	0	3	0	0	0	6	0	0	0	2	1	0	0
			(40)	(10)	(0)	(0)	(30)	(0)	(0)	(0)	(60)	(0)	(0)	(0)	(20)	(10)	(0)	(0)
lung			<10>				<10>				<10>				<10>			
	osseous metaplasia		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Hematopoietic system]																		
bone marrow			<10>				<10>				<10>				<10>			
	granulation		0	1	0	0	1	0	0	0	0	1	0	0	1	1	0	0
			(0)	(10)	(0)	(0)	(10)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(10)	(10)	(0)	(0)
spleen			<10>				<10>				<10>				<10>			
	deposit of hemosiderin		0	0	0	0	0	0	0	0	10	0	0	0 **	1	9	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(100)	(0)	(0)	(0)	(10)	(90)	(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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	8000 ppm				10000 ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]										
nasal cavit			<10>				<10>			
	inflammation		2	0	0	0	0	0	0	0
			(20)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	respiratory metaplasia:gland		4	0	0	0	3	0	0	0
			(40)	(0)	(0)	(0)	(30)	(0)	(0)	(0)
lung			<10>				<10>			
	osseous metaplasia		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Hematopoietic system]										
bone marrow			<10>				<10>			
	granulation		0	1	0	0	0	1	0	0
			(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)
spleen			<10>				<10>			
	deposit of hemosiderin		0	10	0	0 **	0	10	0	0 **
			(0)	(100)	(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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				1250 ppm				2500 ppm				5000 ppm			
		No. of Animals on Study	10				10				10				10			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Hematopoietic system]																		
spleen			<10>				<10>				<10>				<10>			
	engorgement of erythrocyte		0	0	0	0	0	0	0	0	1	0	0	0	10	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(100)	(0)	(0)	(0)
[Digestive system]																		
liver			<10>				<10>				<10>				<10>			
	herniation		1	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0
			(10)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hepatocellular hypertrophy: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			<10>				<10>				<10>				<10>			
	cyst		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)	(10)	(0)	(0)	(0)
	deposit of hemosiderin		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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	8000 ppm				10000 ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Hematopoietic system]										
spleen			<10>				<10>			
	engorgement of erythrocyte		6	4	0	0 **	0	10	0	0 **
			(60)	(40)	(0)	(0)	(0)	(100)	(0)	(0)
[Digestive system]										
liver			<10>				<10>			
	herniation		1	0	0	0	0	0	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hepatocellular hypertrophy:central		10	0	0	0 **	10	0	0	0 **
			(100)	(0)	(0)	(0)	(100)	(0)	(0)	(0)
[Urinary system]										
kidney			<10>				<10>			
	cyst		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	deposit of hemosiderin		0	0	0	0	9	1	0	0 **
			(0)	(0)	(0)	(0)	(90)	(10)	(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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				1250 ppm				2500 ppm				5000 ppm			
		No. of Animals on Study	10				10				10				10			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Urinary system]																		
kidney			<10>				<10>				<10>				<10>			
	hyaline cast		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)
	papillary necrosis		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization:cortico-medullary junction		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization:papilla		0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
	atypical tubule hyperplasia		0	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)	(10)	(0)	(0)
	eosinophilic droplet:proximal tubule		0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0 *
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(50)	(0)	(0)	(0)
[Endocrine system]																		
pituitary			<10>				<10>				<10>				<10>			
	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)

