プロピオノニトリルのラットを用いた
吸入による１３週間毒性試験報告書

試験番号：0455

APPENDICES

APPENDICES

APPENDICES (CONTINUED)

APPENDIX A 1

BODY WEIGHT CHANGES : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0455
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	123± 3	151± 7	179± 9	201± 10	221± 9	236± 9	251± 11
6ppm	123± 4	151± 5	181± 6	204± 6	223± 8	237± 7	250± 7
12ppm	123± 3	149± 3	177± 4	197± 6	216± 7	231± 7	243± 8
25ppm	123± 3	149± 3	178± 4	202± 8	224± 10	239± 13	251± 15
50ppm	123± 3	150± 5	179± 8	203± 8	222± 11	238± 12	251± 13
100ppm	123± 3	138± 3**	165± 5**	186± 8**	207± 9**	222± 10**	231± 9**

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

STUDY NO. : 0455
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	262± 13	275± 14	282± 15	291± 16	296± 16	300± 15	301± 18
6ppm	262± 9	271± 8	282± 10	287± 13	291± 11	295± 14	300± 12
12ppm	256± 8	266± 11	275± 13	281± 13	285± 14	290± 16	291± 15
25ppm	263± 20	274± 19	283± 19	292± 21	295± 20	298± 21	298± 21
50ppm	264± 14	277± 15	286± 17	293± 16	296± 18	300± 19	304± 19
100ppm	245± 10*	254± 11**	261± 12**	267± 14**	271± 16**	275± 18*	277± 19*

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

APPENDIX A 2

BODY WEIGHT CHANGES : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0455
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	96± 3	110± 4	121± 5	130± 7	137± 5	144± 5	147± 5
6ppm	96± 3	110± 4	123± 5	133± 6	139± 7	145± 7	150± 7
12ppm	96± 3	109± 4	120± 6	130± 5	137± 6	143± 6	148± 7
25ppm	96± 3	108± 3	121± 3	129± 3	137± 5	143± 4	147± 5
50ppm	96± 3	110± 5	120± 7	129± 7	136± 7	142± 9	147± 9
100ppm	96± 3	106± 2	117± 2	127± 4	135± 4	141± 5	146± 4

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

STUDY NO. : 0455
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	152± 5	155± 6	158± 6	163± 7	164± 5	165± 5	164± 6
6ppm	155± 6	159± 7	163± 8	166± 8	168± 7	170± 7	168± 6
12ppm	152± 7	154± 6	157± 7	161± 7	165± 6	165± 7	164± 7
25ppm	152± 6	156± 7	160± 8	163± 8	166± 8	167± 9	168± 9
50ppm	151± 10	155± 10	157± 11	160± 11	164± 12	165± 10	164± 11
100ppm	151± 6	154± 5	159± 6	161± 6	162± 5	163± 4	163± 5

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

APPENDIX B 1

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0455
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 1	2	3	4	5	6	7
Control	14.1± 0.8	15.2± 1.1	15.8± 1.0	16.5± 0.9	15.6± 1.3	15.4± 0.9	15.2± 0.9
6ppm	13.9± 0.6	15.3± 0.7	16.4± 0.8	16.7± 0.6	16.0± 0.8	15.7± 0.7	15.6± 0.8
12ppm	13.8± 0.8	14.7± 0.7	15.6± 0.6	16.0± 0.6	15.2± 0.7	15.4± 0.6	15.2± 0.7
25ppm	13.7± 0.8	15.2± 1.2	15.9± 1.0	16.5± 1.4	16.0± 1.3	15.2± 1.4	15.7± 1.7
50ppm	13.5± 0.6	14.9± 0.9	16.0± 0.6	16.3± 1.1	15.9± 0.9	15.5± 1.1	15.4± 0.8
100ppm	10.7± 0.5**	13.2± 0.6**	14.2± 0.9**	15.2± 1.1*	15.2± 0.7	14.3± 0.6*	14.9± 1.2

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

STUDY NO. : 0455
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 8	9	10	11	12	13
Control	15.1± 0.8	15.5± 1.2	15.3± 0.9	14.8± 0.7	14.6± 0.8	15.0± 0.9
6ppm	15.5± 0.8	15.6± 1.1	14.6± 1.8	14.8± 1.1	14.8± 1.3	15.4± 1.1
12ppm	15.2± 0.8	15.3± 0.7	14.6± 0.5	14.4± 0.8	14.4± 1.1	14.8± 1.1
25ppm	15.7± 1.3	16.0± 1.1	15.4± 1.1	14.2± 1.1	14.5± 1.2	14.8± 1.1
50ppm	15.5± 0.8	15.7± 0.9	15.4± 0.8	14.9± 1.2	14.3± 1.1	14.5± 0.9
100ppm	15.1± 1.0	14.9± 0.9	14.3± 1.2	14.0± 0.8	13.9± 1.2	14.1± 1.3

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

APPENDIX B 2

FOOD CONSUMPTION CHANGES : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0455
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 1	2	3	4	5	6	7
Control	10.0± 0.6	10.4± 0.6	10.6± 0.6	10.5± 0.6	10.5± 0.7	10.0± 0.5	10.0± 0.5
6ppm	10.1± 0.7	10.9± 0.6	10.7± 0.9	10.5± 0.9	10.7± 0.8	10.1± 0.5	10.3± 0.5
12ppm	9.8± 0.6	10.3± 0.7	10.9± 0.7	10.5± 0.6	10.4± 0.5	9.8± 0.8	10.1± 0.8
25ppm	10.0± 0.3	10.5± 0.6	10.6± 0.4	10.2± 0.5	10.4± 0.6	10.0± 0.7	9.8± 0.8
50ppm	9.8± 0.7	10.4± 0.7	10.7± 0.6	10.2± 0.5	10.7± 0.7	9.7± 0.5	9.9± 0.6
100ppm	8.8± 0.5**	10.1± 0.3	10.3± 0.4	10.3± 0.5	10.4± 0.4	10.0± 0.4	9.8± 0.5

