アントラセンのラット及びマウスを用いた
経口投与によるがん原性予備試験(混餌試験)報告書

試験番号：ラット/0242；マウス/0243

APPENDIXES

(K1～S4)

APPENDIXES (CONTINUED)

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APPENDIXES (CONTINUED)

APPENDIX K 1

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

RAT : MALE : ALL ANIMALS

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
ALL ANIMALS (0-105W)

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Integumentary system/appandage]																		
skin/app		<50>																
	hemorrhage		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	epidermal cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	sebaceous hyperplasia		0 (0)	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 (2)	0 (0)	0 (0)
subcutis		<50>																
	abscess		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Respiratory system]																		
nasal cavit		<50>																
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammation		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	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 / No. of Animals on Study / Grade	Control 50				8000 ppm 50				20000 ppm 50				50000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Respiratory system]																		
nasal cavit			<50>				<50>				<50>				<50>			
	eosinophilic change:olfactory epithelium		22 (44)	23 (46)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0) **	0 (0)	0 (0)	0 (0)	0 (0) **	0 (0)	0 (0)	0 (0)	0 (0) **
	eosinophilic change:respiratory epithelium		35 (70)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0) **	0 (0)	0 (0)	0 (0)	0 (0) **	0 (0)	0 (0)	0 (0)	0 (0) **
	inflammation:foreign body		10 (20)	11 (22)	0 (0)	0 (0)	7 (14)	10 (20)	0 (0)	0 (0)	12 (24)	13 (26)	2 (4)	0 (0)	6 (12)	7 (14)	1 (2)	0 (0)
	respiratory metaplasia:olfactory epithelium		7 (14)	0 (0)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	respiratory metaplasia:gland		31 (62)	3 (6)	0 (0)	0 (0)	27 (54)	4 (8)	0 (0)	0 (0)	19 (38)	0 (0)	0 (0)	0 (0) **	18 (36)	1 (2)	0 (0)	0 (0) **
larynx			<50>				<50>				<50>				<50>			
	inflammatory infiltration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
lung			<50>				<50>				<50>				<50>			
	congestion		3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	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 / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Respiratory system]																		
lung		<50>	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	deposit of hemosiderin		(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation		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)	(2)	(0)	(0)
	inflammatory infiltration		1	0	0	0	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)
	osseous metaplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	bronchiolar-alveolar cell 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)	(2)	(0)	(0)
[Hematopoietic system]																		
bone marrow		<50>	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	congestion		(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	granulation		1	2	0	0	2	1	0	0	0	0	0	0	3	0	0	0
			(2)	(4)	(0)	(0)	(4)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(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 50 1 (%)	2 (%)	3 (%)	4 (%)	8000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	20000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	50000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
[Hematopoietic system]																		
bone marrow			<50>				<50>				<50>				<50>			
	increased hematopoiesis		2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	decreased hematopoiesis		0 (0)	0 (0)	1 (2)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)
	granulopoiesis:increased		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
lymph node			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
spleen			<50>				<50>				<50>				<50>			
	atrophy		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)
	congestion		7 (14)	4 (8)	0 (0)	0 (0)	8 (16)	1 (2)	0 (0)	0 (0)	12 (24)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)
	deposit of hemosiderin		1 (2)	1 (2)	1 (2)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)	8 (16)	1 (2)	0 (0)	0 (0)	9 (18)	5 (10)	0 (0)	0 (0) **

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
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(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 50				8000 ppm 50				20000 ppm 50				50000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Hematopoietic system]																		
spleen			<50>				<50>				<50>				<50>			
	fibrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		2 (4)	2 (4)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)	2 (4)	2 (4)	0 (0)	0 (0)	5 (10)	3 (6)	1 (2)	0 (0)
	engorgement of erythrocyte		0 (0)	0 (0)	0 (0)	0 (0)	13 (26)	2 (4)	0 (0)	0 (0) **	14 (28)	0 (0)	0 (0)	0 (0) **	10 (20)	0 (0)	0 (0)	0 (0) **
[Circulatory system]																		
heart			<50>				<50>				<50>				<50>			
	thrombus		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	myocardial fibrosis		3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	4 (8)	0 (0)	0 (0)
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
artery/aort			<50>				<50>				<50>				<50>			
	mineralization		0 (0)	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 (2)	0 (0)	0 (0)

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< 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 50				8000 ppm 50				20000 ppm 50				50000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Circulatory system]																		
artery/aort			<50>				<50>				<50>				<50>			
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Digestive system]																		
tongue			<50>				<50>				<50>				<50>			
	arteritis		3 (6)	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
salivary gl			<50>				<50>				<50>				<50>			
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
stomach			<50>				<50>				<50>				<50>			
	mineralization		0 (0)	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 (2)	0 (0)	0 (0)
	ulcer:forestomach		1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:forestomach		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)

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Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				8000 ppm 50				20000 ppm 50				50000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Digestive system]																		
stomach			<50>				<50>				<50>				<50>			
	erosion:glandular stomach		1	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	ulcer:glandular stomach		4	3	0	0	5	0	0	0	2	1	0	0	2	0	0	0
			(8)	(6)	(0)	(0)	(10)	(0)	(0)	(0)	(4)	(2)	(0)	(0)	(4)	(0)	(0)	(0)
	hyperplasia:glandular stomach		2	0	0	0	2	0	0	0	1	1	0	0	3	1	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(6)	(2)	(0)	(0)
small intes			<50>				<50>				<50>				<50>			
	diverticula		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
liver			<50>				<50>				<50>				<50>			
	herniation		0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	necrosis:central		1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
			(2)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	necrosis:focal		1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)

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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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Digestive system]																		
liver			<50>				<50>				<50>				<50>			
	collapse		0 (0)	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 (2)	0 (0)	0 (0)
	fatty change		0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	degeneration:central		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	granulation		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	clear cell focus		6 (12)	2 (4)	1 (2)	0 (0)	2 (4)	12 (24)	17 (34)	11 ** (22)	2 (4)	13 (26)	14 (28)	14 ** (28)	5 (10)	20 (40)	8 (16)	5 ** (10)
	acidophilic cell focus		4 (8)	0 (0)	0 (0)	0 (0)	5 (10)	14 (28)	14 (28)	7 ** (14)	3 (6)	9 (18)	13 (26)	15 ** (30)	3 (6)	6 (12)	8 (16)	15 ** (30)
	basophilic cell focus		5 (10)	8 (16)	0 (0)	0 (0)	8 (16)	9 (18)	4 (8)	0 (0)	6 (12)	13 (26)	0 (0)	1 (2)	11 (22)	9 (18)	3 (6)	0 (0)
	spongiosis hepatis		0 (0)	1 (2)	0 (0)	0 (0)	11 (22)	3 (6)	0 (0)	0 ** (0)	8 (16)	3 (6)	1 (2)	0 ** (0)	9 (18)	5 (10)	1 (2)	0 ** (0)

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< 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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
liver			<50>				<50>				<50>				<50>			
	bile duct hyperplasia		10	36	0	0	10	37	0	0	18	22	2	0 *	18	22	1	0 *
			(20)	(72)	(0)	(0)	(20)	(74)	(0)	(0)	(36)	(44)	(4)	(0)	(36)	(44)	(2)	(0)
	cholangiofibrosis		0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	biliary cyst		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)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		3	3	0	0	5	7	2	0	7	5	1	0	10	6	0	0 *
			(6)	(6)	(0)	(0)	(10)	(14)	(4)	(0)	(14)	(10)	(2)	(0)	(20)	(12)	(0)	(0)
	hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	arteritis		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)	(4)	(0)	(0)	(0)	(0)	(0)	(0)
[Urinary system]																		
kidney			<50>				<50>				<50>				<50>			
	hyperplasia:tubular epithelial cell		0	0	0	0	4	0	0	0	0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Urinary system]																		
kidney		<50>																
	infarct		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	deposit of hemosiderin		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	eosinophilic body		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	chronic nephropathy		6 (12)	12 (24)	17 (34)	10 (20)	1 (2)	15 (30)	11 (22)	15 (30)	3 (6)	13 (26)	14 (28)	15 (30)	7 (14)	13 (26)	16 (32)	7 (14)
	tubular necrosis		0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)
	papillary necrosis		0 (0)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	5 (10)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	mineralization:cortico-medullary junction		0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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 / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	8000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	20000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	50000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
[Urinary system]																		
kidney			<50>				<50>				<50>				<50>			
	mineralization:papilla		2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	2 (4)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	6 (12)	1 (2)	0 (0)	0 (0)
	mineralization:pelvis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	2 (4)	0 (0)	1 (2)
	mineralization:cortex		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	simple hyperplasia:transitional epithelium		2 (4)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)
	nodular hyperplasia:transitional epithelium		4 (8)	0 (0)	0 (0)	0 (0)	5 (10)	3 (6)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	eosinophilic droplet:proximal tubule		1 (2)	0 (0)	0 (0)	0 (0)	19 (38)	4 (8)	0 (0)	0 (0) **	27 (54)	5 (10)	0 (0)	0 (0) **	23 (46)	13 (26)	0 (0)	0 (0) **
urin bladd			<50>				<50>				<50>				<50>			
	hemorrhage		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	simple hyperplasia:transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Urinary system]																		
urin bladd			<50>				<50>				<50>				<50>			
	nodular hyperplasia:transitional epithelium		0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
[Endocrine system]																		
pituitary			<49>				<50>				<50>				<50>			
	angiectasis		2	1	0	0	1	0	0	0	0	0	0	0	1	2	0	0
			(4)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(4)	(0)	(0)
	cyst		1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia		6	2	0	0	5	1	0	0	6	3	0	0	7	2	0	0
			(12)	(4)	(0)	(0)	(10)	(2)	(0)	(0)	(12)	(6)	(0)	(0)	(14)	(4)	(0)	(0)
	hyperplasia:gland		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	Rathke pouch		0	0	0	0	2	0	0	0	2	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
thyroid			<50>				<50>				<50>				<50>			
	C-cell hyperplasia		1	2	0	0	4	0	0	0	3	0	0	0	2	3	0	0
			(2)	(4)	(0)	(0)	(8)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(6)	(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 50				8000 ppm 50				20000 ppm 50				50000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Endocrine system]																		
thyroid			<50>				<50>				<50>				<50>			
	focal follicular cell hyperplasia		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 (2)	0 (0)	0 (0)	0 (0)
panc islet			<50>				<50>				<50>				<50>			
	islet cell hyperplasia		1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
adrenal			<50>				<50>				<50>				<50>			
	peliosis-like lesion		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:medulla		3 (6)	5 (10)	0 (0)	0 (0)	4 (8)	7 (14)	0 (0)	0 (0)	7 (14)	4 (8)	0 (0)	0 (0)	5 (10)	1 (2)	0 (0)	0 (0)
	focal fatty change:cortex		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Reproductive system]																		
testis			<50>				<50>				<50>				<50>			
	atrophy		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	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 / No. of Animals on Study / Grade	Control 50				8000 ppm 50				20000 ppm 50				50000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Reproductive system]																		
testis		<50>					<50>				<50>				<50>			
	mineralization		6	0	0	0	7	0	0	0	14	1	0	0	16	1	0	0 *
			(12)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(28)	(2)	(0)	(0)	(32)	(2)	(0)	(0)
	arteritis		5	0	0	0	0	0	0	0	3	0	0	0	1	0	0	0
			(10)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	interstitial cell hyperplasia		8	0	0	0	2	0	0	0	2	0	0	0	3	0	0	0
			(16)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
prostate		<50>					<50>				<50>				<50>			
	inflammation		4	0	0	0	7	0	0	0	4	0	1	0	7	0	0	0
			(8)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(8)	(0)	(2)	(0)	(14)	(0)	(0)	(0)
	hyperplasia		8	0	0	0	6	0	0	0	11	0	0	0	11	0	0	0
			(16)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(22)	(0)	(0)	(0)	(22)	(0)	(0)	(0)
mammary gl		<50>					<50>				<50>				<50>			
	hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	galactocele		0	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(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 / No. of Animals on Study / Grade	Control 50				8000 ppm 50				20000 ppm 50				50000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Nervous system]																		
periph nerv			<50>				<50>				<50>				<50>			
	adhesion		0 (0)	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 (2)	0 (0)	0 (0)
[Special sense organs/appandage]																		
eye			<50>				<50>				<50>				<50>			
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		0 (0)	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 (2)	0 (0)	0 (0)
	cataract		0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)
	retinal atrophy		2 (4)	10 (20)	0 (0)	0 (0)	2 (4)	16 (32)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	4 (8)	9 (18)	0 (0)	0 (0)
	keratitis		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Harder gl			<50>				<50>				<50>				<50>			
	degeneration		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	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 / No. of Animals on Study / Grade	Control 50				8000 ppm 50				20000 ppm 50				50000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Special sense organs/appandage]																		
Harder gl			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0 (0)	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 (2)	0 (0)	0 (0)
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
nasolacr d			<50>				<50>				<50>				<50>			
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
[Body cavities]																		
retroperit			<50>				<50>				<50>				<50>			
	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)	1 (2)	0 (0)	0 (0)
adipose			<50>				<50>				<50>				<50>			
	necrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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

APPENDIX K 2

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

RAT : FEMALE : ALL ANIMALS

Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Integumentary system/appandage]																		
skin/app			<50>				<50>				<50>				<50>			
	inflammation		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)	(2)	(0)	(0)
[Respiratory system]																		
nasal cavit			<50>				<50>				<50>				<50>			
	follicle		1	0	0	0	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)
	atrophy		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)	(2)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		4	29	16	0	0	0	0	0 **	0	0	0	0 **	0	0	0	0 **
			(8)	(58)	(32)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	eosinophilic change:respiratory epithelium		36	0	0	0	0	0	0	0 **	0	0	0	0 **	0	0	0	0 **
			(72)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation:foreign body		5	2	0	0	1	1	0	0	2	1	0	0	6	1	0	0
			(10)	(4)	(0)	(0)	(2)	(2)	(0)	(0)	(4)	(2)	(0)	(0)	(12)	(2)	(0)	(0)
	disarrangement:olfactory epithelium		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)	(2)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
nasal cavit			<50>				<50>				<50>				<50>			
	respiratory metaplasia:olfactory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(16)	(0)	(0)	(0)
	respiratory metaplasia:gland		30	2	0	0	18	0	0	0 *	23	0	0	0	15	0	0	0 **
			(60)	(4)	(0)	(0)	(36)	(0)	(0)	(0)	(46)	(0)	(0)	(0)	(30)	(0)	(0)	(0)
	necrosis:olfactory epithelium		0	0	0	0	3	0	0	0	14	0	0	0 **	25	0	0	0 **
			(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(28)	(0)	(0)	(0)	(50)	(0)	(0)	(0)
lung			<50>				<50>				<50>				<50>			
	congestion		1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hemorrhage		1	0	0	0	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)
	inflammation		0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		1	0	0	0	1	0	0	0	3	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	lymphocytic infiltration		1	0	0	0	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)

