1,4 - ジクロロ - 2 - ニトロベンゼンのラットを用いた
経口投与による 2 週間毒性試験(混餌試験)報告書

試験番号：０２９８

APPENDIX

APPENDIXES

APPENDIXES (CONTINUED)

APPENDIX A 1

CLINICAL OBSERVATION : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1 2

CLINICAL OBSERVATION (SUMMARY)
ALL ANIMALS

SEX : MALE

Clinical sign	Group Name	Administration Week-day 1-1	1-4	1-7	2-4	2-7
SOILED PERI GENITALIA	Control	0	0	0	0	0
	625 ppm	0	0	0	0	0
	1250 ppm	0	0	0	0	0
	2500 ppm	0	0	0	0	0
	5000 ppm	0	0	0	0	0
	10000 ppm	0	0	3	8	8
YELLOW URINE	Control	0	0	0	0	0
	625 ppm	0	0	0	0	0
	1250 ppm	10	10	10	10	10
	2500 ppm	10	10	10	10	10
	5000 ppm	10	10	10	10	10
	10000 ppm	10	10	10	10	10
SMALL STOOL	Control	0	0	0	0	0
	625 ppm	0	0	0	0	0
	1250 ppm	0	0	0	0	0
	2500 ppm	0	0	0	0	0
	5000 ppm	0	0	0	0	0
	10000 ppm	0	1	1	1	0

APPENDIX A 2

CLINICAL OBSERVATION : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

Clinical sign	Group Name	Administration Week-day 1-1	1-4	1-7	2-4	2-7
PILOERECTION	Control	0	0	0	0	0
	625 ppm	0	0	0	0	0
	1250 ppm	0	0	0	0	0
	2500 ppm	0	0	0	0	0
	5000 ppm	0	0	0	0	0
	10000 ppm	0	0	0	1	4
SOILED PERI GENITALIA	Control	0	0	0	0	0
	625 ppm	0	0	0	0	0
	1250 ppm	0	0	0	0	1
	2500 ppm	0	0	0	2	2
	5000 ppm	0	0	1	1	2
	10000 ppm	1	5	8	8	8
YELLOW URINE	Control	0	0	0	0	0
	625 ppm	0	0	0	0	0
	1250 ppm	10	10	10	10	10
	2500 ppm	10	10	10	10	10
	5000 ppm	10	10	10	10	10
	10000 ppm	10	10	10	10	10
SMALL STOOL	Control	0	0	0	0	0
	625 ppm	0	0	0	0	0
	1250 ppm	0	0	0	0	0
	2500 ppm	0	0	0	0	0
	5000 ppm	0	0	0	0	0
	10000 ppm	0	1	1	1	1

APPENDIX B 1

BODY WEIGHT CHANGES :SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 2
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-1	1-4	1-7	2-4	2-7
Control	128± 3	133± 4	144± 4	154± 4	178± 6	192± 6
625 ppm	128± 4	133± 4	145± 5	155± 7	177± 10	191± 12
1250 ppm	128± 4	132± 5	145± 5	155± 6	179± 7	191± 9
2500 ppm	128± 4	129± 3	144± 4	154± 5	177± 6	189± 7
5000 ppm	128± 4	122± 4**	134± 4**	140± 4**	155± 5**	163± 5**
10000 ppm	128± 4	116± 3**	113± 3**	106± 4**	99± 3**	100± 2**

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

APPENDIX B 2

BODY WEIGHT CHANGES : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 2
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-1	1-4	1-7	2-4	2-7
Control	98± 3	100± 3	105± 4	108± 4	119± 4	123± 3
625 ppm	98± 3	100± 3	105± 4	109± 4	120± 5	125± 6
1250 ppm	98± 4	99± 3	106± 4	109± 3	119± 3	124± 4
2500 ppm	98± 3	97± 3*	104± 4	107± 3	118± 5	121± 4
5000 ppm	98± 3	93± 3**	102± 4	104± 4	113± 7**	115± 7**
10000 ppm	98± 3	88± 2**	88± 2**	84± 3**	81± 3**	78± 4**

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

APPENDIX C 1

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 2
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 1-4(4)	1-7(3)	2-4(4)	2-7(3)
Control	12.6± 0.6	13.0± 0.8	14.3± 0.9	14.7± 0.8
625 ppm	12.6± 0.7	13.1± 0.8	13.9± 1.4	14.4± 1.2
1250 ppm	12.9± 0.8	13.6± 0.9	14.6± 0.8	14.4± 1.0
2500 ppm	12.5± 0.4	13.2± 0.6	14.5± 0.6	14.7± 0.7
5000 ppm	10.8± 0.7**	12.0± 0.7	12.9± 1.4*	12.6± 2.0*
10000 ppm	7.2± 1.2**	7.3± 1.9**	6.1± 1.1**	5.0± 0.6**

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

APPENDIX C 2

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 2
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 1-4(4)	1-7(3)	2-4(4)	2-7(3)
Control	9.4± 0.4	9.2± 0.4	10.4± 0.5	10.0± 0.5
625 ppm	9.3± 0.5	9.4± 0.3	10.5± 0.6	10.4± 0.9
1250 ppm	9.0± 0.4	9.2± 0.5	10.2± 1.2	9.9± 0.9
2500 ppm	8.8± 0.5	9.1± 0.7	9.8± 0.5	9.4± 0.7
5000 ppm	7.9± 0.5**	8.8± 0.5	9.0± 0.8**	8.5± 0.8**
10000 ppm	6.4± 1.7**	6.0± 1.2**	5.1± 1.2**	4.4± 0.6**

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

APPENDIX D 1

CHEMICAL INTAKE CHANGES : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
UNIT : g/kgBW/day
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week			
	1(1-4)	1(1-7)	2(2-4)	2(2-7)
Control	0.000	0.000	0.000	0.000
625ppm	0.054	0.053	0.049	0.047
1250ppm	0.111	0.110	0.102	0.094
2500ppm	0.217	0.214	0.205	0.194
5000ppm	0.403	0.429	0.416	0.387
10000ppm	0.637	0.689	0.616	0.500

APPENDIX D 2

CHEMICAL INTAKE CHANGES : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
UNIT : g/kgBW/day
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week			
	1(1-4)	1(1-7)	2(2-4)	2(2-7)
Control	0.000	0.000	0.000	0.000
625ppm	0.055	0.054	0.055	0.052
1250ppm	0.106	0.106	0.107	0.100
2500ppm	0.212	0.213	0.208	0.194
5000ppm	0.387	0.423	0.398	0.370
10000ppm	0.727	0.714	0.630	0.564

APPENDIX E 1

HEMATOLOGY : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (2W)

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 $10^3/\mu\ell$	
Control	7	7.19±	0.21	13.6±	0.3	40.7±	0.8	56.6±	0.7	18.9±	0.2	33.4±	0.4	662±	41
625 ppm	7	7.12±	0.12	13.4±	0.4	40.5±	0.7	56.9±	0.3	18.8±	0.2	33.1±	0.4	615±	91
1250 ppm	6	7.25±	0.32	13.5±	0.6	41.1±	1.7	56.7±	0.3	18.7±	0.3	33.0±	0.6	601±	45
2500 ppm	5	7.31±	0.14	13.5±	0.2	41.6±	0.9	57.0±	0.6	18.5±	0.2	32.5±	0.4	535±	91*
5000 ppm	6	7.70±	0.14**	14.0±	0.2	43.1±	1.0**	56.1±	0.9	18.2±	0.1**	32.4±	0.6*	443±	31**
10000 ppm	7	8.68±	0.11**	15.4±	0.4**	46.6±	0.6**	53.6±	0.4**	17.8±	0.3**	33.1±	0.5	222±	67**