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

STUDY NO. : 0455
ANIMAL : RAT F344/DuCrj
UNIT : g
REPORT TYPE : A1 13
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 8	9	10	11	12	13
Control	9.7± 0.6	10.1± 0.6	10.0± 0.5	10.2± 0.4	9.6± 0.5	9.6± 0.5
6ppm	10.0± 1.0	10.4± 0.9	10.5± 1.0	10.5± 0.8	10.4± 0.7	10.1± 0.8
12ppm	9.3± 0.6	9.9± 0.5	9.9± 0.7	10.3± 0.6	9.9± 0.6	9.7± 0.6
25ppm	9.6± 0.9	10.3± 0.8	9.9± 0.7	10.1± 1.0	9.7± 1.0	9.6± 0.7
50ppm	9.6± 0.5	9.8± 0.7	9.8± 0.8	10.2± 0.8	9.7± 0.8	9.7± 0.6
100ppm	9.9± 0.5	10.0± 0.8	9.6± 0.6	9.8± 0.6	9.6± 0.6	9.4± 0.8

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

APPENDIX C 1

URINALYSIS : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0455
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

URINALYSIS

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

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

STUDY NO. : 0455 URINALYSIS
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

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	
6ppm	10	9	1	0	0	0		10	0	0	0	0	
12ppm	10	10	0	0	0	0		10	0	0	0	0	
25ppm	10	9	0	1	0	0		10	0	0	0	0	
50ppm	10	10	0	0	0	0		10	0	0	0	0	
100ppm	10	10	0	0	0	0		10	0	0	0	0	

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

APPENDIX C 2

URINALYSIS : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0455 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	7	3		8	2	0	0	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	
6ppm	10	0	0	0	0	1	4	5		5	4	1	0	0	0		10	0	0	0	0	0		9	1	0	0	0	0		10	0	0	0	
12ppm	10	0	0	0	0	0	10	0		5	4	1	0	0	0		10	0	0	0	0	0		8	2	0	0	0	0		10	0	0	0	
25ppm	10	0	0	1	0	3	5	1		9	1	0	0	0	0		10	0	0	0	0	0		10	0	0	0	0	0		10	0	0	0	
50ppm	10	0	0	0	0	1	5	4		7	3	0	0	0	0		10	0	0	0	0	0		8	2	0	0	0	0		10	0	0	0	
100ppm	10	0	0	0	1	0	4	5		6	4	0	0	0	0		10	0	0	0	0	0		9	1	0	0	0	0		10	0	0	0	

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

STUDY NO. : 0455 URINALYSIS
ANIMAL : RAT F344/DuCrj
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

Group Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
Control	10	10	0	0	0	0		10	0	0	0	0	
6ppm	10	10	0	0	0	0		10	0	0	0	0	
12ppm	10	10	0	0	0	0		10	0	0	0	0	
25ppm	10	10	0	0	0	0		10	0	0	0	0	
50ppm	10	10	0	0	0	0		10	0	0	0	0	
100ppm	10	10	0	0	0	0		10	0	0	0	0	

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

APPENDIX D 1

HEMATOLOGY : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0455
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 f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	10	9.61± 0.14	16.2± 0.2	45.8± 0.5	47.7± 0.5	16.9± 0.4	35.4± 0.6	758± 38
6ppm	10	9.57± 0.18	16.0± 0.3	45.4± 0.9	47.4± 0.5	16.7± 0.3	35.3± 0.5	765± 78
12ppm	10	9.67± 0.17	16.2± 0.3	45.7± 0.8	47.3± 0.5	16.7± 0.3	35.4± 0.3	747± 49
25ppm	10	9.59± 0.29	16.1± 0.4	45.5± 1.1	47.5± 0.8	16.8± 0.5	35.3± 0.6	738± 50
50ppm	10	9.49± 0.21	15.9± 0.3	45.2± 0.9	47.6± 0.4	16.8± 0.3	35.3± 0.4	745± 53
100ppm	10	9.14± 0.22**	15.4± 0.4**	44.5± 1.0**	48.6± 0.6**	16.9± 0.4	34.7± 0.6	778± 107

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

STUDY NO. : 0455
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	1.7± 0.2	18.4± 2.7	24.1± 2.6
6ppm	10	1.8± 0.4	17.5± 1.8	23.7± 1.0
12ppm	10	1.8± 0.2	17.6± 1.6	23.4± 2.0
25ppm	10	1.7± 0.2	16.9± 0.8	22.7± 2.2
50ppm	10	1.9± 0.2	18.5± 2.0	23.8± 2.4
100ppm	10	2.8± 0.3**	16.3± 1.3	22.5± 1.6

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

STUDY NO. : 0455
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	5.17±	1.03	1±	1	20±	3	2±	1	0±	0	2±	1	75±	4	0±	0
6ppm	10	4.95±	1.02	1±	1	21±	3	2±	1	0±	0	2±	1	75±	4	0±	0
12ppm	10	5.16±	0.86	1±	1	21±	1	1±	1	0±	0	3±	1	75±	2	0±	0
25ppm	10	5.45±	2.37	1±	1	20±	5	1±	1	0±	0	2±	1	77±	5	0±	0
50ppm	10	4.76±	0.98	1±	1	19±	4	1±	1	0±	0	3±	2	76±	4	0±	0
100ppm	10	4.14±	1.35	1±	1	21±	4	1±	1	0±	0	3±	1	74±	5	0±	0