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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
lung			<50>				<50>				<50>				<50>			
	accumulation of foamy cells		0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Hematopoietic system]																		
bone marrow			<50>				<50>				<50>				<50>			
	granulation		2	4	0	0	2	5	0	0	1	2	0	0	5	5	0	0
			(4)	(8)	(0)	(0)	(4)	(10)	(0)	(0)	(2)	(4)	(0)	(0)	(10)	(10)	(0)	(0)
	increased hematopoiesis		5	0	0	0	2	0	0	0	4	0	0	0	4	1	0	0
			(10)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(8)	(2)	(0)	(0)
	decreased hematopoiesis		0	1	0	0	0	0	0	0	0	0	0	0	0	2	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)
	granulopoiesis:increased		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
spleen			<50>				<50>				<50>				<50>			
	atrophy		1	0	0	0	0	1	0	0	0	2	0	0	0	1	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Hematopoietic system]																		
spleen			<50>				<50>				<50>				<50>			
	congestion		6	0	0	0	6	0	0	0	2	0	0	0	7	0	0	0
			(12)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(14)	(0)	(0)	(0)
	deposit of hemosiderin		15	9	0	0	22	8	1	0	28	7	1	0 *	21	9	0	0
			(30)	(18)	(0)	(0)	(44)	(16)	(2)	(0)	(56)	(14)	(2)	(0)	(42)	(18)	(0)	(0)
	extramedullary hematopoiesis		3	3	0	0	2	1	0	0	0	2	0	0	2	3	0	0
			(6)	(6)	(0)	(0)	(4)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(4)	(6)	(0)	(0)
	engorgement of erythrocyte		0	0	0	0	22	6	0	0 **	29	4	0	0 **	20	8	0	0 **
			(0)	(0)	(0)	(0)	(44)	(12)	(0)	(0)	(58)	(8)	(0)	(0)	(40)	(16)	(0)	(0)
[Circulatory system]																		
heart			<50>				<50>				<50>				<50>			
	thrombus		0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	necrosis:focal		1	0	0	0	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)
	mineralization		0	1	0	0	0	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)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
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(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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Circulatory system]																		
heart		<50>	1	0	0	0	2	0	0	0	0	1	0	0	3	0	0	0
	myocardial fibrosis		(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(6)	(0)	(0)	(0)
artery/aort		<50>	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
	arteritis		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
[Digestive system]																		
tooth		<50>	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
	epidermal cyst		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
tongue		<50>	1	0	0	0	1	1	0	0	2	1	0	0	1	0	0	0
	arteritis		(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(4)	(2)	(0)	(0)	(2)	(0)	(0)	(0)
stomach		<50>	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0
	mineralization		(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	arteritis		0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
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Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
stomach			<50>				<50>				<50>				<50>			
	ulcer:forestomach		0	0	0	0	0	1	0	0	0	0	1	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(2)	(0)	(0)	(0)
	hyperplasia:forestomach		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)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	erosion:glandular stomach		0	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	ulcer:glandular stomach		2	0	0	0	0	0	0	1	0	0	0	0	1	1	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
	hyperplasia:glandular stomach		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)	(2)	(0)	(0)	(0)
small intes			<50>				<50>				<50>				<50>			
	inflammation		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)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
liver			<50>				<50>				<50>				<50>			
	herniation		3	0	0	0	2	0	0	0	1	0	0	0	1	0	0	0
			(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Digestive system]																		
liver			<50>				<50>				<50>				<50>			
	peliosis-like lesion		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	necrosis:central		0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)
	necrosis:focal		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	fatty change		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	granulation		17 (34)	9 (18)	0 (0)	0 (0)	20 (40)	8 (16)	1 (2)	0 (0)	24 (48)	10 (20)	2 (4)	0 (0)	20 (40)	12 (24)	2 (4)	0 (0)
	extramedullary hematopoiesis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	clear cell focus		1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	6 (12)	0 (0)	0 * (0)	8 (16)	7 (14)	0 (0)	0 ** (0)	5 (10)	6 (12)	2 (4)	0 ** (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
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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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
liver			<50>				<50>				<50>				<50>			
	acidophilic cell focus		0	0	0	0	6	11	3	0 **	6	10	3	1 **	10	5	1	1 **
			(0)	(0)	(0)	(0)	(12)	(22)	(6)	(0)	(12)	(20)	(6)	(2)	(20)	(10)	(2)	(2)
	basophilic cell focus		12	10	0	0	7	11	0	0	9	10	1	1	9	5	1	0
			(24)	(20)	(0)	(0)	(14)	(22)	(0)	(0)	(18)	(20)	(2)	(2)	(18)	(10)	(2)	(0)
	mixed cell focus		0	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	spongiosis hepatis		0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	bile duct hyperplasia		4	0	0	0	3	1	0	0	1	1	0	0	1	1	0	0
			(8)	(0)	(0)	(0)	(6)	(2)	(0)	(0)	(2)	(2)	(0)	(0)	(2)	(2)	(0)	(0)
	cholangiofibrosis		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)	(2)	(0)	(0)	(0)
	biliary cyst		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		4	0	0	0	3	3	0	0	3	7	0	0 *	5	3	0	0
			(8)	(0)	(0)	(0)	(6)	(6)	(0)	(0)	(6)	(14)	(0)	(0)	(10)	(6)	(0)	(0)

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< a > a : Number of animals examined at the site
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(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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Urinary system]																		
kidney		<50>					<50>				<50>				<50>			
	infarct		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	cyst		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	chronic nephropathy		23 (46)	11 (22)	3 (6)	3 (6)	10 (20)	15 (30)	15 (30)	4 ** (8)	10 (20)	21 (42)	8 (16)	5 * (10)	17 (34)	18 (36)	7 (14)	0 (0)
	hydronephrosis		0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	tubular necrosis		0 (0)	3 (6)	4 (8)	0 (0)	0 (0)	1 (2)	3 (6)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)
	papillary necrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:cortico-medullary junction		21 (42)	2 (4)	0 (0)	0 (0)	13 (26)	4 (8)	0 (0)	0 (0)	15 (30)	0 (0)	0 (0)	0 (0)	13 (26)	0 (0)	0 (0)	0 (0)
	mineralization:papilla		2 (4)	0 (0)	0 (0)	0 (0)	11 (22)	1 (2)	0 (0)	0 * (0)	7 (14)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
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(c) c : b / a * 100
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Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Urinary system]																		
kidney			<50>				<50>				<50>				<50>			
	mineralization:pelvis		5	1	0	0	4	2	0	0	7	0	0	0	7	1	0	0
			(10)	(2)	(0)	(0)	(8)	(4)	(0)	(0)	(14)	(0)	(0)	(0)	(14)	(2)	(0)	(0)
	mineralization:cortex		0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	dilatation:tubular lumen		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	simple tubule hyperplasia		0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	atypical tubule hyperplasia		0	0	0	0	12	0	0	0 **	13	0	0	0 **	7	0	0	0 *
			(0)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(26)	(0)	(0)	(0)	(14)	(0)	(0)	(0)
	eosinophilic droplet:proximal tubule		2	0	0	0	14	32	0	0 **	4	38	0	0 **	8	37	0	0 **
			(4)	(0)	(0)	(0)	(28)	(64)	(0)	(0)	(8)	(76)	(0)	(0)	(16)	(74)	(0)	(0)
urin bladd			<50>				<50>				<50>				<50>			
	nodular hyperplasia:transitional epithelium		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Endocrine system]																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		6	5	0	0	0	1	0	0 **	1	0	0	0 **	4	0	0	0
			(12)	(10)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(8)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Endocrine system]																		
pituitary			<50>				<50>				<50>				<50>			
	cyst		3	0	0	0	8	0	0	0	1	1	0	0	9	0	0	0
			(6)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(18)	(0)	(0)	(0)
	hyperplasia		6	0	0	0	6	1	0	0	4	1	0	0	7	1	0	0
			(12)	(0)	(0)	(0)	(12)	(2)	(0)	(0)	(8)	(2)	(0)	(0)	(14)	(2)	(0)	(0)
	Rathke pouch		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
thyroid			<50>				<50>				<50>				<49>			
	cyst		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	ultimibranchial body remanet		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	C-cell hyperplasia		4	0	0	0	3	1	0	0	2	0	0	0	1	0	0	0
			(8)	(0)	(0)	(0)	(6)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	focal follicular cell hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
adrenal			<50>				<50>				<50>				<50>			
	peliosis-like lesion		6	0	0	0	5	0	0	0	2	1	0	0	5	0	0	0
			(12)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(4)	(2)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Endocrine system]																		
adrenal			<50>				<50>				<50>				<50>			
	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)	(2)	(0)	(0)	(0)
	hyperplasia:cortical cell		0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia:medulla		6	1	0	0	6	0	0	0	3	1	0	0	9	2	0	0
			(12)	(2)	(0)	(0)	(12)	(0)	(0)	(0)	(6)	(2)	(0)	(0)	(18)	(4)	(0)	(0)
	focal fatty change:cortex		2	1	0	0	3	0	0	0	3	0	0	0	0	0	0	0
			(4)	(2)	(0)	(0)	(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Reproductive system]																		
ovary			<50>				<50>				<50>				<50>			
	cyst		0	0	0	0	1	0	0	0	0	2	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)
uterus			<50>				<50>				<50>				<50>			
	dilatation		1	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Reproductive system]																		
uterus		<50>	3	2	0	0	4	1	0	0	4	5	0	0	9	2	0	0
	cystic endometrial hyperplasia		(6)	(4)	(0)	(0)	(8)	(2)	(0)	(0)	(8)	(10)	(0)	(0)	(18)	(4)	(0)	(0)
mammary gl		<50>	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	duct ectasia		(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia		3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Nervous system]																		
brain		<50>	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
	hemorrhage		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
[Special sense organs/appandage]																		
eye		<50>	0	3	0	0	0	2	0	0	0	3	0	0	0	2	0	0
	cataract		(0)	(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(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 50 1 (%)	2 (%)	3 (%)	4 (%)	8000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	20000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	50000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
[Special sense organs/appandage]																		
eye			<50>				<50>				<50>				<50>			
	retinal atrophy		9 (18)	4 (8)	0 (0)	0 (0)	5 (10)	4 (8)	1 (2)	0 (0)	1 (2)	9 (18)	0 (0)	0 * (0)	2 (4)	5 (10)	0 (0)	0 (0)
	keratitis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	vascularization:cornea		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Harder gl			<50>				<50>				<50>				<50>			
	atrophy		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	degeneration		0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		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 (2)	1 (2)	0 (0)	0 (0)
	lymphocytic infiltration		3 (6)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
nasolacr d			<50>				<50>				<50>				<50>			
	inflammation		1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	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 / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Musculoskeletal system]																		
muscle		<50>																
	hematoma		0 (0)	0 (0)	0 (0)	1 (2)	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		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
bone		<50>																
	osteosclerosis		5 (10)	6 (12)	0 (0)	0 (0)	4 (8)	3 (6)	3 (6)	0 (0)	2 (4)	4 (8)	1 (2)	0 (0)	2 (4)	2 (4)	2 (4)	0 (0)
[Body cavities]																		
pleura		<50>																
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
peritoneum		<50>																
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
retroperit		<50>																
	hematoma		0 (0)	0 (0)	0 (0)	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 (2)

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 3

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

RAT : MALE : SACRIFICED ANIMALS

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (105W)

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 33				8000 ppm 43				20000 ppm 43				50000 ppm 38			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Integumentary system/appandage]																		
skin/app			<33>				<43>				<43>				<38>			
	epidermal cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
subcutis			<33>				<43>				<43>				<38>			
	abscess		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Respiratory system]																		
nasal cavit			<33>				<43>				<43>				<38>			
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
	eosinophilic change:olfactory epithelium		15 (45)	18 (55)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0) **	0 (0)	0 (0)	0 (0)	0 (0) **	0 (0)	0 (0)	0 (0)	0 (0) **
	eosinophilic change:respiratory epithelium		26 (79)	1 (3)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0) **	0 (0)	0 (0)	0 (0)	0 (0) **	0 (0)	0 (0)	0 (0)	0 (0) **
	inflammation:foreign body		8 (24)	7 (21)	0 (0)	0 (0)	7 (16)	10 (23)	0 (0)	0 (0)	12 (28)	10 (23)	2 (5)	0 (0)	2 (5)	7 (18)	1 (3)	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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	33				43				43				38			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
nasal cavit			<33>				<43>				<43>				<38>			
	respiratory metaplasia:olfactory epithelium		4	0	0	0	2	0	0	0	4	0	0	0	4	0	0	0
			(12)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(9)	(0)	(0)	(0)	(11)	(0)	(0)	(0)
	respiratory metaplasia:gland		24	3	0	0	25	3	0	0	18	0	0	0 **	15	1	0	0 **
			(73)	(9)	(0)	(0)	(58)	(7)	(0)	(0)	(42)	(0)	(0)	(0)	(39)	(3)	(0)	(0)
lung			<33>				<43>				<43>				<38>			
	osseous metaplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	bronchiolar-alveolar cell 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)	(3)	(0)	(0)
[Hematopoietic system]																		
bone marrow			<33>				<43>				<43>				<38>			
	granulation		1	2	0	0	2	1	0	0	0	0	0	0	3	0	0	0
			(3)	(6)	(0)	(0)	(5)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	increased hematopoiesis		1	0	0	0	2	1	0	0	3	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(5)	(2)	(0)	(0)	(7)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	33				43				43				38			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Hematopoietic system]																		
bone marrow			<33>				<43>				<43>				<38>			
	decreased hematopoiesis		0	0	0	0	1	0	0	0	0	1	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(3)	(0)	(0)
	granulopoiesis:increased		1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
lymph node			<33>				<43>				<43>				<38>			
	lymphocytic infiltration		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
spleen			<33>				<43>				<43>				<38>			
	atrophy		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)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	congestion		6	4	0	0	8	1	0	0	12	0	0	0	6	0	0	0
			(18)	(12)	(0)	(0)	(19)	(2)	(0)	(0)	(28)	(0)	(0)	(0)	(16)	(0)	(0)	(0)
	deposit of hemosiderin		0	0	0	0	2	1	0	0	7	0	0	0 *	7	3	0	0 **
			(0)	(0)	(0)	(0)	(5)	(2)	(0)	(0)	(16)	(0)	(0)	(0)	(18)	(8)	(0)	(0)
	fibrosis		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(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 / No. of Animals on Study / Grade	Control 33				8000 ppm 43				20000 ppm 43				50000 ppm 38			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Hematopoietic system]																		
spleen			<33>				<43>				<43>				<38>			
	extramedullary hematopoiesis		2	0	0	0	2	2	0	0	1	1	0	0	2	2	0	0
			(6)	(0)	(0)	(0)	(5)	(5)	(0)	(0)	(2)	(2)	(0)	(0)	(5)	(5)	(0)	(0)
	engorgement of erythrocyte		0	0	0	0	12	2	0	0 **	14	0	0	0 **	10	0	0	0 **
			(0)	(0)	(0)	(0)	(28)	(5)	(0)	(0)	(33)	(0)	(0)	(0)	(26)	(0)	(0)	(0)
[Circulatory system]																		
heart			<33>				<43>				<43>				<38>			
	myocardial fibrosis		3	0	0	0	2	0	0	0	1	0	0	0	2	3	0	0
			(9)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(5)	(8)	(0)	(0)
	arteritis		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
artery/aort			<33>				<43>				<43>				<38>			
	arteritis		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Digestive system]																		
tongue			<33>				<43>				<43>				<38>			
	arteritis		3	1	0	0	3	0	0	0	3	0	0	0	2	1	0	0
			(9)	(3)	(0)	(0)	(7)	(0)	(0)	(0)	(7)	(0)	(0)	(0)	(5)	(3)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	33				43				43				38			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
salivary gl			<33>				<43>				<43>				<38>			
	inflammation		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)	(3)	(0)	(0)
stomach			<33>				<43>				<43>				<38>			
	ulcer:forestomach		0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	erosion:glandular stomach		1	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(5)	(0)	(0)	(0)
	ulcer:glandular stomach		2	0	0	0	5	0	0	0	2	0	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(5)	(0)	(0)	(0)
	hyperplasia:glandular stomach		1	0	0	0	2	0	0	0	1	1	0	0	2	1	0	0
			(3)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(5)	(3)	(0)	(0)
small intes			<33>				<43>				<43>				<38>			
	diverticula		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
liver			<33>				<43>				<43>				<38>			
	herniation		0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(5)	(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 / No. of Animals on Study / Grade	Control 33				8000 ppm 43				20000 ppm 43				50000 ppm 38			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Digestive system]																		
liver			<33>				<43>				<43>				<38>			
	necrosis:focal		1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	granulation		0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
	clear cell focus		6	2	1	0	2	10	17	11 **	1	12	14	14 **	2	19	8	5 **
			(18)	(6)	(3)	(0)	(5)	(23)	(40)	(26)	(2)	(28)	(33)	(33)	(5)	(50)	(21)	(13)
	acidophilic cell focus		4	0	0	0	4	13	14	7 **	2	9	13	15 **	2	5	8	15 **
			(12)	(0)	(0)	(0)	(9)	(30)	(33)	(16)	(5)	(21)	(30)	(35)	(5)	(13)	(21)	(39)
	basophilic cell focus		5	7	0	0	8	9	4	0	6	13	0	1	9	8	3	0
			(15)	(21)	(0)	(0)	(19)	(21)	(9)	(0)	(14)	(30)	(0)	(2)	(24)	(21)	(8)	(0)
	spongiosis hepatis		0	0	0	0	9	3	0	0 **	7	3	1	0 *	9	5	0	0 **
			(0)	(0)	(0)	(0)	(21)	(7)	(0)	(0)	(16)	(7)	(2)	(0)	(24)	(13)	(0)	(0)
	bile duct hyperplasia		4	28	0	0	9	33	0	0	16	22	2	0 *	15	19	1	0 *
			(12)	(85)	(0)	(0)	(21)	(77)	(0)	(0)	(37)	(51)	(5)	(0)	(39)	(50)	(3)	(0)
	cholangiofibrosis		0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(5)	(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 33				8000 ppm 43				20000 ppm 43				50000 ppm 38			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Digestive system]																		
liver			<33>				<43>				<43>				<38>			
	biliary cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
pancreas			<33>				<43>				<43>				<38>			
	atrophy		3 (9)	3 (9)	0 (0)	0 (0)	5 (12)	6 (14)	2 (5)	0 (0)	7 (16)	5 (12)	1 (2)	0 (0)	9 (24)	6 (16)	0 (0)	0 (0)
	hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Urinary system]																		
kidney			<33>				<43>				<43>				<38>			
	hyperplasia:tubular epithelial cell		0 (0)	0 (0)	0 (0)	0 (0)	4 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
	infarct		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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 / No. of Animals on Study / Grade	Control 33				8000 ppm 43				20000 ppm 43				50000 ppm 38			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Urinary system]																		
kidney			<33>				<43>				<43>				<38>			
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	deposit of hemosiderin		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	eosinophilic body		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
	chronic nephropathy		3 (9)	9 (27)	14 (42)	7 (21)	1 (2)	15 (35)	11 (26)	15 (35)	3 (7)	11 (26)	14 (33)	14 (33)	4 (11)	11 (29)	15 (39)	6 (16)
	papillary necrosis		0 (0)	0 (0)	0 (0)	0 (0)	4 (9)	0 (0)	0 (0)	0 (0)	5 (12)	1 (2)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
	mineralization:cortico-medullary junction		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:papilla		2 (6)	0 (0)	0 (0)	0 (0)	3 (7)	1 (2)	0 (0)	0 (0)	6 (14)	0 (0)	0 (0)	0 (0)	5 (13)	1 (3)	0 (0)	0 (0)
	mineralization:pelvis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	2 (5)	1 (3)	0 (0)	1 (3)