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (2W)

Group Name	NO. of Animals	RETICULOCYTE ‰	METHEMOGLOBIN %	PROTHROMBIN TIME sec	APTT sec
Control	7	54± 7	0.2± 0.1	12.2± 0.2	14.4± 0.9
625 ppm	7	61± 13	0.3± 0.1	12.1± 0.3	12.9± 1.0
1250 ppm	6	56± 3	0.3± 0.1	12.0± 0.4	14.6± 1.4
2500 ppm	5	57± 8	0.3± 0.1	12.0± 0.3	13.3± 1.1
5000 ppm	6	45± 11	0.5± 0.1*	12.0± 0.2	13.7± 1.8
10000 ppm	7	9± 4**	1.0± 0.4**	14.6± 0.7**	16.3± 1.8

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (2W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) N-BAND		N-SEG		EOSINO		BASO		MONO		LYMPHO		OTHERS	
Control	7	1.91±	0.72	0±	0	19±	3	1±	0	0±	0	5±	1	74±	3	2±	1
625 ppm	7	1.83±	0.45	0±	0	19±	3	1±	1	0±	0	4±	2	75±	3	1±	1
1250 ppm	6	1.65±	0.27	0±	0	22±	3	1±	1	0±	0	4±	1	72±	4	1±	2
2500 ppm	5	2.05±	0.85	0±	1	18±	4	1±	1	0±	0	5±	1	74±	4	2±	1
5000 ppm	6	1.66±	0.11	0±	0	19±	3	1±	1	0±	0	4±	1	75±	4	2±	1
10000 ppm	7	1.53±	0.64	0±	0	18±	4	1±	1	0±	0	4±	1	76±	5	1±	1

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

APPENDIX E 2

HEMATOLOGY : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (2W)

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 $10^3/\mu\ell$
Control	6	7.80± 0.15	14.8± 0.2	43.5± 0.9	55.7± 0.4	18.9± 0.3	33.9± 0.7	484± 84
625 ppm	6	7.64± 0.16	14.5± 0.2	42.3± 1.3	55.4± 0.6	19.0± 0.2	34.4± 0.6	457± 141
1250 ppm	6	7.73± 0.21	14.6± 0.4	42.7± 1.4	55.2± 0.4	19.0± 0.2	34.4± 0.5	513± 57
2500 ppm	7	7.78± 0.25	14.4± 0.5	43.0± 1.2	55.3± 0.5	18.5± 0.1*	33.5± 0.3	404± 73
5000 ppm	6	7.89± 0.19	14.5± 0.2	43.3± 1.2	54.8± 0.5*	18.3± 0.3**	33.5± 0.6	378± 16
10000 ppm	7	8.34± 0.22**	14.9± 0.4	45.3± 1.0	54.3± 0.4**	17.8± 0.1**	32.8± 0.3*	177± 80**

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (2W)

Group Name	NO. of Animals	RETICULOCYTE ‰		METHEMOGLOBIN %		PROTHROMBIN TIME sec		APTT sec	
Control	6	24±	4	0.3±	0.1	12.5±	0.4	14.8±	1.2
625 ppm	6	31±	4	0.4±	0.1	12.6±	0.4	14.0±	2.1
1250 ppm	6	32±	10	0.2±	0.1	12.7±	0.3	13.5±	1.0
2500 ppm	7	23±	7	0.3±	0.1	12.9±	0.4	13.2±	1.5
5000 ppm	6	28±	10	0.3±	0.1	12.7±	0.5	13.3±	0.9
10000 ppm	7	15±	4	0.6±	0.2*	14.6±	0.5**	15.0±	0.8

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (2W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) N-BAND		N-SEG		EOSINO		BASO		MONO		LYMPHO		OTHERS	
Control	6	1.26±	0.79	0±	0	23±	5	0±	1	0±	0	5±	3	70±	7	2±	2
625 ppm	6	2.00±	0.41	1±	1	24±	12	1±	1	0±	0	4±	1	68±	12	3±	3
1250 ppm	6	1.65±	0.22	0±	0	19±	3	1±	1	0±	0	3±	1	75±	4	2±	2
2500 ppm	7	1.28±	0.53	0±	0	21±	7	1±	1	0±	0	3±	1	71±	6	3±	1
5000 ppm	6	1.52±	0.31	0±	1	17±	4	1±	1	0±	0	2±	2	77±	4	2±	2
10000 ppm	7	1.78±	0.63	0±	0	20±	6	0±	1	0±	0	4±	1	74±	5	2±	1

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

APPENDIX F 1

BIOCHEMISTRY : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (2W)

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	PHOSPHOLIPID mg/dl
Control	5	5.7± 0.1	3.6± 0.1	1.7± 0.1	0.14± 0.00	188± 6	63± 3	126± 4
625 ppm	5	6.0± 0.1**	3.8± 0.0**	1.7± 0.0	0.15± 0.01	183± 13	83± 7**	160± 9**
1250 ppm	5	6.2± 0.1**	3.8± 0.1**	1.7± 0.1	0.15± 0.01	185± 8	90± 8**	176± 11**
2500 ppm	5	6.3± 0.1**	4.0± 0.1**	1.7± 0.1	0.16± 0.01	181± 6	111± 9**	211± 16**
5000 ppm	5	6.3± 0.2**	4.0± 0.2**	1.7± 0.0	0.20± 0.01	172± 3*	135± 13**	258± 23**
10000 ppm	5	6.2± 0.2**	4.2± 0.1**	2.0± 0.1**	0.24± 0.03	145± 9**	87± 10**	173± 18**

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (2W)

Group Name	NO. of Animals	GOT IU/ℓ		GPT IU/ℓ		LDH IU/ℓ		G-GTP IU/ℓ		CPK IU/ℓ		UREA NITROGEN mg/dℓ		CREATININE mg/dℓ	
Control	5	60±	6	30±	3	149±	17	2±	2	164±	23	13.9±	1.5	0.4±	0.0
625 ppm	5	52±	3	27±	2	144±	19	2±	1	138±	12	13.5±	2.0	0.4±	0.0
1250 ppm	5	58±	7	32±	8	207±	87	2±	0	177±	37	14.5±	0.9	0.4±	0.0
2500 ppm	5	55±	3	34±	3	142±	27	2±	1	147±	25	14.2±	1.4	0.4±	0.0
5000 ppm	5	57±	1	41±	3	151±	30	4±	1	133±	11	15.7±	1.1	0.4±	0.0
10000 ppm	5	58±	7	41±	8	216±	63	13±	2**	130±	22	24.8±	0.7**	0.4±	0.0

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (2W)

Group Name	NO. of Animals	SODIUM mEq/ℓ		POTASSIUM mEq/ℓ		CHLORIDE mEq/ℓ		CALCIUM mg/dℓ		INORGANIC PHOSPHORUS mg/dℓ	
Control	5	141±	1	4.2±	0.1	105±	1	11.1±	0.3	8.8±	0.4
625 ppm	5	141±	2	4.1±	0.1	104±	1	11.5±	0.2	9.2±	0.5
1250 ppm	5	140±	1	4.0±	0.3	104±	1	11.5±	0.2*	9.0±	0.5
2500 ppm	5	141±	1	4.0±	0.1	103±	2	11.7±	0.3**	8.9±	0.8
5000 ppm	5	140±	1	4.0±	0.2	105±	1	11.4±	0.2	7.8±	0.4*
10000 ppm	5	141±	1	4.3±	0.3	112±	1**	10.5±	0.1**	6.4±	0.3**