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

APPENDIX D 2

HEMATOLOGY : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0455
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 f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	10	8.89± 0.15	16.1± 0.2	44.4± 0.4	49.9± 0.6	18.2± 0.2	36.4± 0.3	822± 88
6ppm	10	8.86± 0.19	16.1± 0.3	44.3± 0.8	50.0± 0.7	18.2± 0.2	36.4± 0.5	826± 60
12ppm	10	8.76± 0.27	16.0± 0.3	43.7± 1.2	49.9± 0.3	18.2± 0.3	36.5± 0.4	814± 65
25ppm	9	8.83± 0.29	16.1± 0.5	44.0± 1.3	49.9± 0.5	18.2± 0.3	36.5± 0.4	786± 59
50ppm	10	8.83± 0.17	16.1± 0.4	44.2± 0.9	50.1± 0.5	18.2± 0.3	36.4± 0.3	805± 66
100ppm	10	8.43± 0.26**	15.4± 0.3**	43.1± 1.0	51.2± 0.7**	18.3± 0.3	35.8± 0.4**	857± 52

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

STUDY NO. : 0455
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	1.7± 0.1	16.4± 0.6	18.6± 1.2
6ppm	10	1.6± 0.2	16.6± 0.6	19.1± 1.8
12ppm	10	1.8± 0.4	16.6± 0.8	19.2± 2.4
25ppm	9	1.9± 0.4	16.5± 0.7	18.1± 1.1
50ppm	10	2.0± 0.3	16.6± 0.5	18.4± 2.3
100ppm	10	2.9± 0.4**	16.4± 0.5	18.3± 1.6

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

STUDY NO. : 0455
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	3.17± 1.00	1± 1	20± 4	1± 1	0± 0	2± 1	76± 5	0± 0
6ppm	10	3.42± 2.27	0± 1	20± 4	1± 1	0± 0	2± 1	76± 5	0± 0
12ppm	10	3.86± 1.76	1± 1	18± 2	1± 1	0± 0	3± 1	77± 2	0± 0
25ppm	9	3.08± 0.66	1± 1	20± 5	1± 1	0± 0	1± 1	76± 6	0± 0
50ppm	10	3.22± 0.88	1± 1	20± 5	1± 1	0± 0	3± 1	75± 6	0± 0
100ppm	10	3.11± 0.98	1± 1	20± 4	1± 1	0± 0	3± 2	76± 5	0± 0

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

APPENDIX E 1

BIOCHEMISTRY : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0455
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	6.4±	0.2	3.5±	0.1	1.2±	0.1	0.12±	0.01	190±	9	56±	6	50±	11
6ppm	10	6.4±	0.1	3.6±	0.1	1.3±	0.1	0.12±	0.01	189±	12	59±	6	55±	14
12ppm	10	6.4±	0.2	3.6±	0.1	1.3±	0.1	0.12±	0.01	187±	9	54±	6	45±	15
25ppm	10	6.4±	0.1	3.5±	0.1	1.3±	0.1	0.11±	0.01	183±	12	57±	5	50±	13
50ppm	10	6.5±	0.2	3.6±	0.1	1.2±	0.0	0.12±	0.01	188±	15	61±	2	55±	18
100ppm	10	6.6±	0.1	3.7±	0.1**	1.3±	0.1	0.12±	0.01	183±	11	63±	7*	43±	18

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

STUDY NO. : 0455
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	111± 8	69± 10	49± 6	216± 60	267± 29	1± 1	127± 21
6ppm	10	116± 9	83± 23	55± 11	215± 51	268± 21	1± 0	121± 14
12ppm	10	108± 9	73± 29	51± 14	200± 64	269± 21	1± 1	120± 17
25ppm	10	111± 8	75± 22	51± 9	209± 38	265± 31	1± 1	116± 13
50ppm	10	116± 7	92± 40	56± 17	241± 68	254± 23	1± 1	119± 14
100ppm	10	117± 12	75± 24	50± 12	197± 37	224± 26**	1± 1	118± 14

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

STUDY NO. : 0455
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	20.0± 1.6	0.5± 0.1	141± 1	3.6± 0.2	105± 1	10.1± 0.1	5.8± 0.6
6ppm	10	20.7± 1.3	0.5± 0.1	141± 1	3.5± 0.3	104± 1	10.2± 0.2	5.9± 0.8
12ppm	10	20.1± 1.5	0.5± 0.1	141± 1	3.6± 0.3	105± 1	10.0± 0.1	5.7± 0.8
25ppm	10	21.2± 1.7	0.5± 0.1	141± 1	3.6± 0.4	104± 1	10.1± 0.1	5.7± 0.7
50ppm	10	19.8± 1.1	0.5± 0.1	141± 1	3.6± 0.2	104± 2	10.2± 0.2	5.7± 0.8
100ppm	10	20.9± 1.8	0.5± 0.1	140± 1	3.7± 0.2	105± 2	10.2± 0.1	6.0± 0.9

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

APPENDIX E 2

BIOCHEMISTRY : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0455
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	6.2±	0.2	3.5±	0.2	1.3±	0.1	0.14±	0.01	139±	15	66±	10	11±	2
6ppm	10	6.3±	0.1	3.5±	0.1	1.3±	0.1	0.14±	0.01	147±	13	66±	7	12±	4
12ppm	10	6.2±	0.1	3.4±	0.1	1.3±	0.0	0.14±	0.01	145±	12	64±	9	12±	2
25ppm	9	6.3±	0.2	3.5±	0.1	1.3±	0.1	0.15±	0.01	149±	8	64±	10	10±	2
50ppm	10	6.4±	0.2	3.6±	0.1	1.3±	0.1	0.15±	0.02	138±	16	68±	7	10±	2
100ppm	10	6.4±	0.2	3.6±	0.1	1.3±	0.1	0.14±	0.01	149±	15	65±	5	11±	2