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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	33				43				43				38			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Urinary system]																		
kidney			<33>				<43>				<43>				<38>			
	simple hyperplasia:transitional epithelium		2	0	0	0	5	0	0	0	4	1	0	0	7	0	0	0
			(6)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(9)	(2)	(0)	(0)	(18)	(0)	(0)	(0)
	nodular hyperplasia:transitional epithelium		3	0	0	0	5	3	0	0	8	0	0	0	4	0	0	0
			(9)	(0)	(0)	(0)	(12)	(7)	(0)	(0)	(19)	(0)	(0)	(0)	(11)	(0)	(0)	(0)
	eosinophilic droplet:proximal tubule		1	0	0	0	19	4	0	0 **	26	5	0	0 **	20	13	0	0 **
			(3)	(0)	(0)	(0)	(44)	(9)	(0)	(0)	(60)	(12)	(0)	(0)	(53)	(34)	(0)	(0)
urin bladd			<33>				<43>				<43>				<38>			
	simple hyperplasia:transitional epithelium		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	nodular hyperplasia:transitional epithelium		0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(5)	(0)	(0)	(0)
[Endocrine system]																		
pituitary			<32>				<43>				<43>				<38>			
	angiectasis		2	1	0	0	1	0	0	0	0	0	0	0	1	1	0	0
			(6)	(3)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(3)	(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 33 1 (%)	Control 33 2 (%)	Control 33 3 (%)	Control 33 4 (%)	8000 ppm 43 1 (%)	8000 ppm 43 2 (%)	8000 ppm 43 3 (%)	8000 ppm 43 4 (%)	20000 ppm 43 1 (%)	20000 ppm 43 2 (%)	20000 ppm 43 3 (%)	20000 ppm 43 4 (%)	50000 ppm 38 1 (%)	50000 ppm 38 2 (%)	50000 ppm 38 3 (%)	50000 ppm 38 4 (%)
[Endocrine system]																		
pituitary			<32>				<43>				<43>				<38>			
	cyst		1 (3)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
	hyperplasia		5 (16)	2 (6)	0 (0)	0 (0)	4 (9)	1 (2)	0 (0)	0 (0)	6 (14)	3 (7)	0 (0)	0 (0)	7 (18)	2 (5)	0 (0)	0 (0)
	hyperplasia:gland		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Rathke pouch		0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
thyroid			<33>				<43>				<43>				<38>			
	C-cell hyperplasia		0 (0)	1 (3)	0 (0)	0 (0)	4 (9)	0 (0)	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)	0 (0)	1 (3)	3 (8)	0 (0)	0 (0)
panc islet			<33>				<43>				<43>				<38>			
	islet cell hyperplasia		1 (3)	1 (3)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
adrenal			<33>				<43>				<43>				<38>			
	peliosis-like lesion		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (5)	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	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	33				43				43				38			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Endocrine system]																		
adrenal			<33>				<43>				<43>				<38>			
	hyperplasia:medulla		3	4	0	0	4	7	0	0	7	4	0	0	5	1	0	0
			(9)	(12)	(0)	(0)	(9)	(16)	(0)	(0)	(16)	(9)	(0)	(0)	(13)	(3)	(0)	(0)
	focal fatty change:cortex		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Reproductive system]																		
testis			<33>				<43>				<43>				<38>			
	atrophy		1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0
			(3)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
	mineralization		5	0	0	0	7	0	0	0	13	1	0	0	10	0	0	0
			(15)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(30)	(2)	(0)	(0)	(26)	(0)	(0)	(0)
	arteritis		3	0	0	0	0	0	0	0	2	0	0	0	1	0	0	0
			(9)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
	interstitial cell hyperplasia		3	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(9)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
prostate			<33>				<43>				<43>				<38>			
	inflammation		3	0	0	0	6	0	0	0	2	0	1	0	7	0	0	0
			(9)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(5)	(0)	(2)	(0)	(18)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	33				43				43				38			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Reproductive system]																		
prostate			<33>				<43>				<43>				<38>			
	hyperplasia		8	0	0	0	6	0	0	0	10	0	0	0	11	0	0	0
			(24)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(23)	(0)	(0)	(0)	(29)	(0)	(0)	(0)
mammary gl			<33>				<43>				<43>				<38>			
	hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	galactocele		0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(3)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Special sense organs/appandage]																		
eye			<33>				<43>				<43>				<38>			
	cataract		0	4	0	0	0	4	0	0	0	3	0	0	0	4	0	0
			(0)	(12)	(0)	(0)	(0)	(9)	(0)	(0)	(0)	(7)	(0)	(0)	(0)	(11)	(0)	(0)
	retinal atrophy		2	7	0	0	1	16	0	0	0	9	0	0	4	9	0	0
			(6)	(21)	(0)	(0)	(2)	(37)	(0)	(0)	(0)	(21)	(0)	(0)	(11)	(24)	(0)	(0)
Harder gl			<33>				<43>				<43>				<38>			
	degeneration		0	0	0	0	1	0	0	0	0	0	0	0	0	2	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(5)	(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 33 1 (%)	Control 33 2 (%)	Control 33 3 (%)	Control 33 4 (%)	8000 ppm 43 1 (%)	8000 ppm 43 2 (%)	8000 ppm 43 3 (%)	8000 ppm 43 4 (%)	20000 ppm 43 1 (%)	20000 ppm 43 2 (%)	20000 ppm 43 3 (%)	20000 ppm 43 4 (%)	50000 ppm 38 1 (%)	50000 ppm 38 2 (%)	50000 ppm 38 3 (%)	50000 ppm 38 4 (%)
[Special sense organs/appandage]																		
Harder gl			<33>				<43>				<43>				<38>			
	lymphocytic infiltration		1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
nasolacr d			<33>				<43>				<43>				<38>			
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
[Body cavities]																		
retroperit			<33>				<43>				<43>				<38>			
	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)	1 (3)	0 (0)	0 (0)
adipose			<33>				<43>				<43>				<38>			
	necrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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

APPENDIX K 4

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

RAT : FEMALE : SACRIFICED ANIMALS

Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Integumentary system/appandage]																		
skin/app			<40>				<40>				<40>				<37>			
	inflammation		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)	(3)	(0)	(0)
[Respiratory system]																		
nasal cavit			<40>				<40>				<40>				<37>			
	follicle		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	atrophy		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)	(3)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		3	22	15	0	0	0	0	0 **	0	0	0	0 **	0	0	0	0 **
			(8)	(55)	(38)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	eosinophilic change:respiratory epithelium		30	0	0	0	0	0	0	0 **	0	0	0	0 **	0	0	0	0 **
			(75)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation:foreign body		4	2	0	0	1	1	0	0	2	1	0	0	4	1	0	0
			(10)	(5)	(0)	(0)	(3)	(3)	(0)	(0)	(5)	(3)	(0)	(0)	(11)	(3)	(0)	(0)
	disarrangement:olfactory epithelium		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)	(3)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
nasal cavit			<40>				<40>				<40>				<37>			
	respiratory metaplasia:olfactory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0 *
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(16)	(0)	(0)	(0)
	respiratory metaplasia:gland		24	1	0	0	17	0	0	0	21	0	0	0	14	0	0	0
			(60)	(3)	(0)	(0)	(43)	(0)	(0)	(0)	(53)	(0)	(0)	(0)	(38)	(0)	(0)	(0)
	necrosis:olfactory epithelium		0	0	0	0	3	0	0	0	14	0	0	0 **	24	0	0	0 **
			(0)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(35)	(0)	(0)	(0)	(65)	(0)	(0)	(0)
lung			<40>				<40>				<40>				<37>			
	hemorrhage		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	lymphocytic infiltration		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	accumulation of foamy cells		0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(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

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
SACRIFICED ANIMALS (105W)

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 40				8000 ppm 40				20000 ppm 40				50000 ppm 37			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Respiratory system]																		
lung			<40>				<40>				<40>				<37>			
	bronchiolar-alveolar cell hyperplasia		1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Hematopoietic system]																		
bone marrow			<40>				<40>				<40>				<37>			
	granulation		2 (5)	3 (8)	0 (0)	0 (0)	2 (5)	5 (13)	0 (0)	0 (0)	1 (3)	2 (5)	0 (0)	0 (0)	5 (14)	5 (14)	0 (0)	0 (0)
	increased hematopoiesis		1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
	granulopoiesis:increased		0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
spleen			<40>				<40>				<40>				<37>			
	congestion		6 (15)	0 (0)	0 (0)	0 (0)	6 (15)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	7 (19)	0 (0)	0 (0)	0 (0)
	deposit of hemosiderin		14 (35)	8 (20)	0 (0)	0 (0)	21 (53)	7 (18)	0 (0)	0 (0)	25 (63)	5 (13)	0 (0)	0 * (0)	21 (57)	6 (16)	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 / No. of Animals on Study / Grade	Control 40				8000 ppm 40				20000 ppm 40				50000 ppm 37			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Hematopoietic system]																		
spleen			<40>				<40>				<40>				<37>			
	extramedullary hematopoiesis		2 (5)	1 (3)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
	engorgement of erythrocyte		0 (0)	0 (0)	0 (0)	0 (0)	21 (53)	6 (15)	0 (0)	0 (0) **	27 (68)	4 (10)	0 (0)	0 (0) **	17 (46)	7 (19)	0 (0)	0 (0) **
[Circulatory system]																		
heart			<40>				<40>				<40>				<37>			
	thrombus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	myocardial fibrosis		0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	3 (8)	0 (0)	0 (0)	0 (0)
artery/aort			<40>				<40>				<40>				<37>			
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Digestive system]																		
tongue			<40>				<40>				<40>				<37>			
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)	2 (5)	1 (3)	0 (0)	0 (0)	1 (3)	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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
stomach			<40>				<40>				<40>				<37>			
	arteritis		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)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
	ulcer:forestomach		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)	(3)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:forestomach		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)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
	erosion:glandular stomach		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	ulcer:glandular stomach		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)	(3)	(0)	(0)	(0)
liver			<40>				<40>				<40>				<37>			
	herniation		3	0	0	0	2	0	0	0	1	0	0	0	1	0	0	0
			(8)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
	peliosis-like lesion		0	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	lymphocytic infiltration		0	1	0	0	0	1	0	0	1	1	0	0	0	0	0	0
			(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(3)	(3)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
liver			<40>				<40>				<40>				<37>			
	granulation		15	9	0	0	20	8	1	0	21	9	2	0	18	10	2	0
			(38)	(23)	(0)	(0)	(50)	(20)	(3)	(0)	(53)	(23)	(5)	(0)	(49)	(27)	(5)	(0)
	clear cell focus		1	0	0	0	3	6	0	0 *	8	7	0	0 **	5	6	2	0 **
			(3)	(0)	(0)	(0)	(8)	(15)	(0)	(0)	(20)	(18)	(0)	(0)	(14)	(16)	(5)	(0)
	acidophilic cell focus		0	0	0	0	6	11	3	0 **	6	10	3	1 **	7	4	1	1 **
			(0)	(0)	(0)	(0)	(15)	(28)	(8)	(0)	(15)	(25)	(8)	(3)	(19)	(11)	(3)	(3)
	basophilic cell focus		10	10	0	0	7	10	0	0	9	10	1	1	8	4	1	0
			(25)	(25)	(0)	(0)	(18)	(25)	(0)	(0)	(23)	(25)	(3)	(3)	(22)	(11)	(3)	(0)
	mixed cell focus		0	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(3)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)
	spongiosis hepatis		0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	bile duct hyperplasia		4	0	0	0	3	1	0	0	1	1	0	0	1	0	0	0
			(10)	(0)	(0)	(0)	(8)	(3)	(0)	(0)	(3)	(3)	(0)	(0)	(3)	(0)	(0)	(0)
	cholangiofibrosis		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)	(3)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
liver			<40>				<40>				<40>				<37>			
	biliary cyst		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
pancreas			<40>				<40>				<40>				<37>			
	atrophy		3	0	0	0	3	2	0	0	2	7	0	0 *	5	3	0	0
			(8)	(0)	(0)	(0)	(8)	(5)	(0)	(0)	(5)	(18)	(0)	(0)	(14)	(8)	(0)	(0)
[Urinary system]																		
kidney			<40>				<40>				<40>				<37>			
	infarct		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)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
	cyst		0	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(0)	(3)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
	chronic nephropathy		22	10	2	3	7	15	15	2 **	8	20	7	4 **	14	16	6	0
			(55)	(25)	(5)	(8)	(18)	(38)	(38)	(5)	(20)	(50)	(18)	(10)	(38)	(43)	(16)	(0)
	papillary necrosis		0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(3)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Urinary system]																		
kidney			<40>				<40>				<40>				<37>			
	mineralization:cortico-medullary junction		18	1	0	0	13	2	0	0	13	0	0	0	9	0	0	0
			(45)	(3)	(0)	(0)	(33)	(5)	(0)	(0)	(33)	(0)	(0)	(0)	(24)	(0)	(0)	(0)
	mineralization:papilla		1	0	0	0	10	0	0	0 **	6	0	0	0	3	0	0	0
			(3)	(0)	(0)	(0)	(25)	(0)	(0)	(0)	(15)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	mineralization:pelvis		5	0	0	0	3	1	0	0	4	0	0	0	6	0	0	0
			(13)	(0)	(0)	(0)	(8)	(3)	(0)	(0)	(10)	(0)	(0)	(0)	(16)	(0)	(0)	(0)
	mineralization:cortex		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	dilatation:tubular lumen		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	simple tubule hyperplasia		0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	atypical tubule hyperplasia		0	0	0	0	10	0	0	0 **	13	0	0	0 **	7	0	0	0 *
			(0)	(0)	(0)	(0)	(25)	(0)	(0)	(0)	(33)	(0)	(0)	(0)	(19)	(0)	(0)	(0)
	eosinophilic droplet:proximal tubule		2	0	0	0	11	29	0	0 **	1	37	0	0 **	4	33	0	0 **
			(5)	(0)	(0)	(0)	(28)	(73)	(0)	(0)	(3)	(93)	(0)	(0)	(11)	(89)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Urinary system]																		
urin bladd			<40>				<40>				<40>				<37>			
	nodular hyperplasia:transitional epithelium		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Endocrine system]																		
pituitary			<40>				<40>				<40>				<37>			
	angiectasis		6	3	0	0	0	1	0	0 *	1	0	0	0 *	3	0	0	0
			(15)	(8)	(0)	(0)	(0)	(3)	(0)	(0)	(3)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	cyst		3	0	0	0	7	0	0	0	1	1	0	0	9	0	0	0
			(8)	(0)	(0)	(0)	(18)	(0)	(0)	(0)	(3)	(3)	(0)	(0)	(24)	(0)	(0)	(0)
	hyperplasia		5	0	0	0	6	1	0	0	4	1	0	0	7	1	0	0
			(13)	(0)	(0)	(0)	(15)	(3)	(0)	(0)	(10)	(3)	(0)	(0)	(19)	(3)	(0)	(0)
	Rathke pouch		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
thyroid			<40>				<40>				<40>				<37>			
	ultimibranchial body remanet		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(3)	(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 / No. of Animals on Study / Grade	Control 40				8000 ppm 40				20000 ppm 40				50000 ppm 37			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Endocrine system]																		
thyroid			<40>				<40>				<40>				<37>			
	C-cell hyperplasia		4 (10)	0 (0)	0 (0)	0 (0)	3 (8)	1 (3)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
	focal follicular cell hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
adrenal			<40>				<40>				<40>				<37>			
	peliosis-like lesion		6 (15)	0 (0)	0 (0)	0 (0)	5 (13)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	5 (14)	0 (0)	0 (0)	0 (0)
	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)	1 (3)	0 (0)	0 (0)	0 (0)
	hyperplasia:cortical cell		0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
	hyperplasia:medulla		6 (15)	0 (0)	0 (0)	0 (0)	5 (13)	0 (0)	0 (0)	0 (0)	3 (8)	1 (3)	0 (0)	0 (0)	8 (22)	2 (5)	0 (0)	0 (0)
	focal fatty change:cortex		2 (5)	1 (3)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	3 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Reproductive system]																		
ovary			<40>				<40>				<40>				<37>			
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	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	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Reproductive system]																		
uterus			<40>				<40>				<40>				<37>			
	dilatation		0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
	cystic endometrial hyperplasia		3	2	0	0	3	1	0	0	4	4	0	0	7	2	0	0
			(8)	(5)	(0)	(0)	(8)	(3)	(0)	(0)	(10)	(10)	(0)	(0)	(19)	(5)	(0)	(0)
mammary gl			<40>				<40>				<40>				<37>			
	duct ectasia		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia		3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(8)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Special sense organs/appandage]																		
eye			<40>				<40>				<40>				<37>			
	cataract		0	1	0	0	0	1	0	0	0	2	0	0	0	1	0	0
			(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(3)	(0)	(0)
	retinal atrophy		8	3	0	0	5	4	1	0	1	8	0	0 *	2	5	0	0
			(20)	(8)	(0)	(0)	(13)	(10)	(3)	(0)	(3)	(20)	(0)	(0)	(5)	(14)	(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 40				8000 ppm 40				20000 ppm 40				50000 ppm 37			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Special sense organs/appandage]																		
eye			<40>				<40>				<40>				<37>			
	keratitis		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 (3)	0 (0)	0 (0)	0 (0)
	vascularization:cornea		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Harder gl			<40>				<40>				<40>				<37>			
	atrophy		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	degeneration		0 (0)	1 (3)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		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 (3)	1 (3)	0 (0)	0 (0)
	lymphocytic infiltration		3 (8)	1 (3)	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
nasolacr d			<40>				<40>				<40>				<37>			
	inflammation		1 (3)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)	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	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	40				40				40				37			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Musculoskeletal system]																		
bone			<40>				<40>				<40>				<37>			
	osteosclerosis		4	4	0	0	2	3	2	0	1	3	1	0	2	2	2	0
			(10)	(10)	(0)	(0)	(5)	(8)	(5)	(0)	(3)	(8)	(3)	(0)	(5)	(5)	(5)	(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 5