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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	8000 ppm				10000 ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Urinary system]										
kidney			<10>				<10>			
	hyaline cast		0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
	papillary necrosis		0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
	mineralization:cortico-medullary junction		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization:papilla		4	0	0	0	1	1	0	0
			(40)	(0)	(0)	(0)	(10)	(10)	(0)	(0)
	atypical tubule hyperplasia		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	eosinophilic droplet:proximal tubule		10	0	0	0 **	3	7	0	0 **
			(100)	(0)	(0)	(0)	(30)	(70)	(0)	(0)
[Endocrine system]										
pituitary			<10>				<10>			
	cyst		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				1250 ppm				2500 ppm				5000 ppm			
		No. of Animals on Study	10				10				10				10			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Endocrine system]																		
pituitary			<10>				<10>				<10>				<10>			
	Rathke pouch		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)	(10)	(0)	(0)	(0)
thyroid			<10>				<10>				<10>				<10>			
	ultimibranchial body remanet		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)
[Reproductive system]																		
ovary			<10>				<10>				<10>				<10>			
	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)
[Special sense organs/appendage]																		
Harder gl			<10>				<10>				<10>				<10>			
	degeneration		0	0	0	0	0	0	0	0	1	0	0	0	3	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(30)	(0)	(0)	(0)
	lymphocytic infiltration		0	1	0	0	2	0	0	0	0	0	0	0	4	1	0	0
			(0)	(10)	(0)	(0)	(20)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(40)	(10)	(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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	8000 ppm				10000 ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Endocrine system]										
pituitary			<10>				<10>			
	Rathke pouch		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
thyroid			<10>				<10>			
	ultimibranchial body remanet		1	0	0	0	0	0	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Reproductive system]										
ovary			<10>				<10>			
	cyst		1	0	0	0	0	0	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Special sense organs/appendage]										
Harder gl			<10>				<10>			
	degeneration		9	0	0	0 **	10	0	0	0 **
			(90)	(0)	(0)	(0)	(100)	(0)	(0)	(0)
	lymphocytic infiltration		9	0	0	0 **	4	1	0	0
			(90)	(0)	(0)	(0)	(40)	(10)	(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 ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

APPENDIX L 1

HISTOLOGICAL FINDINGS : NEOPLASTIC LESIONS : SUMMARY

RAT : FEMALE : ALL ANIMALS

(13-WEEK STUDY)

STUDY NO. : 0369
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

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

Organ	Findings	Group Name / No. of animals on Study	Control 10	1250 ppm 10	2500 ppm 10	5000 ppm 10
[Urinary system]						
kidney			<10>	<10>	<10>	<10>
	renal cell carcinoma		0 (0%)	0 (0%)	0 (0%)	1 (10%)

< a > a : Number of animals examined at the site
b (c) b : Number of animals with neoplasm c : b / a * 100

Organ	Findings	Group Name	8000 ppm	10000 ppm
		No. of animals on Study	10	10
[Urinary system]				
kidney			<10>	<10>
	renal cell carcinoma		0 (0%)	0 (0%)

< a > a : Number of animals examined at the site
b (c) b : Number of animals with neoplasm c : b / a * 100

APPENDIX M 1

IDENTITY AND IMPURITY OF p-NITROANISOLE

IN THE 13-WEEK FEED STUDY

IDENTITY AND IMPURITY OF p-NITROANISOLE IN THE 13-WEEK FEED STUDY

Test Substance : p-Nitroanisole (Wako Pure Chemical Industries, LTD.)