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

STUDY NO. : 0455
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	131± 17	80± 5	43± 7	337± 141	192± 25	1± 1	155± 45
6ppm	10	133± 10	77± 9	41± 8	303± 82	190± 20	2± 1	148± 20
12ppm	10	129± 14	73± 8	35± 4	358± 130	197± 19	2± 1	158± 39
25ppm	9	130± 15	82± 17	47± 19	389± 130	197± 24	1± 1	163± 38
50ppm	10	134± 12	75± 8	36± 4	439± 251	197± 21	2± 1	189± 76
100ppm	10	130± 8	77± 12	46± 17	379± 187	190± 20	2± 1	175± 55

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

STUDY NO. : 0455
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	21.3± 2.4	0.6± 0.0	139± 1	3.6± 0.4	105± 2	9.8± 0.2	5.7± 1.1
6ppm	10	20.0± 1.4	0.6± 0.1	140± 1	3.5± 0.3	106± 2	9.8± 0.2	5.0± 0.7
12ppm	10	19.7± 1.6	0.6± 0.1	139± 1	3.7± 0.3	106± 2	9.7± 0.1	5.4± 0.8
25ppm	9	19.8± 1.9	0.5± 0.1	140± 1	3.6± 0.2	105± 2	9.8± 0.2	5.2± 0.8
50ppm	10	20.7± 2.3	0.6± 0.1	140± 1	3.5± 0.4	107± 2	9.8± 0.2	5.2± 1.0
100ppm	10	21.3± 2.7	0.6± 0.1	139± 1	3.4± 0.2	106± 2	9.8± 0.2	5.3± 0.8

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

APPENDIX F 1

GROSS FINDINGS : SUMMARY, RAT : MALE : SACRIFICED ANIMALS

(13-WEEK STUDY)

STUDY NO. : 0455
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

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

Organ	Findings	Group Name	Control	6ppm	12ppm	25ppm
		NO. of Animals	10 (%)	10 (%)	10 (%)	10 (%)
liver	herniation		0 (0)	1 (10)	1 (10)	1 (10)

STUDY NO. : 0455
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

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

Organ	Findings	Group Name	50ppm		100ppm	
		NO. of Animals	10	(%)	10	(%)
liver	herniation		1	(10)	0	(0)

APPENDIX F 2

GROSS FINDINGS : SUMMARY, RAT : FEMALE : SACRIFICED ANIMALS

(13-WEEK STUDY)

STUDY NO. : 0455
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	(%)	6ppm 10	(%)	12ppm 10	(%)	25ppm 10	(%)
liver	herniation		1	(10)	0	(0)	1	(10)	1	(10)
ovary	cyst		0	(0)	1	(10)	0	(0)	1	(10)

Organ	Findings	Group Name	50ppm		100ppm	
		NO. of Animals	10	(%)	10	(%)
liver	herniation		2	(20)	0	(0)
ovary	cyst		0	(0)	0	(0)

APPENDIX G 1

ORGAN WEIGHT, ABSOLUTE : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0455
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	281± 16	0.217± 0.033	0.049± 0.003	3.025± 0.140	0.919± 0.056	0.971± 0.055
6ppm	10	279± 12	0.232± 0.026	0.047± 0.004	2.998± 0.065	0.923± 0.047	0.959± 0.037
12ppm	10	273± 14	0.219± 0.031	0.045± 0.004	3.005± 0.109	0.901± 0.058	0.946± 0.046
25ppm	10	280± 18	0.227± 0.026	0.046± 0.004	3.013± 0.171	0.906± 0.048	0.983± 0.043
50ppm	10	285± 17	0.229± 0.025	0.046± 0.003	3.013± 0.168	0.905± 0.049	0.972± 0.068
100ppm	10	256± 17**	0.196± 0.029	0.046± 0.004	2.918± 0.159	0.892± 0.054	0.937± 0.045

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

STUDY NO. : 0455
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	1.773± 0.086	0.516± 0.029	7.047± 0.451	1.876± 0.072
6ppm	10	1.752± 0.055	0.521± 0.034	7.091± 0.423	1.879± 0.069
12ppm	10	1.734± 0.097	0.510± 0.024	6.834± 0.478	1.869± 0.043
25ppm	10	1.756± 0.117	0.525± 0.035	7.018± 0.621	1.862± 0.043
50ppm	10	1.750± 0.127	0.536± 0.038	7.364± 0.478	1.859± 0.037
100ppm	10	1.637± 0.114	0.543± 0.041	7.058± 0.701	1.852± 0.037

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

APPENDIX G 2

ORGAN WEIGHT, ABSOLUTE: SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0455
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	151± 6	0.182± 0.022	0.053± 0.004	0.094± 0.005	0.573± 0.028	0.700± 0.032
6ppm	10	155± 6	0.175± 0.023	0.055± 0.003	0.099± 0.032	0.593± 0.035	0.709± 0.020
12ppm	10	151± 6	0.170± 0.008	0.053± 0.004	0.092± 0.014	0.594± 0.030	0.718± 0.027
25ppm	10	154± 8	0.173± 0.023	0.055± 0.003	0.099± 0.020	0.589± 0.035	0.705± 0.049
50ppm	10	152± 10	0.157± 0.023	0.053± 0.004	0.088± 0.006	0.588± 0.049	0.699± 0.040
100ppm	10	150± 4	0.165± 0.020	0.054± 0.003	0.094± 0.013	0.583± 0.033	0.705± 0.029

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

STUDY NO. : 0455
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	1.013± 0.046	0.344± 0.024	3.645± 0.170	1.694± 0.044
6ppm	10	1.058± 0.050	0.346± 0.020	3.843± 0.172	1.692± 0.067
12ppm	10	1.038± 0.045	0.353± 0.025	3.701± 0.174	1.678± 0.057
25ppm	10	1.035± 0.042	0.341± 0.018	3.774± 0.215	1.696± 0.060
50ppm	10	0.996± 0.045	0.355± 0.013	3.775± 0.279	1.685± 0.054
100ppm	10	0.996± 0.032	0.366± 0.014	3.849± 0.139	1.701± 0.033