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

MOSUE : MALE :ALL ANIMALS

Organ	Findings	Group Name	Control				3200 ppm				8000 ppm				20000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Integumentary system/appandage]																		
subcutis			<49>				<50>				<50>				<50>			
	inflammation		0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Respiratory system]																		
nasal cavit			<49>				<50>				<50>				<50>			
	inflammation		1	0	0	0	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)
	inflammatory infiltration		0	1	0	0	0	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)
	eosinophilic change:olfactory epithelium		3	1	0	0	7	0	0	0	5	0	0	0	5	0	0	0
			(6)	(2)	(0)	(0)	(14)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	eosinophilic change:respiratory epithelium		3	2	1	0	4	0	0	0	2	2	1	0	6	1	0	0
			(6)	(4)	(2)	(0)	(8)	(0)	(0)	(0)	(4)	(4)	(2)	(0)	(12)	(2)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		6	1	0	0	7	0	0	0	1	3	0	0	11	2	0	0
			(12)	(2)	(0)	(0)	(14)	(0)	(0)	(0)	(2)	(6)	(0)	(0)	(22)	(4)	(0)	(0)
	respiratory metaplasia:gland		7	2	0	0	12	2	0	0	5	3	1	0	11	2	1	0
			(14)	(4)	(0)	(0)	(24)	(4)	(0)	(0)	(10)	(6)	(2)	(0)	(22)	(4)	(2)	(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				3200 ppm				8000 ppm				20000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Respiratory system]																		
lung			<49>				<50>				<50>				<50>			
	congestion		0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hemorrhage		0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	inflammatory infiltration		0	1	0	0	2	0	0	0	3	0	0	0	0	1	0	0
			(0)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Hematopoietic system]																		
spleen			<49>				<50>				<50>				<50>			
	atrophy		0	0	3	0	0	0	0	0	1	0	0	0	0	0	1	0
			(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(2)	(0)
	deposit of melanin		0	3	0	0	2	2	0	0	0	0	0	0	1	0	0	0
			(0)	(6)	(0)	(0)	(4)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	extramedullary hematopoiesis		1	2	0	0	0	5	2	0	1	4	2	0	1	3	1	0
			(2)	(4)	(0)	(0)	(0)	(10)	(4)	(0)	(2)	(8)	(4)	(0)	(2)	(6)	(2)	(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 49				3200 ppm 50				8000 ppm 50				20000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Hematopoietic system]																		
spleen			<49>				<50>				<50>				<50>			
	follicular hyperplasia		3 (6)	1 (2)	2 (4)	0 (0)	1 (2)	0 (0)	2 (4)	0 (0)	3 (6)	3 (6)	1 (2)	0 (0)	3 (6)	2 (4)	1 (2)	0 (0)
[Circulatory system]																		
heart			<49>				<50>				<50>				<50>			
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Digestive system]																		
oral cavity			<49>				<50>				<50>				<50>			
	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)	1 (2)	0 (0)	0 (0)
	inflammation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
tooth			<49>				<50>				<50>				<50>			
	cyst		0 (0)	2 (4)	0 (0)	0 (0)	1 (2)	1 (2)	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 / No. of Animals on Study / Grade	Control 49				3200 ppm 50				8000 ppm 50				20000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Digestive system]																		
tooth			<49>				<50>				<50>				<50>			
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	foreign body granuloma		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)
	dysplasia		13 (27)	4 (8)	0 (0)	0 (0)	7 (14)	2 (4)	0 (0)	0 (0)	4 (8)	0 (0)	2 (4)	0 ** (0)	8 (16)	5 (10)	0 (0)	0 (0)
tongue			<49>				<50>				<50>				<50>			
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
stomach			<49>				<50>				<50>				<50>			
	ulcer:forestomach		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:forestomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	erosion:glandular stomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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	Control				3200 ppm				8000 ppm				20000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Digestive system]																		
stomach			<49>				<50>				<50>				<50>			
	ulcer:glandular stomach		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:glandular stomach		1	1	0	0	0	2	0	0	2	1	0	0	1	1	0	0
			(2)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(4)	(2)	(0)	(0)	(2)	(2)	(0)	(0)
liver			<49>				<50>				<50>				<50>			
	angiectasis		0	0	1	0	0	0	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)
	necrosis		0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	leucocytic infiltration		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	granulation		10	1	0	0	8	2	0	0	7	0	0	0	7	0	0	0
			(20)	(2)	(0)	(0)	(16)	(4)	(0)	(0)	(14)	(0)	(0)	(0)	(14)	(0)	(0)	(0)
	clear cell focus		0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)
	basophilic cell focus		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)	(2)	(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 49				3200 ppm 50				8000 ppm 50				20000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Urinary system]																		
kidney			<49>				<50>				<50>				<50>			
	hyperplasia:tubular epithelial cell		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	infarct		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyaline droplet		2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	basophilic change		16 (33)	0 (0)	0 (0)	0 (0)	21 (42)	0 (0)	0 (0)	0 (0)	21 (42)	0 (0)	0 (0)	0 (0)	20 (40)	0 (0)	0 (0)	0 (0)
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory polyp		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
	vacuolization of proximal tubule		21 (43)	1 (2)	0 (0)	0 (0)	14 (28)	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 / No. of Animals on Study / Grade	Control 49				3200 ppm 50				8000 ppm 50				20000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Urinary system]																		
kidney			<49>				<50>				<50>				<50>			
	hydronephrosis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	2 (4)	0 (0)	3 (6)	2 (4)	1 (2)	0 (0)	1 (2)	0 (0)	2 (4)	0 (0)
	mineralization:papilla		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	mineralization:pelvis		3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	mineralization:cortex		33 (67)	1 (2)	0 (0)	0 (0)	34 (68)	1 (2)	0 (0)	0 (0)	33 (66)	3 (6)	0 (0)	0 (0)	33 (66)	0 (0)	0 (0)	0 (0)
urin bladd			<49>				<50>				<50>				<50>			
	hyaline droplet degeneration:superficial cell of transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	28 (56)	0 (0)	0 (0)	0 ** (0)	38 (76)	4 (8)	0 (0)	0 ** (0)	20 (40)	27 (54)	0 (0)	0 ** (0)
[Endocrine system]																		
pituitary			<49>				<50>				<49>				<50>			
	angiectasis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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 / No. of Animals on Study / Grade	Control 49				3200 ppm 50				8000 ppm 50				20000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Endocrine system]																		
pituitary			<49>				<50>				<49>				<50>			
	cyst		4 (8)	2 (4)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)
	hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Rathke pouch		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
thyroid			<49>				<50>				<50>				<50>			
	focal follicular cell hyperplasia		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
adrenal			<49>				<50>				<50>				<50>			
	extramedullary 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)	1 (2)	0 (0)	0 (0)	0 (0)
	spindle-cell hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:cortical cell		5 (10)	3 (6)	0 (0)	0 (0)	5 (10)	3 (6)	0 (0)	0 (0)	6 (12)	1 (2)	0 (0)	0 (0)	7 (14)	4 (8)	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				3200 ppm				8000 ppm				20000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Endocrine system]																		
adrenal			<49>				<50>				<50>				<50>			
	hyperplasia:medulla		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Reproductive system]																		
testis			<49>				<50>				<50>				<50>			
	atrophy		0	0	0	0	0	0	0	0	1	2	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(4)	(0)	(0)	(2)	(0)	(0)	(0)
	mineralization		12	0	0	0	6	0	0	0	7	1	0	0	11	0	0	0
			(24)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(14)	(2)	(0)	(0)	(22)	(0)	(0)	(0)
epididymis			<49>				<50>				<50>				<50>			
	lymphocytic infiltration		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	spermatogenic granuloma		0	3	0	0	1	0	0	0	0	2	0	0	1	1	0	0
			(0)	(6)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(2)	(2)	(0)	(0)
prep/cli gl			<49>				<50>				<50>				<50>			
	duct ectasia		0	5	0	0	0	2	0	0	0	1	0	0	0	2	0	0
			(0)	(10)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(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 49 1 (%)	Control 49 2 (%)	Control 49 3 (%)	Control 49 4 (%)	3200 ppm 50 1 (%)	3200 ppm 50 2 (%)	3200 ppm 50 3 (%)	3200 ppm 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)
[Reproductive system]																		
prep/cli gl			<49>				<50>				<50>				<50>			
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Nervous system]																		
brain			<49>				<50>				<50>				<50>			
	mineralization		17 (35)	16 (33)	0 (0)	0 (0)	18 (36)	24 (48)	0 (0)	0 (0)	9 (18)	22 (44)	0 (0)	0 (0)	14 (28)	29 (58)	0 (0)	0 * (0)
[Special sense organs/appandage]																		
Harder gl			<49>				<50>				<50>				<50>			
	degeneration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia		0 (0)	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 (2)	0 (0)	0 (0)
[Musculoskeletal system]																		
muscle			<49>				<50>				<50>				<50>			
	mineralization		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	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	Control				3200 ppm				8000 ppm				20000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Musculoskeletal system]																		
muscle			<49>				<50>				<50>				<50>			
	inflammatory infiltration		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Body cavities]																		
adipose			<49>				<50>				<50>				<50>			
	hemorrhage		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)	(2)	(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 K 6

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

MOSUE : FEMALE : ALL ANIMALS

Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
nasal cavit			<50>				<50>				<50>				<50>			
	atrophy		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation		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)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		2	0	0	0	1	1	0	0	1	0	0	0	3	1	0	0
			(4)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(2)	(0)	(0)
	eosinophilic change:respiratory epithelium		13	4	0	0	14	7	0	0	14	10	2	0	14	10	2	0
			(26)	(8)	(0)	(0)	(28)	(14)	(0)	(0)	(28)	(20)	(4)	(0)	(28)	(20)	(4)	(0)
	disarrangement:olfactory epithelium		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		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)	(2)	(0)	(0)	(0)
	respiratory metaplasia:gland		4	3	0	0	6	5	0	0	2	2	0	0	5	4	0	0
			(8)	(6)	(0)	(0)	(12)	(10)	(0)	(0)	(4)	(4)	(0)	(0)	(10)	(8)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Respiratory system]																		
lung			<50>				<50>				<50>				<50>			
	congestion		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	bronchiolar-alveolar cell hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Hematopoietic system]																		
bone marrow			<50>				<50>				<50>				<50>			
	granulation		1 (2)	0 (0)	0 (0)	0 (0)	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			<50>				<50>				<50>				<49>			
	atrophy		0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	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 50 1 (%)	2 (%)	3 (%)	4 (%)	8000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	20000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	50000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
[Hematopoietic system]																		
spleen			<50>				<50>				<50>				<49>			
	deposit of melanin		1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		0 (0)	3 (6)	2 (4)	0 (0)	3 (6)	4 (8)	4 (8)	0 (0)	0 (0)	5 (10)	5 (10)	0 (0)	2 (4)	5 (10)	1 (2)	0 (0)
	follicular hyperplasia		6 (12)	1 (2)	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	0 * (0)	2 (4)	1 (2)	2 (4)	0 (0)	1 (2)	1 (2)	1 (2)	0 (0)
[Circulatory system]																		
heart			<50>				<50>				<50>				<50>			
	thrombus		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	mineralization		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	granulation		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	arteritis		0 (0)	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 (2)	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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Digestive system]																		
tooth			<50>				<50>				<50>				<50>			
	cyst		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)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation		3	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	foreign body granuloma		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)	(2)	(0)	(0)	(0)
	dysplasia		1	0	0	0	1	1	0	0	2	1	1	0	1	3	2	0
			(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(4)	(2)	(2)	(0)	(2)	(6)	(4)	(0)
tongue			<49>				<50>				<50>				<50>			
	arteritis		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)	(2)	(0)	(0)	(0)
stomach			<49>				<50>				<50>				<50>			
	hyperplasia:forestomach		0	1	0	0	0	0	0	0	0	0	0	0	2	1	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(2)	(0)	(0)
	inflammation:forestomach		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)	(2)	(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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Digestive system]																		
stomach			<49>				<50>				<50>				<50>			
	erosion:glandular stomach		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:glandular stomach		2 (4)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
small intes			<50>				<50>				<50>				<50>			
	ulcer		0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
liver			<50>				<50>				<50>				<50>			
	angiectasis		0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
	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)	1 (2)	0 (0)	0 (0)	0 (0)
	granulation		7 (14)	18 (36)	3 (6)	0 (0)	6 (12)	12 (24)	0 (0)	0 (0)	14 (28)	5 (10)	1 (2)	0 ** (0)	6 (12)	10 (20)	1 (2)	0 (0)
	extramedullary hematopoiesis		1 (2)	0 (0)	0 (0)	0 (0)	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	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Digestive system]																		
liver			<50>				<50>				<50>				<50>			
	clear cell focus		1	1	0	3	1	1	0	0	0	3	0	1	1	10	3	1 *
			(2)	(2)	(0)	(6)	(2)	(2)	(0)	(0)	(0)	(6)	(0)	(2)	(2)	(20)	(6)	(2)
	acidophilic cell focus		0	0	1	1	1	1	0	3	0	0	1	0	0	1	1	3
			(0)	(0)	(2)	(2)	(2)	(2)	(0)	(6)	(0)	(0)	(2)	(0)	(0)	(2)	(2)	(6)
	basophilic cell focus		0	0	0	0	1	1	0	0	2	4	0	0 *	0	8	4	2 **
			(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(4)	(8)	(0)	(0)	(0)	(16)	(8)	(4)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		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)	(2)	(0)	(0)	(0)
[Urinary system]																		
kidney			<50>				<50>				<50>				<50>			
	atrophy		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)	(2)	(0)	(0)	(0)	(0)	(0)
	hyaline droplet		5	0	0	0	9	1	0	0	8	0	0	0	6	0	0	0
			(10)	(0)	(0)	(0)	(18)	(2)	(0)	(0)	(16)	(0)	(0)	(0)	(12)	(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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Urinary system]																		
kidney			<50>				<50>				<50>				<50>			
	deposit of amyloid		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (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)	1 (2)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	hydronephrosis		0 (0)	2 (4)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)
	tubular necrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:papilla		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	mineralization:pelvis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
urin bladd			<50>				<50>				<50>				<49>			
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Urinary system]																		
urin bladd			<50>				<50>				<50>				<49>			
	hyaline droplet degeneration:superficial cell of transit		0	0	0	0	5	0	0	0	12	0	0	0 **	24	0	0	0 **
	ional epithelium		(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(49)	(0)	(0)	(0)
[Endocrine system]																		
pituitary			<50>				<50>				<50>				<50>			
	cyst		7	0	0	0	8	0	0	0	8	0	0	0	6	0	0	0
			(14)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(12)	(0)	(0)	(0)
	hyperplasia		1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	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)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
adrenal			<50>				<50>				<50>				<50>			
	hyperplasia:cortical cell		0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	focal fatty change:cortex		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(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 / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	8000 ppm 50 1 (%)	8000 ppm 50 2 (%)	8000 ppm 50 3 (%)	8000 ppm 50 4 (%)	20000 ppm 50 1 (%)	20000 ppm 50 2 (%)	20000 ppm 50 3 (%)	20000 ppm 50 4 (%)	50000 ppm 50 1 (%)	50000 ppm 50 2 (%)	50000 ppm 50 3 (%)	50000 ppm 50 4 (%)
[Reproductive system]																		
ovary			<50>				<50>				<50>				<50>			
	angiectasis		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	cyst		4 (8)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
uterus			<50>				<50>				<50>				<50>			
	dilatation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)
	cystic endometrial hyperplasia		13 (26)	14 (28)	0 (0)	0 (0)	13 (26)	11 (22)	0 (0)	0 (0)	18 (36)	13 (26)	0 (0)	0 (0)	12 (24)	15 (30)	0 (0)	0 (0)
	xanthogranuloma		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Nervous system]																		
brain			<50>				<50>				<50>				<50>			
	mineralization		4 (8)	13 (26)	0 (0)	0 (0)	8 (16)	13 (26)	0 (0)	0 (0)	10 (20)	10 (20)	0 (0)	0 (0)	6 (12)	14 (28)	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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Special sense organs/appandage]																		
Harder gl			<50>				<50>				<50>				<50>			
	degeneration		1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia		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)	(2)	(0)	(0)	(0)
[Musculoskeletal system]																		
bone			<50>				<50>				<50>				<50>			
	fracture		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(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