Lot No. : ACG7156

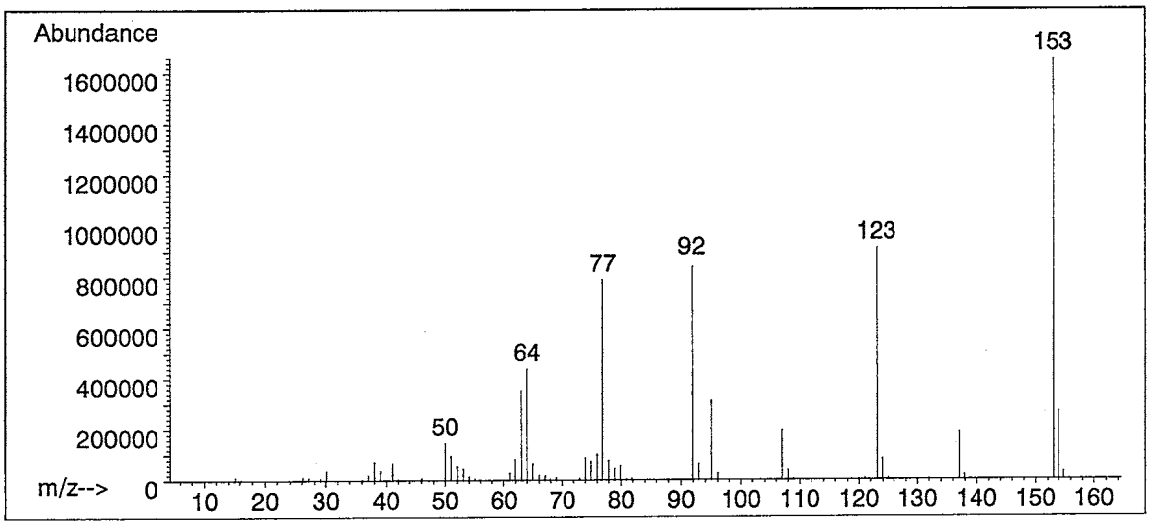
1. Spectral data

Mass Spectrometry

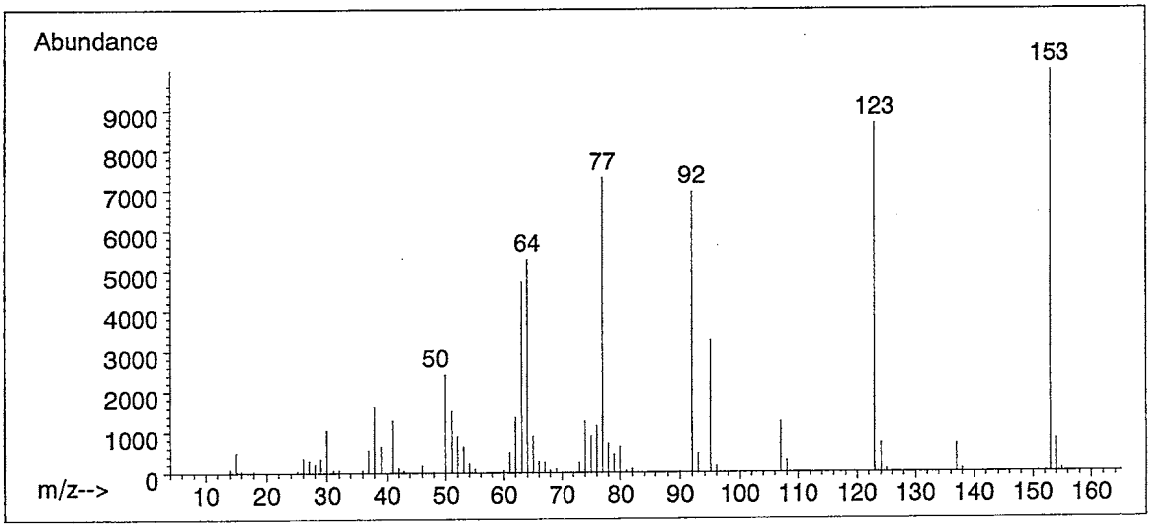
Instrument : Hewlett Packard 5989B Mass Spectrometer

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.

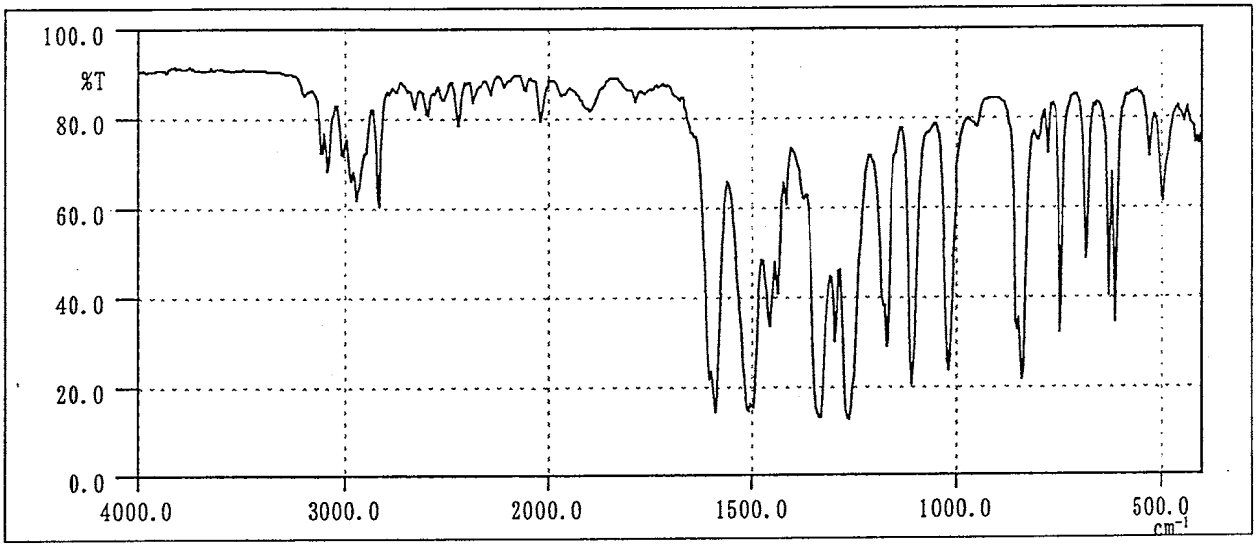
(*Fred W. McLafferty (1994) Wiley Registry of Mass Spectral Data, 6th edition. John Wiley and Sons, Inc. (U.S.), Entry Number 38330)