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

APPENDIX H 1

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : MALE

(13-WEEK STUDY)

STUDY NO. : 0455
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	281± 16	0.077± 0.009	0.018± 0.001	1.078± 0.056	0.327± 0.014	0.346± 0.008
6ppm	10	279± 12	0.083± 0.009	0.017± 0.002	1.075± 0.059	0.331± 0.012	0.343± 0.013
12ppm	10	273± 14	0.080± 0.011	0.017± 0.002	1.103± 0.055	0.330± 0.011	0.347± 0.011
25ppm	10	280± 18	0.081± 0.009	0.016± 0.001	1.078± 0.052	0.324± 0.012	0.352± 0.016
50ppm	10	285± 17	0.080± 0.007	0.016± 0.001	1.056± 0.032	0.318± 0.011	0.341± 0.009
100ppm	10	256± 17**	0.076± 0.010	0.018± 0.002	1.141± 0.055*	0.349± 0.021**	0.366± 0.014**

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

STUDY NO. : 0455
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	0.631± 0.018	0.184± 0.007	2.506± 0.047	0.669± 0.034
6ppm	10	0.627± 0.014	0.187± 0.012	2.538± 0.114	0.673± 0.018
12ppm	10	0.636± 0.013	0.187± 0.007	2.504± 0.085	0.686± 0.031
25ppm	10	0.628± 0.019	0.188± 0.009	2.505± 0.084	0.668± 0.042
50ppm	10	0.613± 0.023	0.188± 0.008	2.581± 0.085	0.653± 0.032
100ppm	10	0.639± 0.021	0.212± 0.007**	2.750± 0.128**	0.725± 0.048**

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

APPENDIX H 2

ORGAN WEIGHT, RELATIVE : SUMMARY, RAT : FEMALE

(13-WEEK STUDY)

STUDY NO. : 0455
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	151± 6	0.121± 0.015	0.035± 0.003	0.062± 0.004	0.381± 0.015	0.465± 0.014
6ppm	10	155± 6	0.113± 0.012	0.036± 0.002	0.064± 0.020	0.383± 0.015	0.458± 0.010
12ppm	10	151± 6	0.113± 0.006	0.035± 0.003	0.061± 0.010	0.393± 0.017	0.475± 0.016
25ppm	10	154± 8	0.113± 0.013	0.036± 0.001	0.064± 0.012	0.383± 0.016	0.459± 0.025
50ppm	10	152± 10	0.104± 0.013	0.035± 0.002	0.059± 0.005	0.389± 0.025	0.462± 0.020
100ppm	10	150± 4	0.110± 0.014	0.036± 0.002	0.063± 0.009	0.390± 0.016	0.471± 0.018

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

STUDY NO. : 0455
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	0.672± 0.022	0.228± 0.012	2.420± 0.078	1.126± 0.056
6ppm	10	0.684± 0.023	0.223± 0.011	2.483± 0.054	1.095± 0.067
12ppm	10	0.686± 0.023	0.234± 0.016	2.447± 0.087	1.111± 0.056
25ppm	10	0.674± 0.024	0.222± 0.007	2.455± 0.084	1.105± 0.062
50ppm	10	0.659± 0.022	0.235± 0.015	2.491± 0.042	1.115± 0.058
100ppm	10	0.666± 0.012	0.244± 0.008*	2.571± 0.082**	1.137± 0.027

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

APPENDIX I 1

HISTOPATHOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS :
SUMMARY, RAT : MALE : SACRIFICED ANIMALS

(13-WEEK STUDY)

Organ	Findings	Group Name	Control				6ppm				12ppm				25ppm			
		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}																		
bone marrow			<10>				<10>				<10>				<10>			
	erythropoiesis:increased		0	0	0	0	0	0	0	0	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			<10>				<10>				<10>				<10>			
	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)
{Circulatory system}																		
heart			<10>				<10>				<10>				<10>			
	granulation		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}																		
liver			<10>				<10>				<10>				<10>			
	herniation		0	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
{Urinary system}																		
kidney			<10>				<10>				<10>				<10>			
	eosinophilic body		10	0	0	0	10	0	0	0	10	0	0	0	10	0	0	0
			(100)	(0)	(0)	(0)	(100)	(0)	(0)	(0)	(100)	(0)	(0)	(0)	(100)	(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	50ppm				100ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Hematopoietic system}										
bone marrow			<10>				<10>			
	erythropoiesis:increased		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
spleen			<10>				<10>			
	deposit of hemosiderin		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
{Circulatory system}										
heart			<10>				<10>			
	granulation		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
{Digestive system}										
liver			<10>				<10>			
	herniation		1	0	0	0	0	0	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Urinary system}										
kidney			<10>				<10>			
	eosinophilic body		10	0	0	0	10	0	0	0
			(100)	(0)	(0)	(0)	(100)	(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				6ppm				12ppm				25ppm			
		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>			
	mineralization:cortico-medullary junction		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Endocrine system}																		
pituitary			<10>				<10>				<10>				<10>			
	Rathke pouch		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)
thyroid			<10>				<10>				<10>				<10>			
	ultimibranchial body remanet		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)
{Reproductive system}																		
prostate			<10>				<10>				<10>				<10>			
	inflammation		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)
{Special sense organs/appendage}																		
Harder gl			<10>				<10>				<10>				<10>			
	lymphocytic infiltration		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)

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	50ppm				100ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}										
kidney			<10>				<10>			
	mineralization:cortico-medullary junction		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
{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		0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
{Reproductive system}										
prostate			<10>				<10>			
	inflammation		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Special sense organs/appendage}										
Harder gl			<10>				<10>			
	lymphocytic infiltration		1	0	0	0	0	0	0	0
			(10)	(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