APPENDIX K 7

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

MOSUE : MALE : SACRIFICED ANIMALS

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 41				3200 ppm 41				8000 ppm 37				20000 ppm 42			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Respiratory system]																		
nasal cavit			<41>				<41>				<37>				<42>			
	inflammation		1	0	0	0	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)
	eosinophilic change:olfactory epithelium		3	1	0	0	6	0	0	0	4	0	0	0	3	0	0	0
			(7)	(2)	(0)	(0)	(15)	(0)	(0)	(0)	(11)	(0)	(0)	(0)	(7)	(0)	(0)	(0)
	eosinophilic change:respiratory epithelium		3	2	1	0	4	0	0	0	1	1	1	0	6	1	0	0
			(7)	(5)	(2)	(0)	(10)	(0)	(0)	(0)	(3)	(3)	(3)	(0)	(14)	(2)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		5	1	0	0	7	0	0	0	1	3	0	0	10	2	0	0
			(12)	(2)	(0)	(0)	(17)	(0)	(0)	(0)	(3)	(8)	(0)	(0)	(24)	(5)	(0)	(0)
	respiratory metaplasia:gland		7	2	0	0	11	2	0	0	5	3	1	0	10	2	1	0
			(17)	(5)	(0)	(0)	(27)	(5)	(0)	(0)	(14)	(8)	(3)	(0)	(24)	(5)	(2)	(0)
lung			<41>				<41>				<37>				<42>			
	bronchiolar-alveolar cell hyperplasia		1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Hematopoietic system]																		
spleen			<41>				<41>				<37>				<42>			
	deposit of melanin		0	2	0	0	2	2	0	0	0	0	0	0	1	0	0	0
			(0)	(5)	(0)	(0)	(5)	(5)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(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				3200 ppm				8000 ppm				20000 ppm			
		No. of Animals on Study	41				41				37				42			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Hematopoietic system]																		
spleen			<41>				<41>				<37>				<42>			
	extramedullary hematopoiesis		1	0	0	0	0	2	0	0	1	0	0	0	0	1	0	0
			(2)	(0)	(0)	(0)	(0)	(5)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	follicular hyperplasia		3	1	2	0	1	0	2	0	3	3	1	0	3	2	1	0
			(7)	(2)	(5)	(0)	(2)	(0)	(5)	(0)	(8)	(8)	(3)	(0)	(7)	(5)	(2)	(0)
[Digestive system]																		
tooth			<41>				<41>				<37>				<42>			
	cyst		0	2	0	0	1	1	0	0	0	0	0	0	0	0	0	0
			(0)	(5)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation		0	0	0	0	0	0	0	0	1	0	0	0	5	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(12)	(0)	(0)	(0)
	foreign body granuloma		1	0	0	0	0	0	0	0	0	0	0	0	3	1	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(7)	(2)	(0)	(0)
	dysplasia		13	2	0	0	7	2	0	0	4	0	2	0 *	8	4	0	0
			(32)	(5)	(0)	(0)	(17)	(5)	(0)	(0)	(11)	(0)	(5)	(0)	(19)	(10)	(0)	(0)
tongue			<41>				<41>				<37>				<42>			
	arteritis		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(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 / No. of Animals on Study / Grade	Control 41				3200 ppm 41				8000 ppm 37				20000 ppm 42			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Digestive system]																		
stomach			<41>				<41>				<37>				<42>			
	ulcer:forestomach		1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:forestomach		0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia:glandular stomach		1	1	0	0	0	2	0	0	2	1	0	0	1	1	0	0
			(2)	(2)	(0)	(0)	(0)	(5)	(0)	(0)	(5)	(3)	(0)	(0)	(2)	(2)	(0)	(0)
liver			<41>				<41>				<37>				<42>			
	angiectasis		0	0	1	0	0	0	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)
	leucocytic infiltration		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	granulation		10	1	0	0	8	2	0	0	7	0	0	0	7	0	0	0
			(24)	(2)	(0)	(0)	(20)	(5)	(0)	(0)	(19)	(0)	(0)	(0)	(17)	(0)	(0)	(0)
	clear cell focus		0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)
	basophilic cell focus		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)	(2)	(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				3200 ppm				8000 ppm				20000 ppm			
		No. of Animals on Study	41				41				37				42			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
[Urinary system]																		
kidney			<41>				<41>				<37>				<42>			
	hyperplasia:tubular epithelial cell		0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	infarct		1	0	0	0	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)
	hyaline droplet		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)	(2)	(0)	(0)	(0)
	basophilic change		16	0	0	0	21	0	0	0	21	0	0	0	19	0	0	0
			(39)	(0)	(0)	(0)	(51)	(0)	(0)	(0)	(57)	(0)	(0)	(0)	(45)	(0)	(0)	(0)
	inflammation		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)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
	lymphocytic infiltration		0	1	0	0	0	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)
	vacuolization of proximal tubule		21	1	0	0	13	0	0	0	0	0	0	0 **	0	0	0	0 **
			(51)	(2)	(0)	(0)	(32)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hydronephrosis		0	0	0	0	1	0	0	0	3	2	0	0	1	0	1	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(8)	(5)	(0)	(0)	(2)	(0)	(2)	(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 41				3200 ppm 41				8000 ppm 37				20000 ppm 42			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Urinary system]																		
kidney			<41>				<41>				<37>				<42>			
	mineralization:papilla		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)	0 (0)
	mineralization:pelvis		3 (7)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (10)	0 (0)	0 (0)	0 (0)
	mineralization:cortex		30 (73)	1 (2)	0 (0)	0 (0)	29 (71)	1 (2)	0 (0)	0 (0)	30 (81)	3 (8)	0 (0)	0 (0)	31 (74)	0 (0)	0 (0)	0 (0)
urin bladd			<41>				<41>				<37>				<42>			
	hyaline droplet degeneration:superficial cell of transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	26 (63)	0 (0)	0 (0)	0 ** (0)	30 (81)	4 (11)	0 (0)	0 ** (0)	16 (38)	26 (62)	0 (0)	0 ** (0)
[Endocrine system]																		
pituitary			<41>				<41>				<36>				<42>			
	angiectasis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	cyst		3 (7)	2 (5)	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)	0 (0)	4 (11)	0 (0)	0 (0)	0 (0)	7 (17)	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 / No. of Animals on Study / Grade	Control 41 1 (%)	Control 41 2 (%)	Control 41 3 (%)	Control 41 4 (%)	3200 ppm 41 1 (%)	3200 ppm 41 2 (%)	3200 ppm 41 3 (%)	3200 ppm 41 4 (%)	8000 ppm 37 1 (%)	8000 ppm 37 2 (%)	8000 ppm 37 3 (%)	8000 ppm 37 4 (%)	20000 ppm 42 1 (%)	20000 ppm 42 2 (%)	20000 ppm 42 3 (%)	20000 ppm 42 4 (%)
[Endocrine system]																		
pituitary			<41>				<41>				<36>				<42>			
	hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Rathke pouch		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
thyroid			<41>				<41>				<37>				<42>			
	focal follicular cell hyperplasia		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
adrenal			<41>				<41>				<37>				<42>			
	extramedullary 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)	1 (2)	0 (0)	0 (0)	0 (0)
	spindle-cell hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:cortical cell		5 (12)	3 (7)	0 (0)	0 (0)	5 (12)	3 (7)	0 (0)	0 (0)	6 (16)	1 (3)	0 (0)	0 (0)	7 (17)	4 (10)	0 (0)	0 (0)
	hyperplasia:medulla		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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 / No. of Animals on Study / Grade	Control 41				3200 ppm 41				8000 ppm 37				20000 ppm 42			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Reproductive system]																		
testis			<41>				<41>				<37>				<42>			
	atrophy		0	0	0	0	0	0	0	0	1	2	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(5)	(0)	(0)	(2)	(0)	(0)	(0)
	mineralization		12	0	0	0	6	0	0	0	6	1	0	0	8	0	0	0
			(29)	(0)	(0)	(0)	(15)	(0)	(0)	(0)	(16)	(3)	(0)	(0)	(19)	(0)	(0)	(0)
epididymis			<41>				<41>				<37>				<42>			
	lymphocytic infiltration		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	spermatogenic granuloma		0	2	0	0	1	0	0	0	0	2	0	0	1	0	0	0
			(0)	(5)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(5)	(0)	(0)	(2)	(0)	(0)	(0)
prep/cli gl			<41>				<41>				<37>				<42>			
	duct ectasia		0	5	0	0	0	2	0	0	0	1	0	0	0	2	0	0
			(0)	(12)	(0)	(0)	(0)	(5)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(5)	(0)	(0)
	inflammation		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Nervous system]																		
brain			<41>				<41>				<37>				<42>			
	mineralization		14	15	0	0	15	21	0	0	7	21	0	0	9	28	0	0 *
			(34)	(37)	(0)	(0)	(37)	(51)	(0)	(0)	(19)	(57)	(0)	(0)	(21)	(67)	(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				3200 ppm				8000 ppm				20000 ppm			
		No. of Animals on Study	41				41				37				42			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Special sense organs/appandage]																		
Harder gl			<41>				<41>				<37>				<42>			
	degeneration		1	0	0	0	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)
	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)	(2)	(0)	(0)
[Body cavities]																		
adipose			<41>				<41>				<37>				<42>			
	hemorrhage		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)	(3)	(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 K 8

HISTOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

MOSUE : FEMALE : SACRIFICED ANIMALS

Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	35				31				34				34			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Respiratory system]																		
nasal cavit			<35>				<31>				<34>				<34>			
	atrophy		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	eosinophilic change:olfactory epithelium		2 (6)	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	2 (6)	1 (3)	0 (0)	0 (0)
	eosinophilic change:respiratory epithelium		8 (23)	3 (9)	0 (0)	0 (0)	9 (29)	5 (16)	0 (0)	0 (0)	10 (29)	8 (24)	2 (6)	0 (0)	12 (35)	9 (26)	2 (6)	0 * (0)
	disarrangement:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (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)	1 (3)	0 (0)	0 (0)	0 (0)
	respiratory metaplasia:gland		4 (11)	2 (6)	0 (0)	0 (0)	3 (10)	4 (13)	0 (0)	0 (0)	2 (6)	2 (6)	0 (0)	0 (0)	5 (15)	2 (6)	0 (0)	0 (0)
lung			<35>				<31>				<34>				<34>			
	inflammatory infiltration		1 (3)	0 (0)	0 (0)	0 (0)	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	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	35				31				34				34			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Respiratory system]																		
lung			<35>				<31>				<34>				<34>			
	lymphocytic infiltration		0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Hematopoietic system]																		
bone marrow			<35>				<31>				<34>				<34>			
	granulation		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
spleen			<35>				<31>				<34>				<33>			
	deposit of melanin		1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(3)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	extramedullary hematopoiesis		0	0	0	0	2	1	1	0	0	1	0	0	2	2	0	0
			(0)	(0)	(0)	(0)	(6)	(3)	(3)	(0)	(0)	(3)	(0)	(0)	(6)	(6)	(0)	(0)
	follicular hyperplasia		5	1	1	0	0	3	0	0	2	1	2	0	1	1	1	0
			(14)	(3)	(3)	(0)	(0)	(10)	(0)	(0)	(6)	(3)	(6)	(0)	(3)	(3)	(3)	(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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	35				31				34				34			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Circulatory system]																		
heart			<35>				<31>				<34>				<34>			
	thrombus		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization		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)	(3)	(0)	(0)	(0)
[Digestive system]																		
tooth			<35>				<31>				<34>				<34>			
	cyst		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)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation		2	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	foreign body granuloma		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)	(3)	(0)	(0)	(0)
	dysplasia		1	0	0	0	0	0	0	0	1	0	1	0	1	2	2	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(3)	(0)	(3)	(6)	(6)	(0)
stomach			<35>				<31>				<34>				<34>			
	hyperplasia:forestomach		0	1	0	0	0	0	0	0	0	0	0	0	2	1	0	0
			(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(3)	(0)	(0)

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Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	35				31				34				34			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
stomach			<35>				<31>				<34>				<34>			
	inflammation:forestomach		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)	(3)	(0)	(0)
	erosion:glandular stomach		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:glandular stomach		2	1	0	0	4	0	0	0	4	0	0	0	1	0	0	0
			(6)	(3)	(0)	(0)	(13)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
liver			<35>				<31>				<34>				<34>			
	angiectasis		0	0	1	0	0	0	1	0	0	3	0	0	2	1	0	0
			(0)	(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(9)	(0)	(0)	(6)	(3)	(0)	(0)
	necrosis		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)	(3)	(0)	(0)	(0)
	granulation		6	18	3	0	6	12	0	0	14	5	1	0 **	6	10	1	0
			(17)	(51)	(9)	(0)	(19)	(39)	(0)	(0)	(41)	(15)	(3)	(0)	(18)	(29)	(3)	(0)
	extramedullary hematopoiesis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	clear cell focus		1	1	0	3	1	1	0	0	0	3	0	1	1	10	3	1 **
			(3)	(3)	(0)	(9)	(3)	(3)	(0)	(0)	(0)	(9)	(0)	(3)	(3)	(29)	(9)	(3)

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Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	35				31				34				34			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Digestive system]																		
liver			<35>				<31>				<34>				<34>			
	acidophilic cell focus		0	0	1	1	1	1	0	2	0	0	1	0	0	1	1	2
			(0)	(0)	(3)	(3)	(3)	(3)	(0)	(6)	(0)	(0)	(3)	(0)	(0)	(3)	(3)	(6)
	basophilic cell focus		0	0	0	0	1	1	0	0	2	4	0	0 *	0	8	3	2 **
			(0)	(0)	(0)	(0)	(3)	(3)	(0)	(0)	(6)	(12)	(0)	(0)	(0)	(24)	(9)	(6)
pancreas			<35>				<31>				<34>				<34>			
	atrophy		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)	(3)	(0)	(0)	(0)
[Urinary system]																		
kidney			<35>				<31>				<34>				<34>			
	atrophy		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)	(3)	(0)	(0)	(0)	(0)	(0)
	hyaline droplet		1	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(3)	(3)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	deposit of amyloid		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(3)	(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	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	35				31				34				34			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Urinary system]																		
kidney			<35>				<31>				<34>				<34>			
	hyaline cast		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)	(3)	(0)	(0)	(0)
	lymphocytic infiltration		1	0	0	0	2	0	0	0	2	0	0	0	0	1	0	0
			(3)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(3)	(0)	(0)
	hydronephrosis		0	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(6)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization:papilla		2	0	0	0	2	0	0	0	0	0	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	mineralization:pelvis		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
urin bladd			<35>				<31>				<34>				<33>			
	lymphocytic infiltration		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyaline droplet degeneration:superficial cell of transit		0	0	0	0	3	0	0	0	11	0	0	0 **	20	0	0	0 **
	ional epithelium		(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(32)	(0)	(0)	(0)	(61)	(0)	(0)	(0)
[Endocrine system]																		
pituitary			<35>				<31>				<34>				<34>			
	cyst		4	0	0	0	5	0	0	0	6	0	0	0	5	0	0	0
			(11)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(18)	(0)	(0)	(0)	(15)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
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(c) c : b / a * 100
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Organ	Findings	Group Name	Control				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	35				31				34				34			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Endocrine system]																		
pituitary			<35>				<31>				<34>				<34>			
	hyperplasia		1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(3)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	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)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
adrenal			<35>				<31>				<34>				<34>			
	hyperplasia:cortical cell		0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(3)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	focal fatty change:cortex		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
[Reproductive system]																		
ovary			<35>				<31>				<34>				<34>			
	angiectasis		0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	cyst		4	0	0	0	5	0	0	0	7	0	0	0	3	0	0	0
			(11)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(21)	(0)	(0)	(0)	(9)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
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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				8000 ppm				20000 ppm				50000 ppm			
		No. of Animals on Study	35				31				34				34			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
[Reproductive system]																		
ovary			<35>				<31>				<34>				<34>			
	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
uterus			<35>				<31>				<34>				<34>			
	dilatation		0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
	cystic endometrial hyperplasia		11 (31)	14 (40)	0 (0)	0 (0)	12 (39)	10 (32)	0 (0)	0 (0)	15 (44)	11 (32)	0 (0)	0 (0)	9 (26)	15 (44)	0 (0)	0 (0)
	xanthogranuloma		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Nervous system]																		
brain			<35>				<31>				<34>				<34>			
	mineralization		2 (6)	10 (29)	0 (0)	0 (0)	6 (19)	10 (32)	0 (0)	0 (0)	10 (29)	7 (21)	0 (0)	0 * (0)	6 (18)	11 (32)	0 (0)	0 (0)
[Special sense organs/appandage]																		
Harder gl			<35>				<31>				<34>				<34>			
	degeneration		1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
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(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 35 1 (%)	Control 35 2 (%)	Control 35 3 (%)	Control 35 4 (%)	8000 ppm 31 1 (%)	8000 ppm 31 2 (%)	8000 ppm 31 3 (%)	8000 ppm 31 4 (%)	20000 ppm 34 1 (%)	20000 ppm 34 2 (%)	20000 ppm 34 3 (%)	20000 ppm 34 4 (%)	50000 ppm 34 1 (%)	50000 ppm 34 2 (%)	50000 ppm 34 3 (%)	50000 ppm 34 4 (%)
[Special sense organs/appandage]																		
Harder gl			<35>				<31>				<34>				<34>			
	hyperplasia		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 (3)	0 (0)	0 (0)	0 (0)
[Musculoskeletal system]																		
bone			<35>				<31>				<34>				<34>			
	fracture		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	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