Infrared Spectrometry

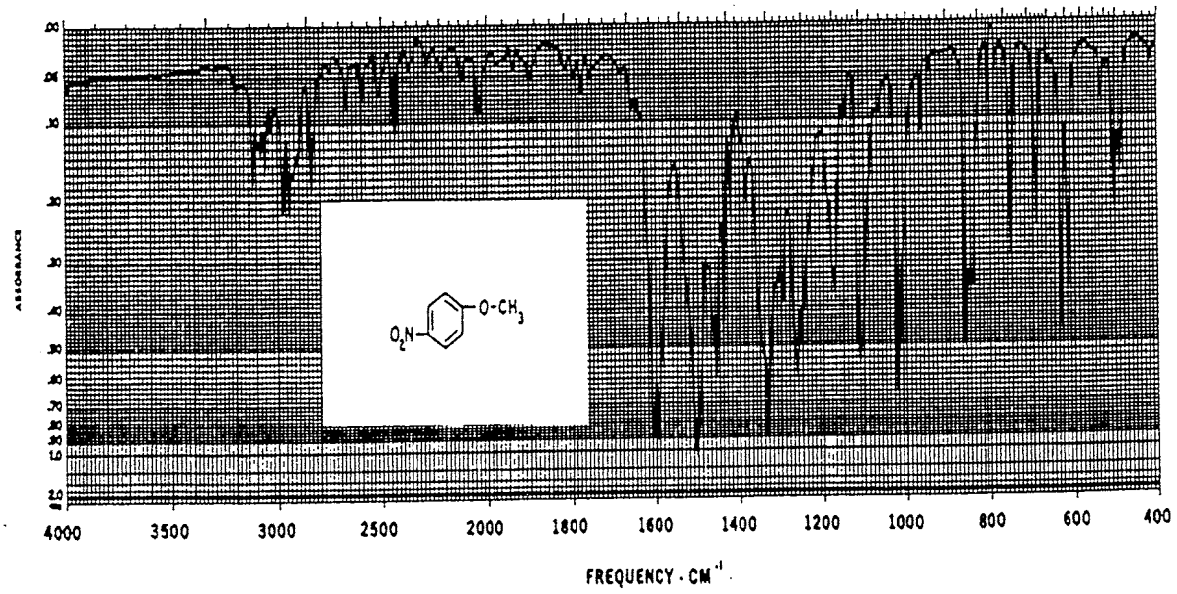
Instrument : Shimadzu FTIR-8200PC Infrared Spectrometer

Cell : KBr Liquid Cell

Resolution : 2.0 cm^{-1}



Infrared Spectrum of Test Substance



Infrared Spectrum of Literature Data*

Results: The infrared spectrum was consistent with literature spectrum.