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

APPENDIX F 2

BIOCHEMISTRY : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (2W)

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		PHOSPHOLIPID mg/dℓ	
Control	5	5.7±	0.1	3.6±	0.1	1.8±	0.1	0.15±	0.01	189±	4	69±	4	123±	8
625 ppm	5	6.0±	0.1**	3.8±	0.1*	1.8±	0.1	0.16±	0.01	186±	5	95±	6**	166±	7**
1250 ppm	5	6.2±	0.1**	3.9±	0.1**	1.8±	0.1	0.16±	0.02	180±	10	107±	5**	187±	8**
2500 ppm	5	6.2±	0.2**	4.0±	0.2**	1.9±	0.1	0.17±	0.01	181±	4	111±	11**	198±	19**
5000 ppm	5	6.3±	0.1**	4.1±	0.0**	1.9±	0.1	0.19±	0.01**	176±	8*	128±	10**	233±	17**
10000 ppm	5	6.2±	0.2**	4.2±	0.2**	2.1±	0.1**	0.28±	0.02**	151±	8**	80±	4	170±	11**

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (2W)

Group Name	NO. of Animals	GOT IU/ℓ		GPT IU/ℓ		LDH IU/ℓ		G-GTP IU/ℓ		CPK IU/ℓ		UREA NITROGEN mg/dℓ		CREATININE mg/dℓ	
Control	5	51±	9	26±	2	303±	102	1±	1	190±	66	15.2±	1.2	0.4±	0.0
625 ppm	5	57±	4	26±	3	254±	120	3±	1	170±	50	15.7±	1.6	0.4±	0.0
1250 ppm	5	55±	3	27±	1	244±	133	2±	1	156±	57	14.7±	1.2	0.4±	0.0
2500 ppm	5	58±	6	31±	4	198±	56	4±	2	131±	14	15.3±	1.8	0.4±	0.0
5000 ppm	5	59±	3	33±	3*	197±	40	12±	3**	152±	32	16.8±	1.5	0.5±	0.1
10000 ppm	5	62±	12	35±	6**	403±	151	40±	3**	191±	81	25.6±	3.7**	0.4±	0.0

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (2W)

Group Name	NO. of Animals	SODIUM mEq／ℓ		POTASSIUM mEq／ℓ		CHLORIDE mEq／ℓ		CALCIUM mg／dℓ		INORGANIC PHOSPHORUS mg／dℓ	
Control	5	140±	2	3.7±	0.1	107±	1	10.6±	0.2	7.1±	0.9
625 ppm	5	140±	2	3.8±	0.3	107±	1	10.9±	0.2	7.3±	1.2
1250 ppm	5	141±	1	3.7±	0.4	108±	1	11.0±	0.1	6.8±	0.8
2500 ppm	5	141±	1	3.5±	0.2	107±	1	10.9±	0.2	6.9±	0.6
5000 ppm	5	140±	1	3.5±	0.4	107±	0	11.0±	0.3*	6.9±	0.8
10000 ppm	5	139±	2	4.2±	0.2	112±	1**	10.2±	0.4	6.4±	0.4

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

APPENDIX G 1

GROSS FINDINGS : SUMMARY, RAT : MALE ALL ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
ALL ANIMALS (0- 2W)

Organ	Findings	Group Name	Control	625 ppm	1250 ppm	2500 ppm
		NO. of Animals	10 (%)	10 (%)	10 (%)	10 (%)
thymus	atrophic		0 (0)	0 (0)	0 (0)	0 (0)
liver	herniation		0 (0)	0 (0)	1 (10)	0 (0)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

GROSS FINDINGS (SUMMARY)
ALL ANIMALS (0- 2W)

Organ	Findings	Group Name NO. of Animals	5000 ppm 10 (%)	10000 ppm 10 (%)
thymus	atrophic		0 (0)	10 (100)
liver	herniation		0 (0)	1 (10)

APPENDIX G 2

GROSS FINDINGS : SUMMARY, RAT : FEMALE ALL ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
ALL ANIMALS (0- 2W)

Organ	Findings	Group Name / NO. of Animals	Control 10 (%)	625 ppm 10 (%)	1250 ppm 10 (%)	2500 ppm 10 (%)
thymus	atrophic		0 (0)	0 (0)	0 (0)	0 (0)
liver	herniation		2 (20)	0 (0)	1 (10)	1 (10)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

GROSS FINDINGS (SUMMARY)
ALL ANIMALS (0- 2W)

Organ	Findings	Group Name NO. of Animals	5000 ppm 10 (%)	10000 ppm 10 (%)
thymus	atrophic		0 (0)	10 (100)
liver	herniation		0 (0)	0 (0)

APPENDIX H 1

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (2W)

Group Name	NO. of Animals	Body Weight	THYMUS	ADRENALS	TESTES	HEART	LUNGS
Control	5	190± 5	0.345± 0.020	0.038± 0.007	2.409± 0.182	0.653± 0.034	0.799± 0.028
625 ppm	5	193± 12	0.337± 0.033	0.039± 0.005	2.423± 0.053	0.661± 0.021	0.817± 0.042
1250 ppm	5	194± 13	0.341± 0.042	0.040± 0.005	2.425± 0.086	0.689± 0.041	0.817± 0.038
2500 ppm	5	190± 9	0.361± 0.034	0.040± 0.005	2.473± 0.072	0.664± 0.034	0.771± 0.031
5000 ppm	5	162± 5	0.293± 0.035	0.038± 0.006	0.969± 0.044**	0.578± 0.014**	0.704± 0.036**
10000 ppm	5	100± 2*	0.097± 0.021**	0.032± 0.003	0.763± 0.068**	0.387± 0.020**	0.547± 0.015**

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (2W)

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
Control	5	1.437± 0.054	0.467± 0.015	7.294± 0.490	1.724± 0.045
625 ppm	5	1.503± 0.061	0.463± 0.032	8.972± 0.976**	1.736± 0.064
1250 ppm	5	1.611± 0.106*	0.476± 0.040	9.848± 0.897**	1.710± 0.124
2500 ppm	5	1.647± 0.124**	0.443± 0.036	10.475± 0.970**	1.764± 0.044
5000 ppm	5	1.450± 0.075	0.393± 0.027**	9.372± 0.401**	1.737± 0.046
10000 ppm	5	1.075± 0.034**	0.241± 0.015**	5.027± 0.409**	1.586± 0.030*

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

APPENDIX H 2

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (2W)

Group Name	NO. of Animals	Body Weight	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
Control	5	124± 2	0.284± 0.024	0.041± 0.005	0.078± 0.009	0.484± 0.018	0.622± 0.017
625 ppm	5	125± 6	0.288± 0.016	0.043± 0.004	0.077± 0.007	0.490± 0.024	0.615± 0.029
1250 ppm	5	125± 5	0.288± 0.020	0.041± 0.003	0.081± 0.006	0.491± 0.018	0.596± 0.038
2500 ppm	5	120± 2	0.277± 0.033	0.035± 0.003	0.067± 0.007	0.463± 0.033	0.599± 0.028
5000 ppm	5	116± 7*	0.279± 0.024	0.037± 0.004	0.064± 0.007*	0.430± 0.043*	0.582± 0.038
10000 ppm	5	80± 4**	0.120± 0.014**	0.030± 0.004**	0.042± 0.010**	0.321± 0.027**	0.475± 0.011**