APPENDIX L 1

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS-TIME RELATED

RAT : MALE

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS - TIME RELATED

Time-related Weeks	Items	Group Name	Control	8000 ppm	20000 ppm	50000 ppm
0 - 52	NO. OF EXAMINED ANIMALS		0	0	1	0
	NO. OF ANIMALS WITH TUMORS		0	0	0	0
	NO. OF ANIMALS WITH SINGLE TUMORS		0	0	0	0
	NO. OF ANIMALS WITH MULTIPLE TUMORS		0	0	0	0
	NO. OF BENIGN TUMORS		0	0	0	0
	NO. OF MALIGNANT TUMORS		0	0	0	0
	NO. OF TOTAL TUMORS		0	0	0	0
53 - 78	NO. OF EXAMINED ANIMALS		3	1	1	2
	NO. OF ANIMALS WITH TUMORS		3	1	1	2
	NO. OF ANIMALS WITH SINGLE TUMORS		1	1	1	0
	NO. OF ANIMALS WITH MULTIPLE TUMORS		2	0	0	2
	NO. OF BENIGN TUMORS		4	0	0	3
	NO. OF MALIGNANT TUMORS		1	1	1	1
	NO. OF TOTAL TUMORS		5	1	1	4
79 - 104	NO. OF EXAMINED ANIMALS		14	6	5	10
	NO. OF ANIMALS WITH TUMORS		14	6	5	10
	NO. OF ANIMALS WITH SINGLE TUMORS		4	1	0	1
	NO. OF ANIMALS WITH MULTIPLE TUMORS		10	5	5	9
	NO. OF BENIGN TUMORS		24	7	10	19
	NO. OF MALIGNANT TUMORS		7	4	5	5
	NO. OF TOTAL TUMORS		31	11	15	24
105 - 105	NO. OF EXAMINED ANIMALS		33	43	43	38
	NO. OF ANIMALS WITH TUMORS		33	42	43	38
	NO. OF ANIMALS WITH SINGLE TUMORS		14	8	8	8
	NO. OF ANIMALS WITH MULTIPLE TUMORS		19	34	35	30
	NO. OF BENIGN TUMORS		56	90	93	69
	NO. OF MALIGNANT TUMORS		10	11	13	20
	NO. OF TOTAL TUMORS		66	101	106	89

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS - TIME RELATED

Time-related Weeks	Items	Group Name	Control	8000 ppm	20000 ppm	50000 ppm
0 - 105	NO. OF EXAMINED ANIMALS		50	50	50	50
	NO. OF ANIMALS WITH TUMORS		50	49	49	50
	NO. OF ANIMALS WITH SINGLE TUMORS		19	10	9	9
	NO. OF ANIMALS WITH MULTIPLE TUMORS		31	39	40	41
	NO. OF BENIGN TUMORS		84	97	103	91
	NO. OF MALIGNANT TUMORS		18	16	19	26
	NO. OF TOTAL TUMORS		102	113	122	117

APPENDIX L 2

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS-TIME RELATED

RAT : FEMALE

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS - TIME RELATED

Time-related Weeks	Items	Group Name	Control	8000 ppm	20000 ppm	50000 ppm
0 - 52	NO. OF EXAMINED ANIMALS		0	0	1	1
	NO. OF ANIMALS WITH TUMORS		0	0	1	1
	NO. OF ANIMALS WITH SINGLE TUMORS		0	0	1	1
	NO. OF ANIMALS WITH MULTIPLE TUMORS		0	0	0	0
	NO. OF BENIGN TUMORS		0	0	1	0
	NO. OF MALIGNANT TUMORS		0	0	0	1
	NO. OF TOTAL TUMORS		0	0	1	1
53 - 78	NO. OF EXAMINED ANIMALS		2	4	2	1
	NO. OF ANIMALS WITH TUMORS		1	4	2	1
	NO. OF ANIMALS WITH SINGLE TUMORS		1	3	2	1
	NO. OF ANIMALS WITH MULTIPLE TUMORS		0	1	0	0
	NO. OF BENIGN TUMORS		1	1	1	0
	NO. OF MALIGNANT TUMORS		0	4	1	1
	NO. OF TOTAL TUMORS		1	5	2	1
79 - 104	NO. OF EXAMINED ANIMALS		8	6	7	11
	NO. OF ANIMALS WITH TUMORS		7	6	7	10
	NO. OF ANIMALS WITH SINGLE TUMORS		3	5	5	6
	NO. OF ANIMALS WITH MULTIPLE TUMORS		4	1	2	4
	NO. OF BENIGN TUMORS		6	4	7	12
	NO. OF MALIGNANT TUMORS		7	3	3	6
	NO. OF TOTAL TUMORS		13	7	10	18
105 - 105	NO. OF EXAMINED ANIMALS		40	40	40	37
	NO. OF ANIMALS WITH TUMORS		24	23	26	25
	NO. OF ANIMALS WITH SINGLE TUMORS		18	11	9	18
	NO. OF ANIMALS WITH MULTIPLE TUMORS		6	12	17	7
	NO. OF BENIGN TUMORS		28	32	42	29
	NO. OF MALIGNANT TUMORS		6	5	11	7
	NO. OF TOTAL TUMORS		34	37	53	36

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS - TIME RELATED

Time-related Weeks	Items	Group Name	Control	8000 ppm	20000 ppm	50000 ppm
0 - 105	NO. OF EXAMINED ANIMALS		50	50	50	50
	NO. OF ANIMALS WITH TUMORS		32	33	36	37
	NO. OF ANIMALS WITH SINGLE TUMORS		22	19	17	26
	NO. OF ANIMALS WITH MULTIPLE TUMORS		10	14	19	11
	NO. OF BENIGN TUMORS		35	37	51	41
	NO. OF MALIGNANT TUMORS		13	12	15	15
	NO. OF TOTAL TUMORS		48	49	66	56

APPENDIX L 3

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS-TIME RELATED

MOUSE : MALE

STUDY NO. : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
SEX : MALE

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS - TIME RELATED

Time-related Weeks	Items	Group Name	Control	3200 ppm	8000 ppm	20000 ppm
0 - 52	NO. OF EXAMINED ANIMALS		1	2	1	0
	NO. OF ANIMALS WITH TUMORS		0	1	0	0
	NO. OF ANIMALS WITH SINGLE TUMORS		0	1	0	0
	NO. OF ANIMALS WITH MULTIPLE TUMORS		0	0	0	0
	NO. OF BENIGN TUMORS		0	0	0	0
	NO. OF MALIGNANT TUMORS		0	1	0	0
	NO. OF TOTAL TUMORS		0	1	0	0
53 - 78	NO. OF EXAMINED ANIMALS		2	0	5	1
	NO. OF ANIMALS WITH TUMORS		1	0	3	1
	NO. OF ANIMALS WITH SINGLE TUMORS		1	0	2	1
	NO. OF ANIMALS WITH MULTIPLE TUMORS		0	0	1	0
	NO. OF BENIGN TUMORS		0	0	0	0
	NO. OF MALIGNANT TUMORS		1	0	4	1
	NO. OF TOTAL TUMORS		1	0	4	1
79 - 104	NO. OF EXAMINED ANIMALS		5	7	7	7
	NO. OF ANIMALS WITH TUMORS		2	5	4	7
	NO. OF ANIMALS WITH SINGLE TUMORS		1	4	4	7
	NO. OF ANIMALS WITH MULTIPLE TUMORS		1	1	0	0
	NO. OF BENIGN TUMORS		0	1	0	0
	NO. OF MALIGNANT TUMORS		3	5	4	7
	NO. OF TOTAL TUMORS		3	6	4	7
105 - 105	NO. OF EXAMINED ANIMALS		41	41	37	42
	NO. OF ANIMALS WITH TUMORS		17	21	13	15
	NO. OF ANIMALS WITH SINGLE TUMORS		16	18	10	13
	NO. OF ANIMALS WITH MULTIPLE TUMORS		1	3	3	2
	NO. OF BENIGN TUMORS		8	12	9	9
	NO. OF MALIGNANT TUMORS		10	12	7	8
	NO. OF TOTAL TUMORS		18	24	16	17

STUDY NO. : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
SEX : MALE

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS - TIME RELATED

Time-related Weeks	Items	Group Name	Control	3200 ppm	8000 ppm	20000 ppm
0 - 105	NO. OF EXAMINED ANIMALS		49	50	50	50
	NO. OF ANIMALS WITH TUMORS		20	27	20	23
	NO. OF ANIMALS WITH SINGLE TUMORS		18	23	16	21
	NO. OF ANIMALS WITH MULTIPLE TUMORS		2	4	4	2
	NO. OF BENIGN TUMORS		8	13	9	9
	NO. OF MALIGNANT TUMORS		14	18	15	16
	NO. OF TOTAL TUMORS		22	31	24	25

APPENDIX L4

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS-TIME RELATED

MOUSE: FEMALE

STUDY NO. : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
SEX : FEMALE

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS - TIME RELATED

Time-related Weeks	Items	Group Name	Control	8000 ppm	20000 ppm	50000 ppm
0 - 52	NO. OF EXAMINED ANIMALS		0	0	1	0
	NO. OF ANIMALS WITH TUMORS		0	0	1	0
	NO. OF ANIMALS WITH SINGLE TUMORS		0	0	1	0
	NO. OF ANIMALS WITH MULTIPLE TUMORS		0	0	0	0
	NO. OF BENIGN TUMORS		0	0	0	0
	NO. OF MALIGNANT TUMORS		0	0	1	0
	NO. OF TOTAL TUMORS		0	0	1	0
53 - 78	NO. OF EXAMINED ANIMALS		4	2	2	4
	NO. OF ANIMALS WITH TUMORS		3	2	2	3
	NO. OF ANIMALS WITH SINGLE TUMORS		2	2	2	1
	NO. OF ANIMALS WITH MULTIPLE TUMORS		1	0	0	2
	NO. OF BENIGN TUMORS		2	0	0	1
	NO. OF MALIGNANT TUMORS		2	2	2	4
	NO. OF TOTAL TUMORS		4	2	2	5
79 - 104	NO. OF EXAMINED ANIMALS		11	17	13	12
	NO. OF ANIMALS WITH TUMORS		9	17	13	11
	NO. OF ANIMALS WITH SINGLE TUMORS		9	14	9	7
	NO. OF ANIMALS WITH MULTIPLE TUMORS		0	3	4	4
	NO. OF BENIGN TUMORS		0	3	3	2
	NO. OF MALIGNANT TUMORS		9	18	15	13
	NO. OF TOTAL TUMORS		9	21	18	15
105 - 105	NO. OF EXAMINED ANIMALS		35	31	34	34
	NO. OF ANIMALS WITH TUMORS		21	21	23	25
	NO. OF ANIMALS WITH SINGLE TUMORS		16	13	19	12
	NO. OF ANIMALS WITH MULTIPLE TUMORS		5	8	4	13
	NO. OF BENIGN TUMORS		10	10	14	25
	NO. OF MALIGNANT TUMORS		18	21	13	17
	NO. OF TOTAL TUMORS		28	31	27	42

STUDY NO. : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
SEX : FEMALE

NUMBER OF ANIMALS WITH TUMORS AND NUMBER OF TUMORS - TIME RELATED

Time-related Weeks	Items	Group Name	Control	8000 ppm	20000 ppm	50000 ppm
0 - 105	NO. OF EXAMINED ANIMALS		50	50	50	50
	NO. OF ANIMALS WITH TUMORS		33	40	39	39
	NO. OF ANIMALS WITH SINGLE TUMORS		27	29	31	20
	NO. OF ANIMALS WITH MULTIPLE TUMORS		6	11	8	19
	NO. OF BENIGN TUMORS		12	13	17	28
	NO. OF MALIGNANT TUMORS		29	41	31	34
	NO. OF TOTAL TUMORS		41	54	48	62

APPENDIX M 1

HISTOLOGICAL FINDINGS : NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

RAT : MALE :

Organ	Findings	Group Name / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Integumentary system/appandage]						
skin/app			<50>	<50>	<50>	<50>
	squamous cell papilloma		1 (2%)	0 (0%)	1 (2%)	1 (2%)
	trichoepithelioma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
	keratoacanthoma		4 (8%)	3 (6%)	2 (4%)	4 (8%)
	sebaceous adenoma		0 (0%)	1 (2%)	1 (2%)	0 (0%)
	squamous cell carcinoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
subcutis			<50>	<50>	<50>	<50>
	fibroma		2 (4%)	4 (8%)	1 (2%)	4 (8%)
	lipoma		0 (0%)	1 (2%)	0 (0%)	0 (0%)
	fibrosarcoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
	schwannoma:malignant		1 (2%)	0 (0%)	1 (2%)	0 (0%)
[Respiratory system]						
lung			<50>	<50>	<50>	<50>
	bronchiolar-alveolar adenoma		0 (0%)	3 (6%)	3 (6%)	2 (4%)
	osteosarcoma		0 (0%)	1 (2%)	0 (0%)	0 (0%)
[Hematopoietic system]						
bone marrow			<50>	<50>	<50>	<50>
	histiocytic sarcoma		0 (0%)	1 (2%)	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

Organ	Findings	Group Name / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Hematopoietic system]						
spleen			<50>	<50>	<50>	<50>
	sarcoma:NOS		0 (0%)	1 (2%)	0 (0%)	0 (0%)
	mononuclear cell leukemia		8 (16%)	1 (2%)	1 (2%)	1 (2%)
	hemangiosarcoma		0 (0%)	1 (2%)	0 (0%)	2 (4%)
[Digestive system]						
oral cavity			<50>	<50>	<50>	<50>
	squamous cell papilloma		1 (2%)	0 (0%)	1 (2%)	0 (0%)
small intes			<50>	<50>	<50>	<50>
	adenoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
liver			<50>	<50>	<50>	<50>
	hepatocellular adenoma		0 (0%)	4 (8%)	9 (18%)	9 (18%)
	hepatocellular carcinoma		0 (0%)	0 (0%)	5 (10%)	5 (10%)
pancreas			<50>	<50>	<50>	<50>
	islet cell adenoma		3 (6%)	2 (4%)	0 (0%)	2 (4%)
	acinar cell adenocarcinoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
[Urinary system]						
kidney			<50>	<50>	<50>	<50>
	renal cell adenoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
	liposarcoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)

< 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 / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Urinary system]						
urin bladd			<50>	<50>	<50>	<50>
	transitional cell papilloma		0 (0%)	0 (0%)	2 (4%)	0 (0%)
	mastcytoma:benign		0 (0%)	1 (2%)	0 (0%)	0 (0%)
	transitional cell carcinoma		0 (0%)	1 (2%)	4 (8%)	3 (6%)
[Endocrine system]						
pituitary			<49>	<50>	<50>	<50>
	adenoma		15 (31%)	10 (20%)	10 (20%)	10 (20%)
thyroid			<50>	<50>	<50>	<50>
	C-cell adenoma		3 (6%)	5 (10%)	5 (10%)	2 (4%)
	follicular adenoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
	C-cell carcinoma		0 (0%)	2 (4%)	1 (2%)	0 (0%)
	follicular adenocarcinoma		4 (8%)	3 (6%)	1 (2%)	5 (10%)
adrenal			<50>	<50>	<50>	<50>
	pheochromocytoma		6 (12%)	10 (20%)	12 (24%)	3 (6%)
	ganglioneuroma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
	pheochromocytoma:malignant		2 (4%)	2 (4%)	2 (4%)	2 (4%)
[Reproductive system]						
testis			<50>	<50>	<50>	<50>
	interstitial cell tumor		43 (86%)	46 (92%)	47 (94%)	47 (94%)