(*William W. Simons (1978) The Sadtler Handbook of Infrared Spectra. Sadtler Research Laboratories, Inc. (U.K.), pp.443)

2. Impurity

Instrument : Hewlett Packard 5890A Gas Chromatograph

Column : INNOWAX (0.2 mmϕ × 50 m)

Column Temperature : 80 °C → (15 °C/min) → 280 °C (5 min)

Flow Rate : 1 mL/min

Detector : FID (Flame Ionization Detector)

Injection Volume : 1 μL

Sample Name	Peak No.	Area (%)	Peak Name
Test Substance	1	0.01	m-Chloronitrobenzene
	2	99.99	p-Nitroanisole

Results: Gas chromatography indicated one major peak (peak No.2) and one impurity. It was identified only by comparing its gas chromatograph with that of m-chloronitrobenzene (peak No.1) in the p-nitroanisole, the amount in the test substance were 0.01%.

3. Conclusions: The test substance was identified as p-nitroanisole, by the mass spectrum and the infrared spectrum. Gas chromatography indicated one major peak (peak No.2) and one impurity. It was identified only by comparing its gas chromatograph with that of m-chloronitrobenzene, the amount in the test substance were 0.01%.

APPENDIX M 2

STABILITY OF p-NITROANISOLE IN THE 13-WEEK FEED STUDY

STABILITY OF p-NITROANISOLE IN THE 13-WEEK FEED STUDY

Test Substance : p-Nitroanisole (Wako Pure Chemical Industries, LTD.)

Lot No. : ACG7156

1. Sample : This lot was used from 1998.10.30 to 1999.2.2. Test substance was stored in a dark place at room temperature.

2. Gas Chromatography

Instrument : Hewlett Packard 5890A Gas Chromatograph

Column : INNOWAX (0.2 mmϕ × 50 m)

Column Temperature : 80 °C → (15 °C/min) → 280 °C (5 min)

Flow Rate : 1 mL/min

Detector : FID (Flame Ionization Detector)

Injection Volume : 1 μL

Date (date analyzed)	Peak No.	Retention Time (min)	Area (%)
1998.10.26	1	10.248	0.01
	2	13.132	99.99
1999.02.24	1	10.251	0.01
	2	13.139	99.99

Results: Gas chromatography indicated one major peak (peak No.2) and one impurity (peak No.1 < 0.02% of total area) analyzed at 1998.10.26 and one major peak (peak No.2) and one impurity (peak No.1 < 0.02% of total area) analyzed at 1999.2.24. No new trace impurity peak in the test substance analyzed at 1999.2.24 was detected.

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

APPENDIX M 3

CONCENTRATION OF p-NITROANISOLE IN FORMULATED DIETS IN THE 13-WEEK FEED STUDY

CONCENTRATION OF p-NITROANISOLE IN FORMULATED DIETS IN THE 13-WEEK FEED STUDY

	Target Concentration				
Date Analyzed	1250[a]	2500	5000	8000	10000
1998.10.29	1200 (96.0)[b]	2430 (97.2)	4760 (95.2)	7630 (95.4)	9430 (94.3)

[a] ppm
[b] %

Analytical method : The samples were analyzed by the high performance liquid chromatography.

Instrument : Hewlett Packard 1090 High Performance Liquid Chromatograph
Column : TSK GEL ODS-80TM (4.6 mmϕ $\times$ 15 cm)
Column Temperature : Room Temperature
Flow Rate : 1 mL/min
Mobile Phase : Distilled Water : Acetonitrile = 1 : 1
Detector : UV (295 nm)
Injection Volume : 20 μL

APPENDIX M 4

STABILITY OF p-NITROANISOLE IN FORMULATED DIETS

IN THE 13-WEEK FEED STUDY

STABILITY OF p-NITROANISOLE IN FORMULATED DIETS IN THE 13-WEEK FEED STUDY

		Target Concentration	
Date Prepared	Date Analyzed	300[a]	40000
1998.09.24	1998.09.24	314 (100)[b]	40500 (100)
	1998.10.02[c]	257 (81.8)	37400 (92.3)
	1998.10.29[d]	304 (96.8)	39400 (97.3)

[a] ppm
[b] % (Percentage was based on the concentration on date of preparation.)
[c] Animal room samples
[d] Cold storage samples

Analytical method : The samples were analyzed by the high performance liquid chromatography.