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

(HCL040)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (2W)

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
Control	5	0.992± 0.032	0.325± 0.025	4.309± 0.161	1.611± 0.040
625 ppm	5	1.029± 0.052	0.321± 0.005	5.335± 0.109**	1.590± 0.041
1250 ppm	5	1.025± 0.015	0.326± 0.019	5.682± 0.416**	1.594± 0.045
2500 ppm	5	1.054± 0.054	0.290± 0.010*	5.895± 0.225**	1.632± 0.041
5000 ppm	5	1.000± 0.075	0.289± 0.019*	6.372± 0.361**	1.600± 0.058
10000 ppm	5	0.849± 0.044**	0.201± 0.026**	4.142± 0.197	1.502± 0.018**

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

APPENDIX I 1

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : MALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (2W)

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	TESTES	HEART	LUNGS
Control	5	190± 5	0.182± 0.013	0.020± 0.004	1.267± 0.100	0.343± 0.010	0.420± 0.008
625 ppm	5	193± 12	0.174± 0.012	0.020± 0.002	1.257± 0.069	0.343± 0.017	0.423± 0.018
1250 ppm	5	194± 13	0.176± 0.022	0.021± 0.002	1.255± 0.088	0.356± 0.018	0.422± 0.019
2500 ppm	5	190± 9	0.190± 0.015	0.021± 0.002	1.305± 0.086	0.350± 0.005	0.406± 0.010
5000 ppm	5	162± 5	0.181± 0.022	0.024± 0.004	0.597± 0.014**	0.357± 0.013	0.434± 0.022
10000 ppm	5	100± 2*	0.096± 0.022**	0.031± 0.003**	0.759± 0.057**	0.386± 0.020**	0.545± 0.020**

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (2W)

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
Control	5	0.756± 0.016	0.245± 0.008	3.832± 0.157	0.907± 0.037
625 ppm	5	0.779± 0.019	0.240± 0.011	4.634± 0.246**	0.901± 0.060
1250 ppm	5	0.831± 0.015**	0.245± 0.007	5.069± 0.156**	0.886± 0.096
2500 ppm	5	0.866± 0.034**	0.233± 0.008	5.504± 0.253**	0.930± 0.049
5000 ppm	5	0.894± 0.021**	0.242± 0.015	5.777± 0.123**	1.071± 0.023**
10000 ppm	5	1.071± 0.026**	0.240± 0.014	5.003± 0.315**	1.580± 0.029**

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

APPENDIX I 2

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : FEMALE

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (2W)

Group Name	NO. of Animals	Body Weight (g)	THYMUS	ADRENALS	OVARIES	HEART	LUNGS
Control	5	124± 2	0.230± 0.023	0.033± 0.004	0.063± 0.008	0.391± 0.020	0.502± 0.021
625 ppm	5	125± 6	0.230± 0.016	0.034± 0.004	0.062± 0.006	0.391± 0.016	0.491± 0.020
1250 ppm	5	125± 5	0.231± 0.023	0.033± 0.003	0.065± 0.006	0.393± 0.021	0.476± 0.027
2500 ppm	5	120± 2	0.231± 0.027	0.030± 0.003	0.056± 0.005	0.388± 0.028	0.501± 0.023
5000 ppm	5	116± 7*	0.241± 0.025	0.032± 0.004	0.055± 0.005	0.370± 0.025	0.502± 0.012
10000 ppm	5	80± 4**	0.151± 0.018**	0.038± 0.004	0.052± 0.011	0.402± 0.017	0.597± 0.019**

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

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (2W)

Group Name	NO. of Animals	KIDNEYS	SPLEEN	LIVER	BRAIN
Control	5	0.800± 0.028	0.262± 0.021	3.476± 0.147	1.299± 0.033
625 ppm	5	0.820± 0.007	0.256± 0.013	4.260± 0.174**	1.270± 0.071
1250 ppm	5	0.820± 0.026	0.261± 0.019	4.534± 0.182**	1.274± 0.033
2500 ppm	5	0.881± 0.044*	0.243± 0.012	4.932± 0.251**	1.364± 0.022
5000 ppm	5	0.863± 0.052	0.249± 0.009	5.494± 0.081**	1.384± 0.116
10000 ppm	5	1.067± 0.031**	0.252± 0.025	5.203± 0.095**	1.889± 0.068*

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

APPENDIX J 1

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : MALE : ALL ANIMALS

(2-WEEK STUDY)

STUDY NO. : 0298
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
ALL ANIMALS (0- 2W)

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 2 1	Control 2 2	Control 2 3	Control 2 4	625 ppm 2 1	625 ppm 2 2	625 ppm 2 3	625 ppm 2 4	1250 ppm 2 1	1250 ppm 2 2	1250 ppm 2 3	1250 ppm 2 4	2500 ppm 2 1	2500 ppm 2 2	2500 ppm 2 3	2500 ppm 2 4
(Hematopoietic system)																		
bone marrow			< 2>				< 2>				< 2>				< 2>			
	decreased hematopoiesis		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
thymus			< 2>				< 2>				< 2>				< 2>			
	atrophy		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
spleen			< 2>				< 2>				< 2>				< 2>			
	engorgement of erythrocyte		0	0	0	0	0	0	0	0	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			< 2>				< 2>				< 2>				< 2>			
	herniation		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(50)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	increase in mitosis		0	0	0	0	0	0	0	0	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	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(50)	(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

Organ	Findings	Group Name	5000 ppm				10000 ppm			
		No. of Animals on Study	2				2			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Hematopoietic system}										
bone marrow			< 2>				< 2>			
	decreased hematopoiesis		0	0	0	0	0	2	0	0
			(0)	(0)	(0)	(0)	(0)	(100)	(0)	(0)
thymus			< 2>				< 2>			
	atrophy		0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(100)	(0)	(0)	(0)
spleen			< 2>				< 2>			
	engorgement of erythrocyte		0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(100)	(0)	(0)	(0)
{Digestive system}										
liver			< 2>				< 2>			
	herniation		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	increase in mitosis		2	0	0	0	0	0	0	0
			(100)	(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)

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

Organ	Findings	Group Name	Control				625 ppm				1250 ppm				2500 ppm			
		No. of Animals on Study	2				2				2				2			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Digestive system}																		
liver				< 2>				< 2>				< 2>				< 2>		
	necrosis:single cell		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Urinary system}																		
kidney				< 2>				< 2>				< 2>				< 2>		
	eosinophilic body		0	0	0	0	0	1	1	0	0	0	2	0	0	0	2	0
			(0)	(0)	(0)	(0)	(0)	(50)	(50)	(0)	(0)	(0)	(100)	(0)	(0)	(0)	(100)	(0)
{Reproductive system}																		
testis				< 2>				< 2>				< 2>				< 2>		
	germ cell 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)
epididymis				< 2>				< 2>				< 2>				< 2>		
	decreased:sperma		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	debris of spermatic elements		0	0	0	0	0	0	0	0	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

Organ	Findings	Group Name	5000 ppm				10000 ppm			
		No. of Animals on Study	2				2			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Digestive system}										
liver				< 2>				< 2>		
	necrosis:single cell		0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(100)	(0)	(0)	(0)
{Urinary system}										
kidney				< 2>				< 2>		
	eosinophilic body		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Reproductive system}										
testis				< 2>				< 2>		
	germ cell necrosis		0	0	2	0	0	0	2	0
			(0)	(0)	(100)	(0)	(0)	(0)	(100)	(0)
epididymis				< 2>				< 2>		
	decreased:sperma		0	0	2	0	0	0	2	0
			(0)	(0)	(100)	(0)	(0)	(0)	(100)	(0)
	debris of spermatic elements		0	2	0	0	0	0	0	0
			(0)	(100)	(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