APPENDIX I 2

HISTOPATHOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS :
SUMMARY, RAT : FEMALE : SACRIFICED ANIMALS

(13-WEEK STUDY)

Organ	Findings	Group Name	Control				6ppm				12ppm				25ppm			
		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}																		
bone marrow			<10>				<10>				<10>				<10>			
	granulation		2	1	0	0	3	1	0	0	4	3	0	0	3	1	0	0
			(20)	(10)	(0)	(0)	(30)	(10)	(0)	(0)	(40)	(30)	(0)	(0)	(30)	(10)	(0)	(0)
spleen			<10>				<10>				<10>				<10>			
	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)
{Circulatory system}																		
heart			<10>				<10>				<10>				<10>			
	granulation		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)	(0)	(0)	(0)	(0)
{Digestive system}																		
liver			<10>				<10>				<10>				<10>			
	herniation		1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	granulation		0	0	0	0	3	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(10)	(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

Organ	Findings	Group Name	50ppm				100ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Hematopoietic system}										
bone marrow			<10>				<10>			
	granulation		1	2	0	0	4	2	0	0
			(10)	(20)	(0)	(0)	(40)	(20)	(0)	(0)
spleen			<10>				<10>			
	deposit of hemosiderin		0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
{Circulatory system}										
heart			<10>				<10>			
	granulation		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}										
liver			<10>				<10>			
	herniation		3	0	0	0	0	0	0	0
			(30)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	granulation		1	0	0	0	0	0	0	0
			(10)	(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				6ppm				12ppm				25ppm			
		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>			
	mineralization:cortico-medullary junction		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)	(0)	(0)	(0)	(0)
{Endocrine system}																		
thyroid			<10>				<10>				<10>				<10>			
	ultimibranchial body remanet		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)
{Reproductive system}																		
ovary			<10>				<10>				<10>				<10>			
	cyst		0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
{Special sense organs/appendage}																		
Harder gl			<10>				<10>				<10>				<10>			
	lymphocytic infiltration		3	0	0	0	4	0	0	0	4	0	0	0	2	0	0	0
			(30)	(0)	(0)	(0)	(40)	(0)	(0)	(0)	(40)	(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

Organ	Findings	Group Name	50ppm				100ppm			
		No. of Animals on Study	10				10			
		Grade	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}										
kidney			<10>				<10>			
	mineralization:cortico-medullary junction		1	0	0	0	0	0	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Endocrine system}										
thyroid			<10>				<10>			
	ultimibranchial body remanet		1	0	0	0	2	0	0	0
			(10)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
{Reproductive system}										
ovary			<10>				<10>			
	cyst		0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Special sense organs/appendage}										
Harder gl			<10>				<10>			
	lymphocytic infiltration		2	0	0	0	3	1	0	0
			(20)	(0)	(0)	(0)	(30)	(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 J 1

IDENTITY OF PROPIONONITRILE IN THE 13-WEEK INHALATION STUDY

IDENTITY OF PROPIONONITRILE IN THE 13-WEEK INHALATION STUDY

Test Substance : Propiononitrile (Wako Pure Chemical Industries, Ltd.)