< 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 / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Reproductive system]						
mammary gl			<50>	<50>	<50>	<50>
	adenoma		0 (0%)	1 (2%)	0 (0%)	1 (2%)
	fibroadenoma		2 (4%)	0 (0%)	3 (6%)	2 (4%)
prep/cli gl			<50>	<50>	<50>	<50>
	adenoma		4 (8%)	4 (8%)	2 (4%)	0 (0%)
	keratoacanthoma		0 (0%)	2 (4%)	0 (0%)	0 (0%)
	squamous cell carcinoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
[Nervous system]						
brain			<50>	<50>	<50>	<50>
	malignant reticulosis		0 (0%)	0 (0%)	0 (0%)	2 (4%)
	glioma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
[Special sense organs/appandage]						
Zymbal gl			<50>	<50>	<50>	<50>
	adenoma		0 (0%)	0 (0%)	1 (2%)	2 (4%)
	squamous cell carcinoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
[Musculoskeletal system]						
bone			<50>	<50>	<50>	<50>
	osteosarcoma		0 (0%)	0 (0%)	1 (2%)	1 (2%)

< 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 / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Body cavities]						
peritoneum			<50>	<50>	<50>	<50>
	mesothelioma		0 (0%)	3 (6%)	2 (4%)	1 (2%)
retroperit			<50>	<50>	<50>	<50>
	paraganglioma:malignant		1 (2%)	0 (0%)	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 2

HISTOLOGICAL FINDINGS : NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

RAT : FEMALE :

Organ	Findings	Group Name / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Integumentary system/appandage]						
subcutis			<50>	<50>	<50>	<50>
	fibroma		1 (2%)	1 (2%)	0 (0%)	0 (0%)
	lipoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
	schwannoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
	sarcoma:NOS		0 (0%)	1 (2%)	0 (0%)	0 (0%)
[Respiratory system]						
lung			<50>	<50>	<50>	<50>
	bronchiolar-alveolar adenoma		1 (2%)	0 (0%)	3 (6%)	0 (0%)
[Hematopoietic system]						
bone marrow			<50>	<50>	<50>	<50>
	histiocytic sarcoma		2 (4%)	0 (0%)	0 (0%)	0 (0%)
thymus			<50>	<50>	<50>	<49>
	thymoma:benign		1 (2%)	0 (0%)	0 (0%)	0 (0%)
spleen			<50>	<50>	<50>	<50>
	mononuclear cell leukemia		6 (12%)	7 (14%)	2 (4%)	6 (12%)
[Digestive system]						
esophagus			<50>	<50>	<50>	<49>
	squamous cell papilloma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
large intes			<50>	<50>	<50>	<50>
	adenoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)

< 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 / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Digestive system]						
liver			<50>	<50>	<50>	<50>
	hepatocellular adenoma		1 (2%)	3 (6%)	3 (6%)	2 (4%)
	cholangiocellular adenoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
	hemangiosarcoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
	hepatocellular carcinoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
pancreas			<50>	<50>	<50>	<50>
	islet cell adenoma		1 (2%)	0 (0%)	1 (2%)	1 (2%)
[Urinary system]						
kidney			<50>	<50>	<50>	<50>
	mesenchymoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
	renal cell adenoma		0 (0%)	3 (6%)	6 (12%)	4 (8%)
	renal cell carcinoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
urin bladd			<50>	<50>	<50>	<50>
	mastcytoma:benign		1 (2%)	0 (0%)	0 (0%)	0 (0%)
	transitional cell carcinoma		0 (0%)	2 (4%)	3 (6%)	2 (4%)
[Endocrine system]						
pituitary			<50>	<50>	<50>	<50>
	adenoma		11 (22%)	12 (24%)	16 (32%)	11 (22%)

< 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 / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Endocrine system]						
pituitary			<50>	<50>	<50>	<50>
	adenocarcinoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
thyroid			<50>	<50>	<50>	<49>
	C-cell adenoma		5 (10%)	2 (4%)	5 (10%)	1 (2%)
	follicular adenocarcinoma		2 (4%)	0 (0%)	1 (2%)	0 (0%)
adrenal			<50>	<50>	<50>	<50>
	pheochromocytoma		0 (0%)	3 (6%)	2 (4%)	3 (6%)
	cortical adenoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
	pheochromocytoma:malignant		1 (2%)	0 (0%)	0 (0%)	1 (2%)
	cortical adenocarcinoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
[Reproductive system]						
ovary			<50>	<50>	<50>	<50>
	granulosa-theca cell tumor:malignant		0 (0%)	1 (2%)	0 (0%)	0 (0%)
uterus			<50>	<50>	<50>	<50>
	leiomyoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
	endometrial stromal polyp		4 (8%)	9 (18%)	8 (16%)	5 (10%)
	adenocarcinoma		0 (0%)	0 (0%)	2 (4%)	0 (0%)
	endometrial stromal sarcoma		0 (0%)	0 (0%)	0 (0%)	3 (6%)

< 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 / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Reproductive system]						
mammary gl			<50>	<50>	<50>	<50>
	adenoma		0 (0%)	2 (4%)	0 (0%)	1 (2%)
	fibroadenoma		3 (6%)	2 (4%)	3 (6%)	9 (18%)
	adenocarcinoma		0 (0%)	0 (0%)	2 (4%)	0 (0%)
prep/cli gl			<50>	<50>	<50>	<50>
	adenoma		2 (4%)	0 (0%)	1 (2%)	0 (0%)
	keratoacanthoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
[Nervous system]						
brain			<50>	<50>	<50>	<50>
	glioma		0 (0%)	0 (0%)	1 (2%)	1 (2%)
[Special sense organs/appandage]						
Zymbal gl			<50>	<50>	<50>	<50>
	squamous cell carcinoma		0 (0%)	1 (2%)	0 (0%)	0 (0%)
[Musculoskeletal system]						
bone			<50>	<50>	<50>	<50>
	osteosarcoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
[Body cavities]						
mediastinum			<50>	<50>	<50>	<50>
	carcinoid tumor:malignant		1 (2%)	0 (0%)	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

Organ	Findings	Group Name / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Body cavities]						
mediastinum			<50>	<50>	<50>	<50>
	sarcoma:NOS		1 (2%)	0 (0%)	0 (0%)	0 (0%)
mesenterium			<50>	<50>	<50>	<50>
	fibroma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
adipose			<50>	<50>	<50>	<50>
	lipoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)

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

APPENDIX M 3

HISTOLOGICAL FINDINGS : NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

MOUSE: MALE

STUDY NO. : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : NEOPLASTIC LESIONS (SUMMARY)
ALL ANIMALS (0-105W)

Organ	Findings	Group Name / No. of animals on Study	Control 49	3200 ppm 50	8000 ppm 50	20000 ppm 50
[Integumentary system/appandage]						
subcutis			<49>	<50>	<50>	<50>
	xanthoma		1 (2%)	1 (2%)	1 (2%)	0 (0%)
	histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)	0 (0%)
[Respiratory system]						
nasal cavit			<49>	<50>	<50>	<50>
	chondroma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
lung			<49>	<50>	<50>	<50>
	bronchiolar-alveolar adenoma		1 (2%)	3 (6%)	2 (4%)	1 (2%)
	bronchiolar-alveolar carcinoma		1 (2%)	1 (2%)	2 (4%)	0 (0%)
[Hematopoietic system]						
lymph node			<49>	<50>	<50>	<50>
	malignant lymphoma		2 (4%)	4 (8%)	4 (8%)	3 (6%)
	mastcytoma:malignant		2 (4%)	1 (2%)	1 (2%)	2 (4%)
spleen			<49>	<50>	<50>	<50>
	hemangioma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
	malignant lymphoma		1 (2%)	2 (4%)	0 (0%)	2 (4%)
	mastcytoma:malignant		0 (0%)	0 (0%)	0 (0%)	1 (2%)
[Circulatory system]						
heart			<49>	<50>	<50>	<50>
	hemangioma		0 (0%)	0 (0%)	1 (2%)	0 (0%)

< 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 / No. of animals on Study	Control 49	3200 ppm 50	8000 ppm 50	20000 ppm 50
[Digestive system]						
salivary gl			<49>	<50>	<50>	<50>
	histiocytic sarcoma		0 (0%)	1 (2%)	0 (0%)	1 (2%)
liver			<49>	<50>	<50>	<50>
	hepatocellular adenoma		4 (8%)	6 (12%)	1 (2%)	5 (10%)
	histiocytic sarcoma		2 (4%)	4 (8%)	5 (10%)	3 (6%)
	hemangiosarcoma		2 (4%)	0 (0%)	1 (2%)	0 (0%)
	hepatocellular carcinoma		1 (2%)	3 (6%)	0 (0%)	0 (0%)
[Urinary system]						
kidney			<49>	<50>	<50>	<50>
	transitional cell carcinoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
urin bladd			<49>	<50>	<50>	<50>
	xanthoma		0 (0%)	2 (4%)	0 (0%)	0 (0%)
	histiocytic sarcoma		0 (0%)	0 (0%)	0 (0%)	2 (4%)
[Endocrine system]						
adrenal			<49>	<50>	<50>	<50>
	cortical adenoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
[Reproductive system]						
testis			<49>	<50>	<50>	<50>
	interstitial cell tumor		1 (2%)	0 (0%)	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

Organ	Findings	Group Name / No. of animals on Study	Control 49	3200 ppm 50	8000 ppm 50	20000 ppm 50
[Reproductive system]						
testis			<49>	<50>	<50>	<50>
	histiocytic sarcoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
epididymis			<49>	<50>	<50>	<50>
	histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)	1 (2%)
[Special sense organs/appandage]						
Harder gl			<49>	<50>	<50>	<50>
	adenoma		0 (0%)	1 (2%)	2 (4%)	3 (6%)

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

APPENDIX M 4

HISTOLOGICAL FINDINGS : NEOPLASTIC LESIONS (2-YEAR STUDY: SUMMARY)

MOUSE: FEMALE

Organ	Findings	Group Name / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Integumentary system/appandage]						
skin/app			<50>	<50>	<50>	<50>
	trichoepithelioma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
subcutis			<50>	<50>	<50>	<50>
	xanthoma		0 (0%)	1 (2%)	0 (0%)	0 (0%)
	histiocytic sarcoma		0 (0%)	1 (2%)	0 (0%)	1 (2%)
	hemangiosarcoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
[Respiratory system]						
lung			<50>	<50>	<50>	<50>
	bronchiolar-alveolar adenoma		1 (2%)	2 (4%)	4 (8%)	0 (0%)
	bronchiolar-alveolar carcinoma		2 (4%)	2 (4%)	2 (4%)	1 (2%)
[Hematopoietic system]						
lymph node			<50>	<50>	<50>	<50>
	malignant lymphoma		11 (22%)	13 (26%)	7 (14%)	7 (14%)
	mastcytoma:malignant		0 (0%)	0 (0%)	1 (2%)	0 (0%)
spleen			<50>	<50>	<50>	<49>
	hemangioma		0 (0%)	1 (2%)	0 (0%)	0 (0%)
	malignant lymphoma		4 (8%)	1 (2%)	4 (8%)	0 (0%)
[Digestive system]						
oral cavity			<50>	<50>	<50>	<50>
	squamous cell papilloma		1 (2%)	0 (0%)	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

Organ	Findings	Group Name / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Digestive system]						
salivary gl			<50>	<50>	<50>	<50>
	histiocytic sarcoma		0 (0%)	1 (2%)	0 (0%)	0 (0%)
stomach			<49>	<50>	<50>	<50>
	mastcytoma:malignant		0 (0%)	0 (0%)	0 (0%)	1 (2%)
large intes			<50>	<50>	<50>	<50>
	leiomyosarcoma		0 (0%)	1 (2%)	0 (0%)	0 (0%)
liver			<50>	<50>	<50>	<50>
	hepatocellular adenoma		2 (4%)	3 (6%)	6 (12%)	20 (40%)
	hepatocholangiocellular adenoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
	histiocytic sarcoma		0 (0%)	3 (6%)	4 (8%)	3 (6%)
	hemangiosarcoma		3 (6%)	1 (2%)	1 (2%)	1 (2%)
	hepatocellular carcinoma		0 (0%)	2 (4%)	5 (10%)	12 (24%)
[Urinary system]						
urin bladd			<50>	<50>	<50>	<49>
	histiocytic sarcoma		0 (0%)	1 (2%)	0 (0%)	0 (0%)
[Endocrine system]						
pituitary			<50>	<50>	<50>	<50>
	adenoma		1 (2%)	0 (0%)	0 (0%)	1 (2%)
thyroid			<49>	<50>	<50>	<50>
	C-cell carcinoma		0 (0%)	1 (2%)	0 (0%)	1 (2%)

< 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 / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Endocrine system]						
adrenal			<50>	<50>	<50>	<50>
	pheochromocytoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
	A-B cell tumor		0 (0%)	0 (0%)	0 (0%)	1 (2%)
[Reproductive system]						
ovary			<50>	<50>	<50>	<50>
	cystadenoma		0 (0%)	1 (2%)	2 (4%)	0 (0%)
	hemangioma		2 (4%)	2 (4%)	0 (0%)	0 (0%)
uterus			<50>	<50>	<50>	<50>
	leiomyoma		0 (0%)	0 (0%)	1 (2%)	0 (0%)
	xanthoma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
	endometrial stromal polyp		2 (4%)	1 (2%)	0 (0%)	0 (0%)
	leiomyosarcoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
	histiocytic sarcoma		6 (12%)	12 (24%)	7 (14%)	7 (14%)
mammary gl			<50>	<50>	<50>	<50>
	adenocarcinoma		0 (0%)	2 (4%)	0 (0%)	0 (0%)
[Special sense organs/appandage]						
Harder gl			<50>	<50>	<50>	<50>
	adenoma		1 (2%)	2 (4%)	3 (6%)	3 (6%)

< 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 / No. of animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Musculoskeletal system]						
muscle			<50>	<50>	<50>	<50>
	hemangioma		0 (0%)	0 (0%)	0 (0%)	1 (2%)
bone			<50>	<50>	<50>	<50>
	osteoma		1 (2%)	0 (0%)	0 (0%)	0 (0%)
	osteosarcoma		1 (2%)	0 (0%)	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 N 1

NEOPLASTIC LESIONS - INCIDENCE AND STATISTICAL ANIMALS

RAT : MALE

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : skin/appendage			
	TUMOR : keratoacanthoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	3/50(6.0)	2/50(4.0)	4/50(8.0)
Adjusted rates(b)	9.09	6.98	4.65	9.09
Terminal rates(c)	3/33(9.1)	3/43(7.0)	2/43(4.7)	3/38(7.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4130			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.8740			
Fisher Exact test(e)		P = 0.4895	P = 0.3574	P = 0.3579
	SITE : skin/appendage			
	TUMOR : squamous cell papilloma,squamous cell carcinoma,keratoacanthoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	3/50(6.0)	3/50(6.0)	5/50(10.0)
Adjusted rates(b)	15.15	6.98	6.98	11.36
Terminal rates(c)	5/33(15.2)	3/43(7.0)	3/43(7.0)	4/38(10.5)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4670			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9734			
Fisher Exact test(e)		P = 0.2728	P = 0.2728	P = 0.4872
	SITE : subcutis			
	TUMOR : fibroma			
Tumor rate				
Overall rates(a)	2/50(4.0)	4/50(8.0)	1/50(2.0)	4/50(8.0)
Adjusted rates(b)	3.03	9.30	2.33	7.32
Terminal rates(c)	1/33(3.0)	4/43(9.3)	1/43(2.3)	2/38(5.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3261			
Prevalence method(d)	P = 0.2803			
Combined analysis(d)	P = 0.2432			
Cochran-Armitage test(e)	P = 0.5403			
Fisher Exact test(e)		P = 0.3574	P = 0.4926	P = 0.3574

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : subcutis TUMOR : fibroma,fibrosarcoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	4/50(8.0)	2/50(4.0)	4/50(8.0)
Adjusted rates(b)	3.03	9.30	2.33	7.32
Terminal rates(c)	1/33(3.0)	4/43(9.3)	1/43(2.3)	2/38(5.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3469			
Prevalence method(d)	P = 0.2803			
Combined analysis(d)	P = 0.2502			
Cochran-Armitage test(e)	P = 0.5514			
Fisher Exact test(e)		P = 0.3574	P = 0.3088	P = 0.3574
	SITE : lung TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	0.0	6.98	6.98	5.26
Terminal rates(c)	0/33(0.0)	3/43(7.0)	3/43(7.0)	2/38(5.3)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.2996			
Combined analysis(d)	P = --------			
Cochran-Armitage test(e)	P = 0.5948			
Fisher Exact test(e)		P = 0.1325	P = 0.1325	P = 0.2574
	SITE : spleen TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	8/50(16.0)	1/50(2.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	10.26	0.0	0.0	2.63
Terminal rates(c)	3/33(9.1)	0/43(0.0)	0/43(0.0)	1/38(2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9857			
Prevalence method(d)	P = 0.8720			
Combined analysis(d)	P = 0.9924			
Cochran-Armitage test(e)	P = 0.0258*			
Fisher Exact test(e)		P = 0.0254*	P = 0.0254*	P = 0.0254*