Organ	Findings	Group Name	Control				625 ppm				1250 ppm				2500 ppm			
		No. of Animals on Study	2				2				2				2			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Reproductive system}																		
prostate			< 2>				< 2>				< 2>				< 2>			
	inflammation		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(50)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Nervous system}																		
brain			< 2>				< 2>				< 2>				< 2>			
	degeneration		0	0	0	0	0	0	0	0	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

Organ	Findings	Group Name	5000 ppm				10000 ppm			
		No. of Animals on Study	2				2			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
(Reproductive system)										
prostate			< 2>				< 2>			
	inflammation		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
(Nervous system)										
brain			< 2>				< 2>			
	degeneration		0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(50)	(0)	(0)

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

APPENDIX J 2

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : SUMMARY

RAT : FEMALE: ALL ANIMALS

(2-WEEK STUDY)

Organ	Findings	Group Name	Control				625 ppm				1250 ppm				2500 ppm			
		No. of Animals on Study	2				2				2				2			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Hematopoietic system}																		
bone marrow			< 2>				< 2>				< 2>				< 2>			
	decreased hematopoiesis		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
thymus			< 2>				< 2>				< 2>				< 2>			
	karyorrhexis		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
spleen			< 2>				< 2>				< 2>				< 2>			
	engorgement of erythrocyte		0	0	0	0	0	0	0	0	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			< 2>				< 2>				< 2>				< 2>			
	increase in mitosis		0	0	0	0	0	0	0	0	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:single cell		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Nervous system}																		
brain			< 2>				< 2>				< 2>				< 2>			
	hemorrhage		0	0	0	0	0	0	0	0	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

Organ	Findings	Group Name	5000 ppm				10000 ppm			
		No. of Animals on Study	2				2			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
(Hematopoietic system)										
bone marrow			< 2>				< 2>			
	decreased hematopoiesis		0	0	0	0	0	2	0	0
			(0)	(0)	(0)	(0)	(0)	(100)	(0)	(0)
thymus			< 2>				< 2>			
	karyorrhexis		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(50)	(0)	(0)	(0)
spleen			< 2>				< 2>			
	engorgement of erythrocyte		0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(100)	(0)	(0)	(0)
(Digestive system)										
liver			< 2>				< 2>			
	increase in mitosis		1	0	0	0	0	0	0	0
			(50)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	necrosis:single cell		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(50)	(0)	(0)	(0)
(Nervous system)										
brain			< 2>				< 2>			
	hemorrhage		0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(50)	(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

Organ	Findings	Group Name	Control				625 ppm				1250 ppm				2500 ppm			
		No. of Animals on Study	2				2				2				2			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
(Nervous system)																		
brain			< 2>				< 2>				< 2>				< 2>			
	degeneration		0	0	0	0	0	0	0	0	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

Organ	Findings	Group Name	5000 ppm				10000 ppm			
		No. of Animals on Study	2				2			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
(Nervous system)										
brain										
	degeneration		< 2>				< 2>			
			0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(50)	(0)	(0)

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

APPENDIX K 1

IDENTITY OF 1,4-DICHLORO-2-NITROBENZENE

IN THE 2-WEEK FEED STUDY

IDENTITY OF 1,4-DICHLORO-2-NITROBENZENE IN THE 2-WEEK FEED STUDY

Test Substance : 1,4-Dichloro-2-nitrobenzene (Wako Pure Chemical Industries, Ltd.)

Lot No. : CAN1112

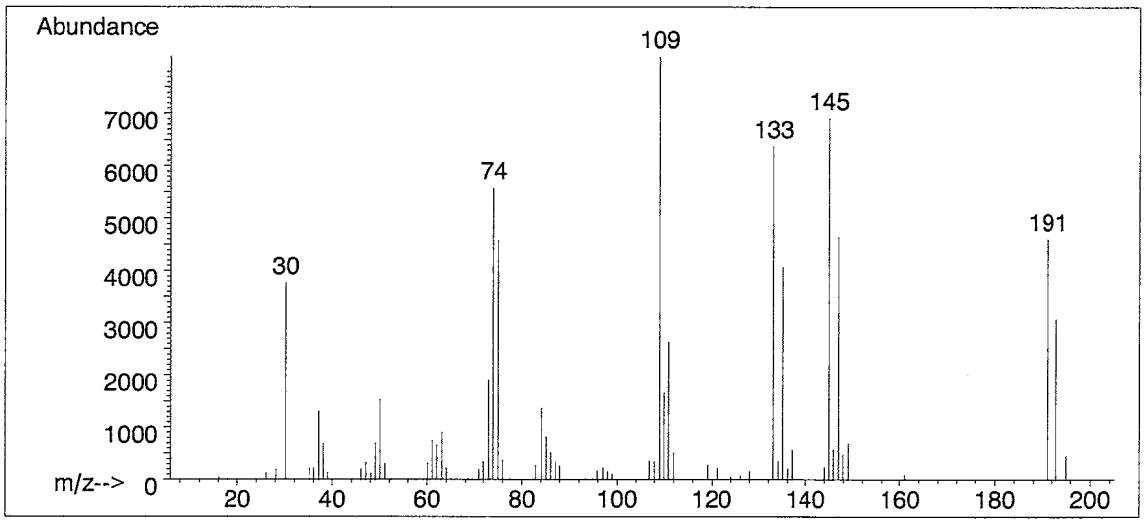
1. Spectral Data

Mass Spectrometry

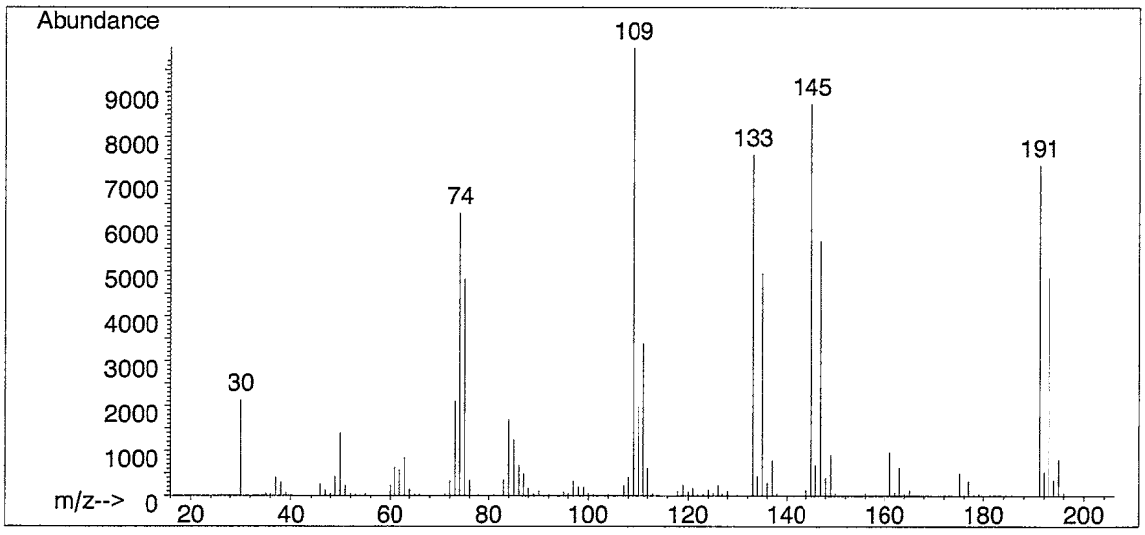
Instrument : Hewlett Packard 5989B Mass Spectrometer

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.