Instrument : Hewlett Packard 1090 High Performance Liquid Chromatograph
Column : TSK GEL ODS-80TM (4.6 mmϕ × 15 cm)
Column Temperature : Room Temperature
Flow Rate : 1 mL/min
Mobile Phase : Distilled Water : Acetonitrile = 1 : 1
Detector : UV (295 nm)
Injection Volume : 20 μL

APPENDIX N 1

METHODS FOR HEMATOLOGY, BIOCHEMISTRY AND URINALSIS IN THE 13-WEEK FEED STUDY OF p-NITROANISOLE

METHODS FOR HEMATOLOGY,BIOCHEMISTRY AND URINALYSIS IN THE 13-WEEK FEED STUDY OF p-NITROANISOLE

Item	Method
Hematology	
Red blood cell (RBC)	Light scattering method [1]
Hemoglobin (Hgb)	Cyanmethemoglobin method [1]
Hematocrit (Hct)	Calculated as RBC×MCV/10 [1]
Mean corpuscular volume (MCV)	Light scattering method [1]
Mean corpuscular hemoglobin (MCH)	Calculated as Hgb/RBC×10 [1]
Mean corpuscular hemoglobin concentration (MCHC)	Calculated as Hgb/Hct×100 [1]
Platelet	Light scattering method [1]
Reticulocyte	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] (Wright staining)
Biochemistry	
Total protein (TP)	Biuret method [4]
Albumin (Alb)	BCG method [4]
A/G ratio	Calculated as Alb/(TP－Alb) [4]
T-bilirubin	Alkaline azobilirubin method [4]
Glucose	GlcK･G-6-PDH method [4]
T-cholesterol	CE･COD･POD method [4]
Triglyceride	LPL･GK･GPO･POD method [4]
Phospholipid	PLD･ChOD･POD method [4]
Glutamic oxaloacetic transaminase (GOT)	JSCC method [4]
Glutamic pyruvic transaminase (GPT)	JSCC method [4]
Lactate dehydrogenase (LDH)	SFBC method [4]
Alkaline phosphatase (ALP)	GSCC method [4]
γ-Glutamyl transpeptidase (γ-GTP)	L-γ-Glutamyl-p-nitroanilide method [4]
Creatine phosphokinase (CPK)	JSCC method [4]
Urea nitrogen	Urease･GLDH method [4]
Creatinine	Jaffe method [4]
Sodium	Ion selective electrode method [4]
Potassium	Ion selective electrode method [4]
Chloride	Ion selective electrode method [4]
Calcium	OCPC method [4]
Inorganic phosphorus	PNP･XOD･POD method [4]
Urinalysis	
pH,Protein,Glucose,Ketone body,Bilirubin,Occult Blood, Urobilinogen	Urinalysis reagent paper method [5]

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

APPENDIX O 1

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 13-WEEK FEED STUDY OF p-NITROANISOLE

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 13-WEEK FEED STUDY OF p-NITROANISOLE

Item	Unit	Decimal place
Hematology		
Red blood cell (RBC)	$\times 10^6/\mu L$	2
Hemoglobin	g/dL	1
Hematocrit	%	1
Mean corpuscular volume (MCV)	fL	1
Mean corpuscular hemoglobin (MCH)	pg	1
Mean corpuscular hemoglobin concentration (MCHC)	g/dL	1
Platelet	$\times 10^3/\mu L$	0
Reticulocyte	‰	0
Prothrombin time	sec	1
Activated partial thromboplastin time (APTT)	sec	1
White blood cell (WBC)	$\times 10^3/\mu L$	2
Differential WBC	%	0
Biochemistry		
Total protein	g/dL	1
Albumin	g/dL	1
A/G ratio	–	1
T-bilirubin	mg/dL	2
Glucose	mg/dL	0
T-cholesterol	mg/dL	0
Triglyceride	mg/dL	0
Phospholipid	mg/dL	0
Glutamic oxaloacetic transminase (GOT)	IU/L	0
Glutamic pyruvic transaminase (GPT)	IU/L	0
Lactate dehydrogenase (LDH)	IU/L	0
Alkaline phosphatase (ALP)	IU/L	0
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