Lot No. : LDG4790

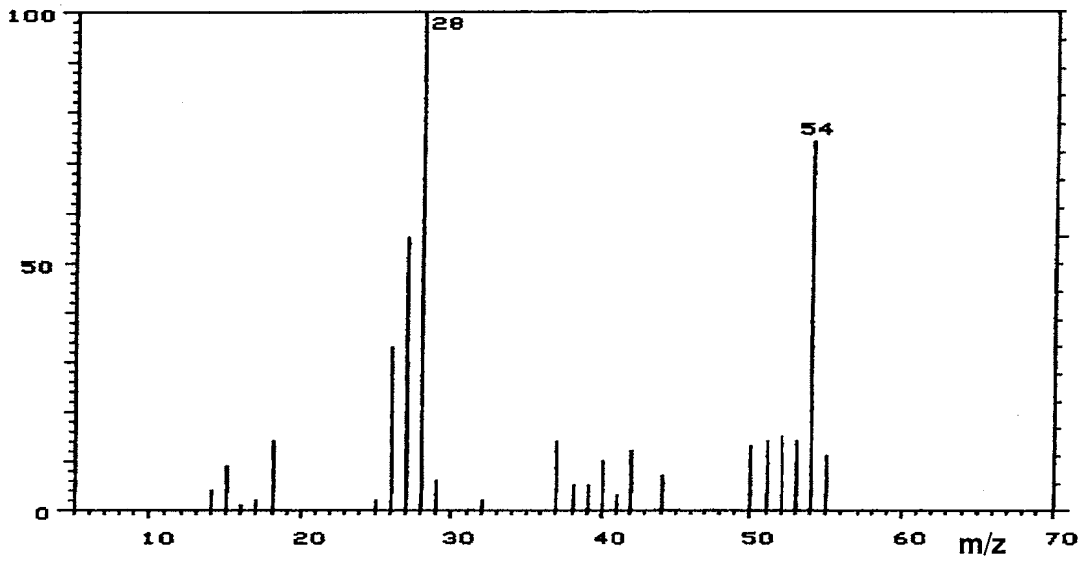
1. Spectral Data

Mass Spectrometry

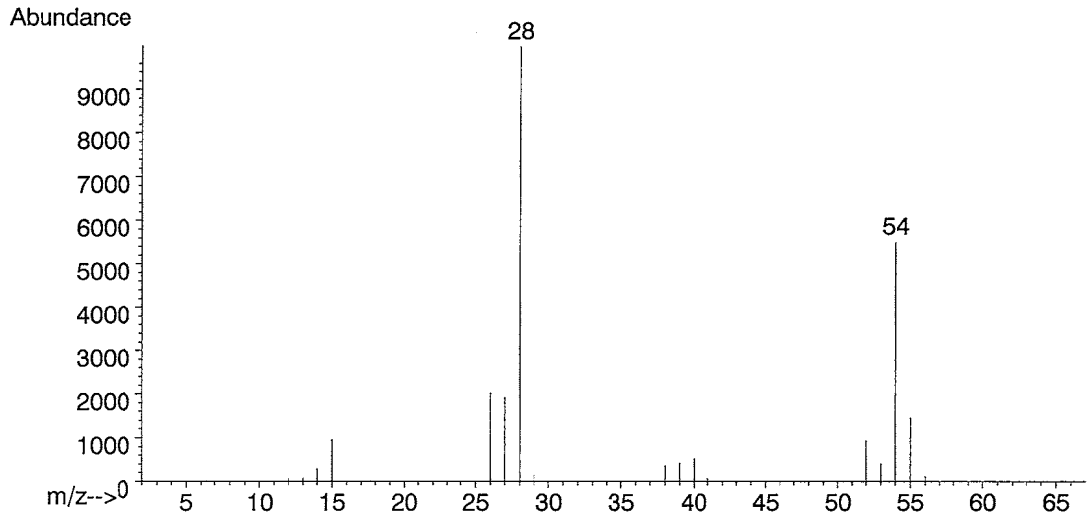
Instrument : Hitachi M-80B Mass Spectrometer

Ionization : EI (Electron Ionization)

Ionization Voltage : 70eV



Mass Spectrum of Test Substance



Mass Spectrum of Literature Data*

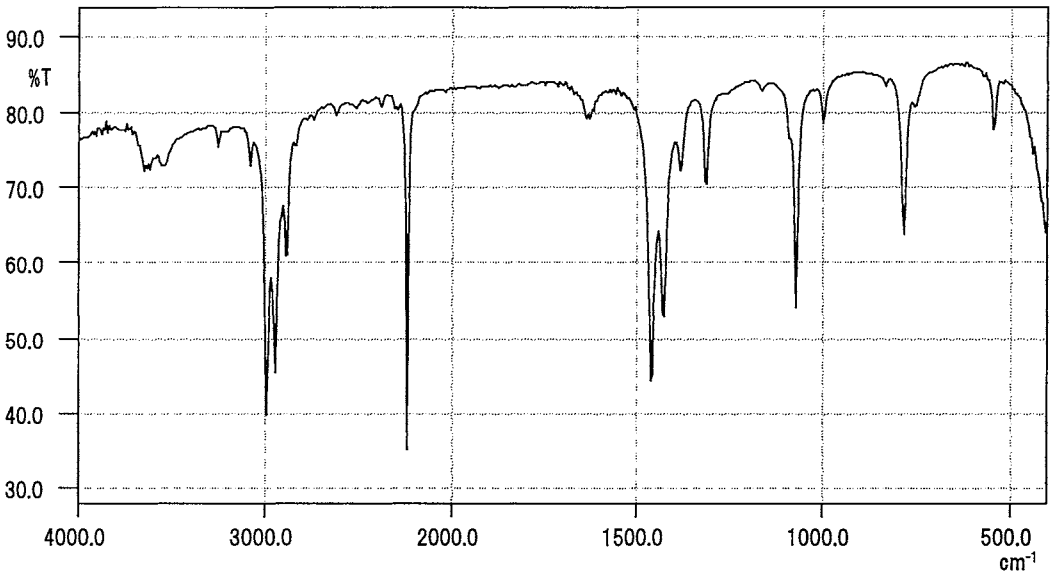
Result: The mass spectrum was consistent with literature spectrum.
(*McLafferty FW, ed. 1994. Wiley Registry of Mass Spectral Data. 6th ed. New York, NY : John Wiley and Sons.)

Infrared Spectrometry

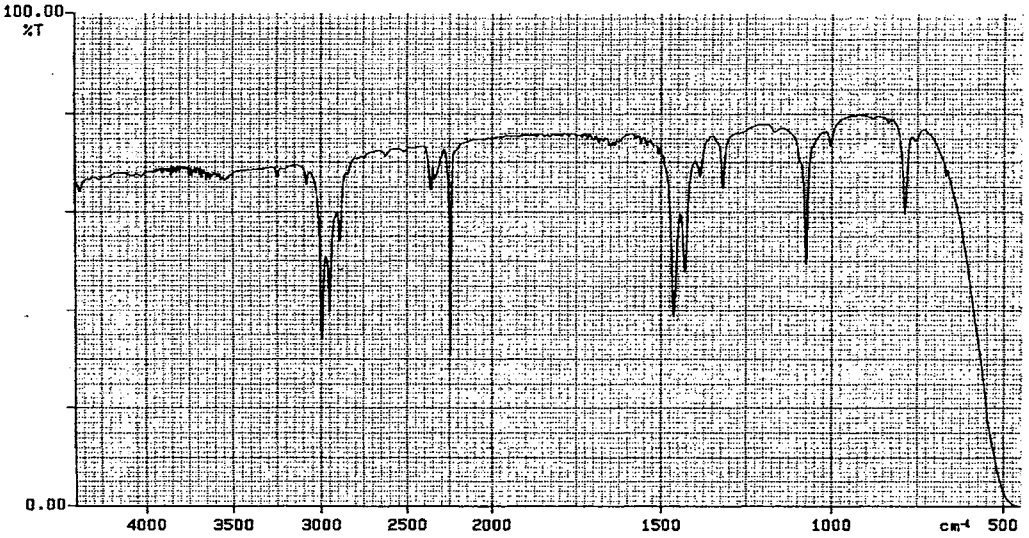
Instrument : Shimadzu FTIR-8200PC Infrared Spectrometer

Cell : KBr Liquid Cell

Resolution : 4 cm^{-1}



Infrared Spectrum of Test Substance



Infrared Spectrum of Literature Data*

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

2. Conclusion: The test substance was identified as propiononitrile by mass spectrum and infrared spectrum.

APPENDIX J 2

STABILITY OF PROPIONONITRILE IN THE 13-WEEK INHALATION STUDY

STABILITY OF PROPIONONITRILE IN THE 13-WEEK INHALATION STUDY

Test Substance : Propiononitrile (Wako Pure Chemical Industries, Ltd.)