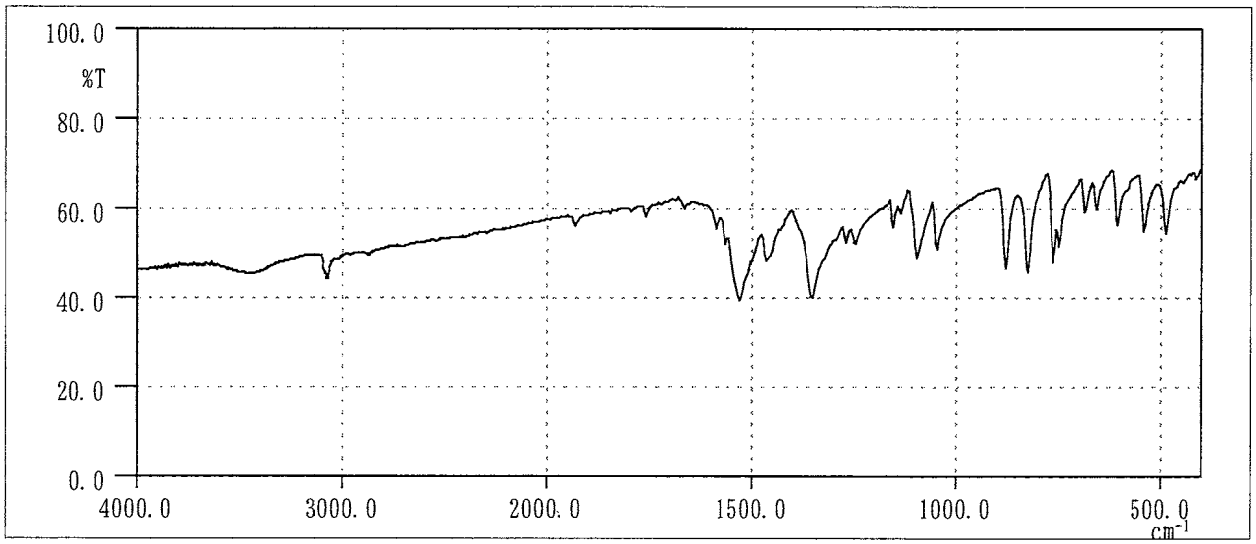
(*Fred W. McLafferty (1994) Wiley Registry of Mass Spectral Data, 6th edition. John Wiley and Sons, Inc. (U.S.), Entry Number 74222)

Infrared Spectrometry

Instrument : Shimadzu FTIR-8200PC Infrared Spectrometer

Cell : KBr

Resolution : 2 cm^{-1}



Infrared Spectrum of Test Substance

Determined Values Wave Number (cm^{-1})	Literature Values* Wave Number (cm^{-1})
460～ 510	460～ 510
510～ 560	510～ 560
560～ 620	560～ 620
620～ 670	620～ 670
670～ 690	670～ 690
690～ 790	690～ 790
790～ 850	790～ 850
850～ 900	850～ 900
900～1060	900～1060
1060～1120	1060～1120
1120～1170	1120～1170
1170～1180	1170～1180
1180～1260	1180～1260
1260～1280	1260～1280
1280～1400	1280～1400
1400～1470	1400～1470
1470～1580	1470～1580
1580～1600	1580～1600
1650～1690	1650～1690
1750～1780	1750～1780
1780～1810	1780～1810
1900～1950	1900～1950
3000～3100	3000～3100

Results: The infrared spectrum was consistent with literature spectrum.
(*Performed by Wako Pure Chemical Industries, Ltd.)

2. Conclusions: The test substance was identified as 1,4-dichloro-2-nitrobenzene by the mass spectrum and the infrared spectrum.

APPENDIX K 2

STABILITY OF 1,4-DICHLORO-2-NITROBENZENE

IN THE 2-WEEK FEED STUDY

STABILITY OF 1,4-DICHLORO-2-NITROBENZENE IN THE 2-WEEK FEED STUDY

Test Substance : 1,4-Dichloro-2-nitrobenzene (Wako Pure Chemical Industries, Ltd.)

Lot No. : CAN1112

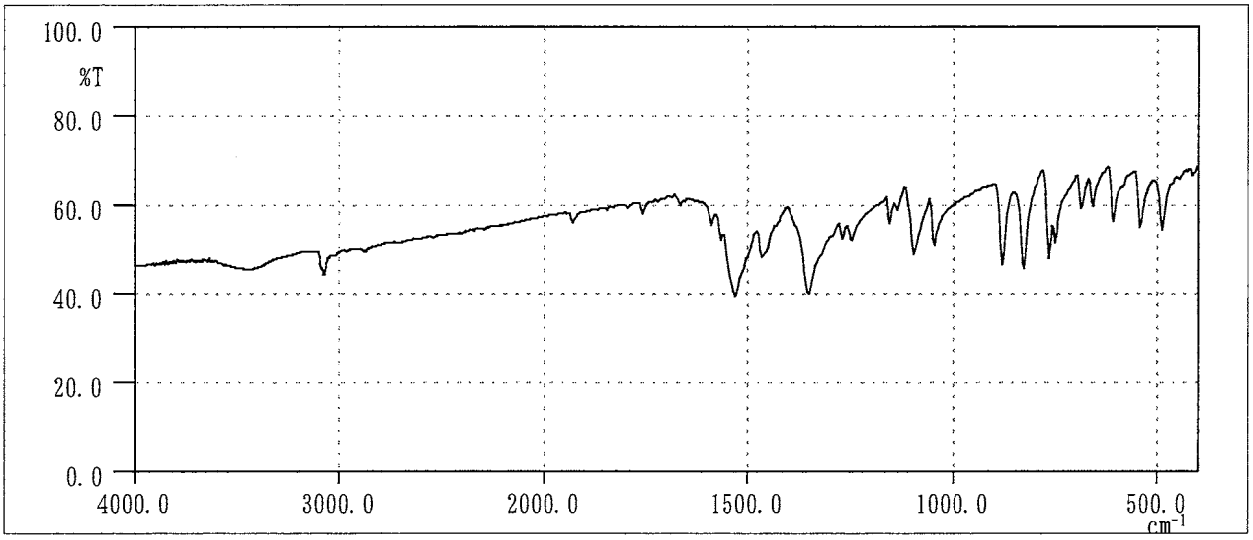
1. Sample : This lot was used from 1995.10.26 to 1995.11.9. Test substance was stored in a dark place at room temperature.

2. Infrared Spectrometry

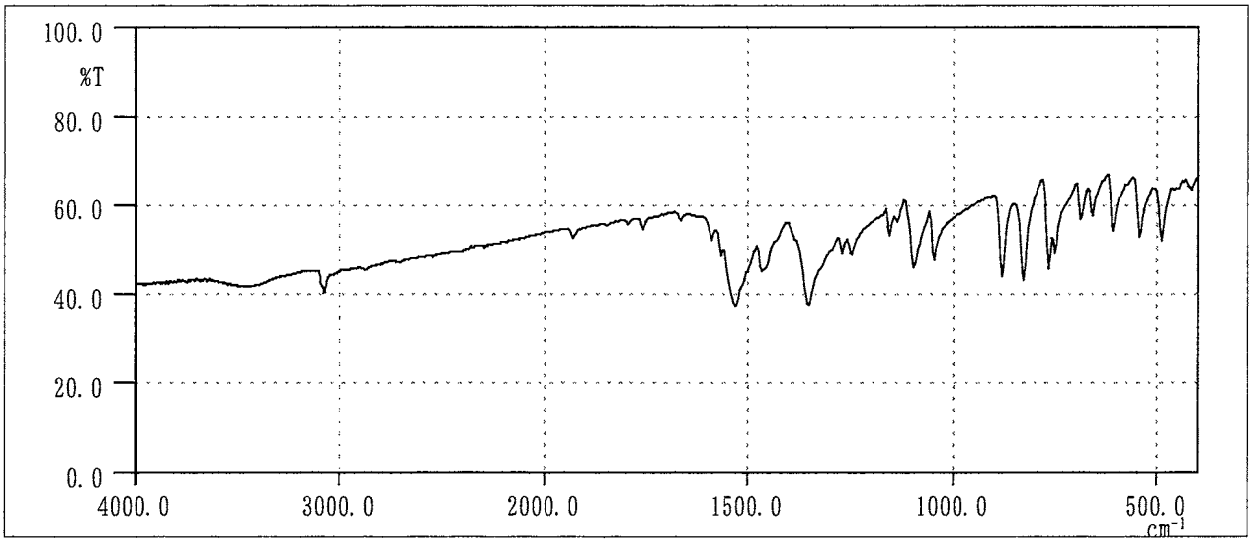
Instrument : Shimadzu FTIR-8200PC Infrared Spectrometer

Cell : KBr

Resolution : 2 cm^{-1}



Infrared Spectrum of Test Substance (date analyzed : 1995.09.21)



Infrared Spectrum of Test Substance (date analyzed : 1995.11.28)

Results: The results of infrared spectrum did not change before and after the study.

3. Gas Chromatography

Instrument : Hewlett Packard 5890A Gas Chromatograph

Column : Methyl Silicone (0.2 mmϕ × 50m)

Column Temperature : 180 °C → (10 °C/min) → 215 °C → (20 °C/min) → 250 °C (2 min)

Flow Rate : 1 mL/min

Detector : FID (Flame Ionization Detector)

Injection Volume : 1 μL

Date (date analyzed)	Peak No.	Retention Time (min)	Area (%)
1995.09.21	1	3.636	100
1995.11.28	1	3.636	100

Results: Gas chromatography indicated one major peak (peak No.1) analyzed on 1995.9.21 and one major peak (peak No.1) analyzed on 1995.11.28. No new trace impurity peak in the test substance analyzed on 1995.11.28 was detected.

4. Conclusions: The test substance was stable for about 2 months in a dark place at room temperature.

APPENDIX K 3

CONCENTRATION OF 1,4-DICHLORO-2-NITROBENZENE IN FORMULATED DIETS IN THE 2-WEEK FEED STUDY

CONCENTRATION OF 1,4-DICHLORO-2-NITROBENZENE IN FORMULATED DIETS IN THE 2-WEEK FEED STUDY

	Target Concentration				
Date Analyzed	625[a]	1250	2500	5000	10000
1995.10.26	601.5 (96.2)[b]	1162.5 (93.0)	2365.5 (94.6)	4945.3 (98.9)	9673.7 (96.7)

[a] ppm
[b] %

Analytical Method : The samples were analyzed by gas chromatography.

Instrument : Hewlett Packard 5890A Gas Chromatograph
Column : Methyl Silicone (0.2 mmϕ × 50m)
Column Temperature : 180 °C → (10 °C/min) → 215 °C → (20 °C/min) → 250 °C (2 min)
Flow Rate : 1 mL/min
Detector : FID (Flame Ionization Detector)
Injection Volume : 1 μL

HOMOGENEITY OF 1,4-DICHLORO-2-NITROBENZENE IN FORMULATED DIETS IN THE 2-WEEK FEED STUDY

	Target Concentration				
	625[a]	1250	2500	5000	10000
Coefficient Variation	1.23[b]	0.47	1.80	6.22	1.70

[a] ppm
[b] % (n=7)

Analytical Method : The samples were analyzed by gas chromatography.

Instrument : Hewlett Packard 5890A Gas Chromatograph
Column : Methyl Silicone (0.2 mmϕ × 50m)
Column Temperature : 180 °C → (10 °C/min) → 215 °C → (20 °C/min) → 250 °C (2 min)
Flow Rate : 1 mL/min
Detector : FID (Flame Ionization Detector)
Injection Volume : 1 µL

APPENDIX K 4

STABILITY OF 1,4-DICHLORO-2-NITROBENZENE

IN FORMULATED DIETSIN THE 2-WEEK FEED STUDY

STABILITY OF 1,4-DICHLORO-2-NITROBENZENE IN FORMULATED DIETS IN THE 2-WEEK FEED STUDY

		Target Concentration				
Date Prepared	Date Analyzed	625[a]	1250	2500	5000	10000
1995.10.25	1995.10.26	601.5 (100)[b]	1162.5 (100)	2365.5 (100)	4945.3 (100)	9673.7 (100)
	1995.10.30[c]	555.1 (92.3)	1064.7 (91.6)	2133.7 (90.2)	4409.3 (89.2)	8996.3 (93.0)
	1995.11.20[d]	620.0 (103)	1331.0 (114)	2269.3 (95.9)	4615.5 (93.3)	9324.0 (96.4)

[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 gas chromatography.

Instrument : Hewlett Packard 5890A Gas Chromatograph
Column : Methyl Silicone (0.2 mmϕ × 50m)
Column Temperature : 180 °C → (10 °C/min) → 215 °C → (20 °C/min) → 250 °C (2 min)
Flow Rate : 1 mL/min
Detector : FID (Flame Ionization Detector)
Injection Volume : 1 μL

APPENDIX L 1

METHODS FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 2-WEEK FEED STUDY OF 1,4-DICHLORO-2-NITROBENZENE

METHODS FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 2-WEEK FEED STUDY OF 1,4-DICHLORO-2-NITROBENZENE

Item	Method
Hematology	
Red blood cell (RBC)	Light scattering method [1]
Hemoglobin (Hgb)	Cyanmethemoglobin method [1]
Methemoglobin	Multiple-wavelength Spectrophotometric method [5]
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] (May-Grunwald-Giemsa staining)
Biochemistry	
Total protein (TP)	Biuret method [4]
Albumin (Alb)	BCG method [4]
A/G ratio	Calculated as Alb/(TP－Alb) [4]
T-bilirubin	Alkaline azobilirubin method [4]
Glucose	Enzymatic method (GLK・G-6-PDH) [4]
T-cholesterol	Enzymatic method (CE・COD・POD) [4]
Phospholipid	Enzymatic method (PLD・COD・POD) [4]
Glutamic oxaloacetic transaminase (GOT)	IFCC method [4]
Glutamic pyruvic transaminase (GPT)	IFCC method [4]
Lactate dehydrogenase (LDH)	Wroblewski-LaDue method [4]
γ-Glutamyl transpeptidase (γ-GTP)	L-γ-Glutamyl-p-nitroanilide method [4]
Creatine phosphokinase (CPK)	GSCC method [4]
Urea nitrogen	Enzymatic method (Urease・GLDH) [4]
Creatinine	Jaffe method [4]
Sodium	Ion selective electrode method [4]
Potassium	Ion selective electrode method [4]
Chloride	Ion selective electrode method [4]
Calcium	OCPC method [4]
Inorganic phosphorus	Enzymatic method (PNP・XOD・POD) [4]