Lot No. : LDG4790

1. Sample : This lot was used from 2002.9.16 to 2002.12.13. Test substance was stored in a dark place at room temperature.

2. Gas Chromatography

Instrument : Hewlett Packard 5890A Gas Chromatograph

Column : Methyl Silicone (0.53 mmϕ × 60 m)

Column Temperature: 80° C

Flow Rate : 10 mL/min

Detector : FID (Flame Ionization Detector)

Injection Volume : 1 μL

Date (date analyzed)	Peak No.	Retention Time (min)	Area (%)
2002.09.13	1	3.822	100
2002.12.27	1	3.817	100

Result: Gas chromatography indicated one major peak (peak No.1) analyzed on 2002.9.13 and one major peak (peak No.1) analyzed on 2002.12.27. No new trace impurity peak in the test substance analyzed on 2002.12.27 was detected.

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

APPENDIX K 1

CONCENTRATION OF PROPIONONITRILE IN THE INHALATION CHAMBER OF THE 13-WEEK INHALATION STUDY

CONCENTRATION OF PROPIONONITRILE IN THE INHALATION CHAMBER
OF THE 13-WEEK INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
6 ppm	6.0 ± 0.0
12 ppm	12.1 ± 0.1
25 ppm	25.2 ± 0.2
50 ppm	50.2 ± 0.3
100 ppm	100.1 ± 0.3

APPENDIX K 2

ENVIRONMENTAL CONDITIONS OF INHALATION CHAMBER IN THE 13-WEEK INHALATION STUDY OF PROPIONONITRILE

ENVIRONMENTAL CONDITIONS OF INHALATION CHAMBER IN THE 13-WEEK INHALATION STUDY OF PROPIONONITRILE

Group Name	Temperature(℃) Mean ± S.D.	Humidity(%) Mean ± S.D.	Ventilation Rate(L/min) Mean ± S.D.	Air Change(time/h) Mean
Control	22.4 ± 0.2	56.6 ± 0.6	212.5 ± 0.7	12.0
6ppm	22.5 ± 0.2	57.1 ± 0.5	212.5 ± 0.8	12.0
12ppm	22.6 ± 0.2	57.3 ± 0.4	212.3 ± 0.9	12.0
25ppm	22.6 ± 0.2	57.1 ± 0.5	212.2 ± 0.8	12.0
50ppm	22.7 ± 0.1	56.7 ± 0.5	212.1 ± 0.8	12.0
100ppm	22.5 ± 0.1	57.3 ± 0.6	212.4 ± 0.5	12.0

APPENDIX L 1

METHODS FOR HEMATOLOGY, BIOCHEMISTRY AND URINALYSIS IN THE 13-WEEK INHALATION STUDY OF PROPIONONITRILE

METHODS FOR HEMATOLOGY,BIOCHEMISTRY AND URINALYSIS IN THE 13-WEEK INHALATION STUDY OF PROPIONONITRILE

Item	Method
Hematology	
Red blood cell (RBC)	Light scattering method [1]
Hemoglobin (Hgb)	Cyanmethemoglobin method [1]
Hematocrit (Hct)	Calculated as RBC×MCV/10 [1]
Mean corpuscular volume (MCV)	Light scattering method [1]
Mean corpuscular hemoglobin (MCH)	Calculated as Hgb/RBC×10 [1]
Mean corpuscular hemoglobin concentration (MCHC)	Calculated as Hgb/Hct×100 [1]
Platelet	Light scattering method [1]
Reticulocyte	Light scattering method [1]
Prothrombin time	Quick one stage method [2]
Activated partial thromboplastin time (APTT)	Ellagic acid activaterd method [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)	JSCC 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 (ADVIA120 : Bayer Corporation)
2) Automatic coagulometer (Sysmex CA-5000 : Sysmex Corporation)
3) Automatic blood cell differential analyzer (MICROX HEG-120NA : OMRON Corporation)
4) Automatic analyzer (Hitachi 7070 : Hitachi,Ltd.)
5) Ames reagent strips for urinalysis (Multistix : Bayer Corporation)

APPENDIX L 2

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 13-WEEK INHALATION STUDY OF PROPIONONITRILE

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY IN THE 13-WEEK INHALATION STUDY OF PROPIONONITRILE

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	%	1
Prothrombin time	sec	1
Activated partial thromboplastin time (APTT)	sec	1
White blood cell (WBC)	$\times 10^3/\mu L$	2
Differential WBC	%	0
Biochemistry		
Total protein	g/dL	1
Albumin	g/dL	1
A/G ratio	–	1
T-bilirubin	mg/dL	2
Glucose	mg/dL	0
T-cholesterol	mg/dL	0
Triglyceride	mg/dL	0
Phospholipid	mg/dL	0
Glutamic oxaloacetic transaminase (GOT)	IU/L	0
Glutamic pyruvic transaminase (GPT)	IU/L	0
Lactate dehydrogenase (LDH)	IU/L	0
Alkaline phosphatase (ALP)	IU/L	0
γ-Glutamyl transpeptidase (γ-GTP)	IU/L	0
Creatine phosphokinase (CPK)	IU/L	0
Urea nitrogen	mg/dL	1
Creatinine	mg/dL	1
Sodium	mEq/L	0
Potassium	mEq/L	1
Chloride	mEq/L	0
Calcium	mg/dL	1
Inorganic phosphorus	mg/dL	1