1) Automatic blood cell analyzer (Technicon H・1 : Technicon Instruments Corporation)

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

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

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

5) CO-oximeter (CIBA・CORNING 270 : Ciba Corning Diagnostics Corp)

APPENDIX M 1

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 2-WEEK FEED STUDY OF 1,4-DICHLORO-2-NITROBENZENE

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 2-WEEK FEED STUDY OF 1,4-DICHLORO-2-NITROBENZENE

Item	Unit	Decimal Place
Hematology		
Red blood cell (RBC)	$\times 10^6/\mu L$	2
Hemoglobin	g/dL	1
Methemoglobin	%	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
Phospholipid	mg/dL	0
Glutamic oxaloacetic transaminase (GOT)	IU/L	0
Glutamic pyruvic transaminase (GPT)	IU/L	0
Lactate dehydrogenase (LDH)	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

APPENDIX N 1

IDENTIFICATION OF URINARY METABOLITE OF 1,4-DICHLORO-2-NITROBENZENE IN THE 2-WEEK FEED STUDY OF 1,4-DICHLORO-2-NITROBENZENE

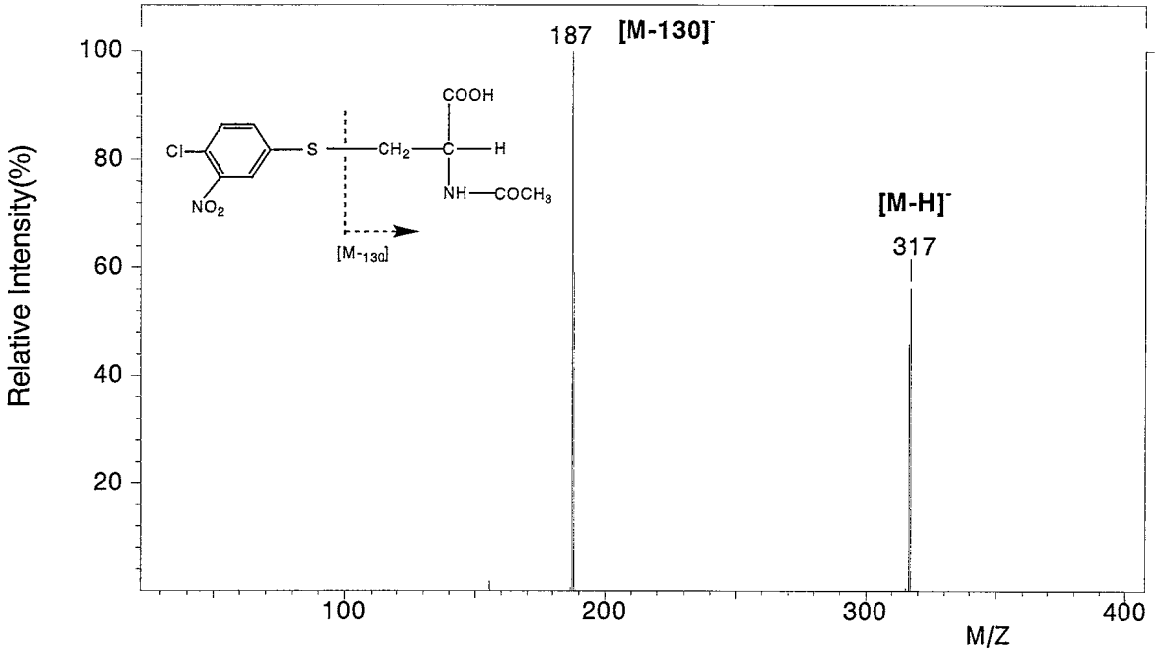


FIGURE 1. A LC-MS/MS spectrum of a urinary metabolite in the rat fed the powdered diet containing 1,4-dichloro-2-nitrobenzene

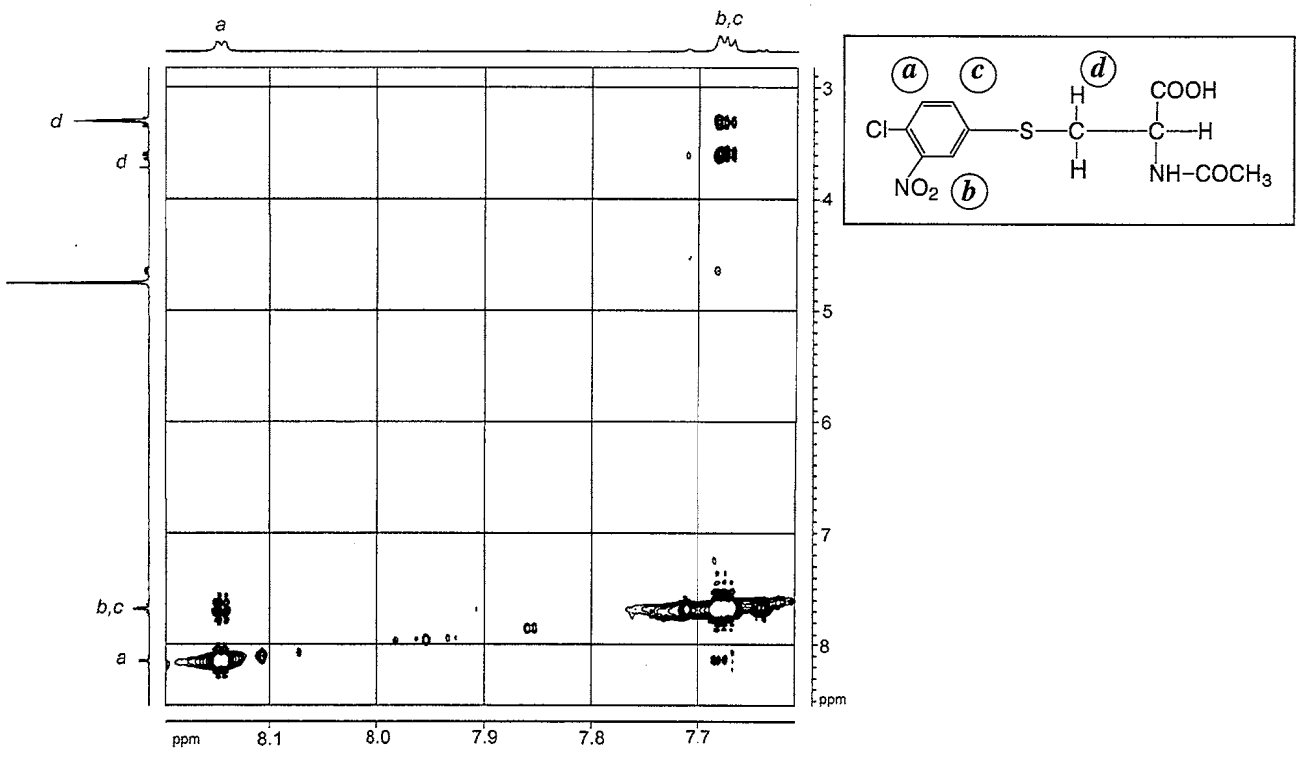


FIGURE 2. A $^{1}H-NMR$ spectrum of a urinary metabolite in the rat fed the powdered diet containing 1,4-dichloro-2-nitrobenzene