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : liver TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	4/50(8.0)	9/50(18.0)	9/50(18.0)
Adjusted rates(b)	0.0	9.30	20.93	21.05
Terminal rates(c)	0/33(0.0)	4/43(9.3)	9/43(20.9)	8/38(21.1)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0032**			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0056**			
Fisher Exact test(e)		P = 0.0688	P = 0.0029**	P = 0.0029**
	SITE : liver TUMOR : hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	5/50(10.0)	5/50(10.0)
Adjusted rates(b)	0.0	0.0	11.63	10.53
Terminal rates(c)	0/33(0.0)	0/43(0.0)	5/43(11.6)	4/38(10.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1138			
Prevalence method(d)	P = 0.0158*			
Combined analysis(d)	P = 0.0056**			
Cochran-Armitage test(e)	P = 0.0081**			
Fisher Exact test(e)		P = 0.5000	P = 0.0360*	P = 0.0360*
	SITE : liver TUMOR : hepatocellular adenoma,hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	4/50(8.0)	13/50(26.0)	13/50(26.0)
Adjusted rates(b)	0.0	9.30	30.23	31.58
Terminal rates(c)	0/33(0.0)	4/43(9.3)	13/43(30.2)	12/38(31.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1138			
Prevalence method(d)	P = 0.0003**			
Combined analysis(d)	P = 0.0001**			
Cochran-Armitage test(e)	P = 0.0002**			
Fisher Exact test(e)		P = 0.0688	P = 0.0003**	P = 0.0003**

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : pancreas TUMOR : islet cell adenoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	0/50(0.0)	2/50(4.0)
Adjusted rates(b)	8.33	4.65	0.0	4.26
Terminal rates(c)	2/33(6.1)	2/43(4.7)	0/43(0.0)	1/38(2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.6405			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.6779			
Fisher Exact test(e)		P = 0.4909	P = 0.1325	P = 0.4909
	SITE : urinary bladder TUMOR : transitional cell carcinoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	1/50(2.0)	4/50(8.0)	3/50(6.0)
Adjusted rates(b)	0.0	2.33	8.33	7.89
Terminal rates(c)	0/33(0.0)	1/43(2.3)	3/43(7.0)	3/38(7.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0552			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1193			
Fisher Exact test(e)		P = 0.4950	P = 0.0688	P = 0.1325
	SITE : urinary bladder TUMOR : transitional cell papilloma,transitional cell carcinoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	1/50(2.0)	6/50(12.0)	3/50(6.0)
Adjusted rates(b)	0.0	2.33	12.50	7.89
Terminal rates(c)	0/33(0.0)	1/43(2.3)	4/43(9.3)	3/38(7.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0689			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1563			
Fisher Exact test(e)		P = 0.4950	P = 0.0190*	P = 0.1325

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : pituitary gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	15/49(30.6)	10/50(20.0)	10/50(20.0)	10/50(20.0)
Adjusted rates(b)	21.88	18.60	20.00	21.05
Terminal rates(c)	7/32(21.9)	8/43(18.6)	8/43(18.6)	8/38(21.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9390			
Prevalence method(d)	P = 0.5542			
Combined analysis(d)	P = 0.8294			
Cochran-Armitage test(e)	P = 0.3632			
Fisher Exact test(e)		P = 0.2377	P = 0.2377	P = 0.2377
	SITE : thyroid TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	5/50(10.0)	5/50(10.0)	2/50(4.0)
Adjusted rates(b)	7.50	11.63	11.63	5.00
Terminal rates(c)	1/33(3.0)	5/43(11.6)	5/43(11.6)	1/38(2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7529			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4581			
Fisher Exact test(e)		P = 0.3790	P = 0.3790	P = 0.4909
	SITE : thyroid TUMOR : follicular adenocarcinoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	3/50(6.0)	1/50(2.0)	5/50(10.0)
Adjusted rates(b)	12.12	6.98	2.33	13.16
Terminal rates(c)	4/33(12.1)	3/43(7.0)	1/43(2.3)	5/38(13.2)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.2775			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5408			
Fisher Exact test(e)		P = 0.4895	P = 0.1998	P = 0.4883

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : thyroid TUMOR : C-cell adenoma,C-cell carcinoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	7/50(14.0)	6/50(12.0)	2/50(4.0)
Adjusted rates(b)	7.50	16.28	13.95	5.00
Terminal rates(c)	1/33(3.0)	7/43(16.3)	6/43(14.0)	1/38(2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8244			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3292			
Fisher Exact test(e)		P = 0.1917	P = 0.2728	P = 0.4909
	SITE : thyroid TUMOR : follicular adenoma,follicular adenocarcinoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	3/50(6.0)	1/50(2.0)	6/50(12.0)
Adjusted rates(b)	12.12	6.98	2.33	14.63
Terminal rates(c)	4/33(12.1)	3/43(7.0)	1/43(2.3)	5/38(13.2)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1360			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3002			
Fisher Exact test(e)		P = 0.4895	P = 0.1998	P = 0.3944
	SITE : adrenal gland TUMOR : pheochromocytoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	10/50(20.0)	12/50(24.0)	3/50(6.0)
Adjusted rates(b)	16.22	23.26	26.67	7.89
Terminal rates(c)	4/33(12.1)	10/43(23.3)	11/43(25.6)	3/38(7.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9270			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1665			
Fisher Exact test(e)		P = 0.2557	P = 0.1474	P = 0.2728

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : adrenal gland TUMOR : pheochromocytoma,pheochromocytoma:malignant			
Tumor rate				
Overall rates(a)	6/50(12.0)	12/50(24.0)	14/50(28.0)	5/50(10.0)
Adjusted rates(b)	16.22	25.58	28.89	13.16
Terminal rates(c)	4/33(12.1)	11/43(25.6)	12/43(27.9)	5/38(13.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5873			
Prevalence method(d)	P = 0.8030			
Combined analysis(d)	P = 0.8226			
Cochran-Armitage test(e)	P = 0.3599			
Fisher Exact test(e)		P = 0.1474	P = 0.0810	P = 0.4872
	SITE : testis TUMOR : interstitial cell tumor			
Tumor rate				
Overall rates(a)	43/50(86.0)	46/50(92.0)	47/50(94.0)	47/50(94.0)
Adjusted rates(b)	97.14	95.74	97.92	97.44
Terminal rates(c)	32/33(97.0)	41/43(95.3)	42/43(97.7)	37/38(97.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0876			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2322			
Fisher Exact test(e)		P = 0.4659	P = 0.4362	P = 0.4362
	SITE : mammary gland TUMOR : fibroadenoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	0/50(0.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	6.06	0.0	6.98	4.35
Terminal rates(c)	2/33(6.1)	0/43(0.0)	3/43(7.0)	1/38(2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.3144			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.6340			
Fisher Exact test(e)		P = 0.2574	P = 0.4909	P = 0.3088

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : mammary gland TUMOR : adenoma,fibroadenoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	1/50(2.0)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	6.06	2.33	6.98	6.52
Terminal rates(c)	2/33(6.1)	1/43(2.3)	3/43(7.0)	2/38(5.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.2273			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4453			
Fisher Exact test(e)		P = 0.4926	P = 0.4909	P = 0.4909
	SITE : preputial/clitoral gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	4/50(8.0)	2/50(4.0)	0/50(0.0)
Adjusted rates(b)	9.09	9.30	4.65	0.0
Terminal rates(c)	3/33(9.1)	4/43(9.3)	2/43(4.7)	0/38(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 1.0000 ?			
Prevalence method(d)	P = 0.9836			
Combined analysis(d)	P = 0.9925			
Cochran-Armitage test(e)	P = 0.0356*			
Fisher Exact test(e)		P = 0.3579	P = 0.3574	P = 0.0688

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : peritoneum TUMOR : mesothelioma			
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	0.0	4.65	4.65	2.38
Terminal rates(c)	0/33(0.0)	2/43(4.7)	2/43(4.7)	0/38(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5618			
Prevalence method(d)	P = 0.3815			
Combined analysis(d)	P = 0.4870			
Cochran-Armitage test(e)	P = 0.9478			
Fisher Exact test(e)		P = 0.1325	P = 0.2574	P = 0.4950

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01

APPENDIX N 2

NEOPLASTIC LESIONS - INCIDENCE AND STATISTICAL ANIMALS

RAT : FEMALE

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	3/50(6.0)	0/50(0.0)
Adjusted rates(b)	2.50	0.0	7.50	0.0
Terminal rates(c)	1/40(2.5)	0/40(0.0)	3/40(7.5)	0/37(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.6319			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.6322			
Fisher Exact test(e)		P = 0.4950	P = 0.3235	P = 0.4950
	SITE : spleen			
	TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	6/50(12.0)	7/50(14.0)	2/50(4.0)	6/50(12.0)
Adjusted rates(b)	7.50	5.00	5.00	8.11
Terminal rates(c)	3/40(7.5)	2/40(5.0)	2/40(5.0)	3/37(8.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6283			
Prevalence method(d)	P = 0.3734			
Combined analysis(d)	P = 0.5188			
Cochran-Armitage test(e)	P = 0.8698			
Fisher Exact test(e)		P = 0.4863	P = 0.1606	P = 0.3807
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	3/50(6.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	2.17	7.50	7.50	5.41
Terminal rates(c)	0/40(0.0)	3/40(7.5)	3/40(7.5)	2/37(5.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4239			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.8787			
Fisher Exact test(e)		P = 0.3235	P = 0.3235	P = 0.4926

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma,hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	3/50(6.0)	4/50(8.0)	2/50(4.0)
Adjusted rates(b)	2.17	7.50	10.00	5.41
Terminal rates(c)	0/40(0.0)	3/40(7.5)	4/40(10.0)	2/37(5.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4204			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.8778			
Fisher Exact test(e)		P = 0.3235	P = 0.1998	P = 0.4926
	SITE : kidney			
	TUMOR : renal cell adenoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	6/50(12.0)	4/50(8.0)
Adjusted rates(b)	0.0	7.50	14.63	8.89
Terminal rates(c)	0/40(0.0)	3/40(7.5)	5/40(12.5)	3/37(8.1)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0937			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1717			
Fisher Exact test(e)		P = 0.1325	P = 0.0190*	P = 0.0688
	SITE : kidney			
	TUMOR : renal cell adenoma,renal cell carcinoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	6/50(12.0)	5/50(10.0)
Adjusted rates(b)	0.0	7.50	14.63	9.09
Terminal rates(c)	0/40(0.0)	3/40(7.5)	5/40(12.5)	3/37(8.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1225			
Prevalence method(d)	P = 0.0899			
Combined analysis(d)	P = 0.0441*			
Cochran-Armitage test(e)	P = 0.0775			
Fisher Exact test(e)		P = 0.1325	P = 0.0190*	P = 0.0360*

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : urinary bladder TUMOR : transitional cell carcinoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	2/50(4.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	0.0	5.00	7.50	5.41
Terminal rates(c)	0/40(0.0)	2/40(5.0)	3/40(7.5)	2/37(5.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1871			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4236			
Fisher Exact test(e)		P = 0.2574	P = 0.1325	P = 0.2574
	SITE : pituitary gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	11/50(22.0)	12/50(24.0)	16/50(32.0)	11/50(22.0)
Adjusted rates(b)	22.50	26.19	32.50	21.43
Terminal rates(c)	9/40(22.5)	9/40(22.5)	13/40(32.5)	6/37(16.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3824			
Prevalence method(d)	P = 0.5781			
Combined analysis(d)	P = 0.5235			
Cochran-Armitage test(e)	P = 0.9383			
Fisher Exact test(e)		P = 0.4826	P = 0.2625	P = 0.4072
	SITE : pituitary gland TUMOR : adenoma,adenocarcinoma			
Tumor rate				
Overall rates(a)	11/50(22.0)	12/50(24.0)	17/50(34.0)	11/50(22.0)
Adjusted rates(b)	22.50	26.19	32.50	21.43
Terminal rates(c)	9/40(22.5)	9/40(22.5)	13/40(32.5)	6/37(16.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3869			
Prevalence method(d)	P = 0.5771			
Combined analysis(d)	P = 0.5214			
Cochran-Armitage test(e)	P = 0.9421			
Fisher Exact test(e)		P = 0.4826	P = 0.2154	P = 0.4072

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : thyroid			
	TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	2/50(4.0)	5/50(10.0)	1/49(2.0)
Adjusted rates(b)	10.42	5.00	10.00	2.70
Terminal rates(c)	4/40(10.0)	2/40(5.0)	4/40(10.0)	1/37(2.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3825			
Prevalence method(d)	P = 0.9078			
Combined analysis(d)	P = 0.8951			
Cochran-Armitage test(e)	P = 0.1947			
Fisher Exact test(e)		P = 0.2425	P = 0.3710	P = 0.1261
	SITE : adrenal gland			
	TUMOR : pheochromocytoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	2/50(4.0)	3/50(6.0)
Adjusted rates(b)	0.0	7.50	4.55	8.11
Terminal rates(c)	0/40(0.0)	3/40(7.5)	1/40(2.5)	3/37(8.1)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1426			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2705			
Fisher Exact test(e)		P = 0.1325	P = 0.2574	P = 0.1325
	SITE : adrenal gland			
	TUMOR : pheochromocytoma,pheochromocytoma:malignant			
Tumor rate				
Overall rates(a)	1/50(2.0)	3/50(6.0)	2/50(4.0)	4/50(8.0)
Adjusted rates(b)	0.0	7.50	4.55	10.81
Terminal rates(c)	0/40(0.0)	3/40(7.5)	1/40(2.5)	4/37(10.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 1.0000 ?			
Prevalence method(d)	P = 0.0640			
Combined analysis(d)	P = 0.1268			
Cochran-Armitage test(e)	P = 0.2385			
Fisher Exact test(e)		P = 0.3235	P = 0.4926	P = 0.1998

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : uterus TUMOR : endometrial stromal polyp			
Tumor rate				
Overall rates(a)	4/50(8.0)	9/50(18.0)	8/50(16.0)	5/50(10.0)
Adjusted rates(b)	9.30	20.00	17.07	13.51
Terminal rates(c)	3/40(7.5)	8/40(20.0)	6/40(15.0)	5/37(13.5)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.5848			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.7820			
Fisher Exact test(e)		P = 0.1562	P = 0.2169	P = 0.4883
	SITE : uterus TUMOR : endometrial stromal sarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	0.0	2.63
Terminal rates(c)	0/40(0.0)	0/40(0.0)	0/40(0.0)	0/37(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0164* ?			
Prevalence method(d)	P = 0.1137			
Combined analysis(d)	P = 0.0032**?			
Cochran-Armitage test(e)	P = 0.0051**			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.1325
	SITE : mammary gland TUMOR : fibroadenoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	3/50(6.0)	9/50(18.0)
Adjusted rates(b)	7.50	5.00	7.50	17.07
Terminal rates(c)	3/40(7.5)	2/40(5.0)	3/40(7.5)	6/37(16.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0172* ?			
Prevalence method(d)	P = 0.0299*			
Combined analysis(d)	P = 0.0057**			
Cochran-Armitage test(e)	P = 0.0094**			
Fisher Exact test(e)		P = 0.4909	P = 0.3392	P = 0.0899

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : mammary gland			
	TUMOR : adenoma,fibroadenoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	4/50(8.0)	3/50(6.0)	10/50(20.0)
Adjusted rates(b)	7.50	7.50	7.50	18.60
Terminal rates(c)	3/40(7.5)	3/40(7.5)	3/40(7.5)	6/37(16.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0822			
Prevalence method(d)	P = 0.0221*			
Combined analysis(d)	P = 0.0077**			
Cochran-Armitage test(e)	P = 0.0122*			
Fisher Exact test(e)		P = 0.4895	P = 0.3392	P = 0.0604
	SITE : mammary gland			
	TUMOR : adenoma,fibroadenoma,adenocarcinoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	4/50(8.0)	5/50(10.0)	10/50(20.0)
Adjusted rates(b)	7.50	7.50	10.00	18.60
Terminal rates(c)	3/40(7.5)	3/40(7.5)	4/40(10.0)	6/37(16.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1061			
Prevalence method(d)	P = 0.0242*			
Combined analysis(d)	P = 0.0098**			
Cochran-Armitage test(e)	P = 0.0157*			
Fisher Exact test(e)		P = 0.4895	P = 0.3790	P = 0.0604

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------- : There is no data which should be statistical analysis.
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01

APPENDIX N 3

NEOPLASTIC LESIONS - INCIDENCE AND STATISTICAL ANIMALS

MOSUE : MALE

Group Name	Control	3200 ppm	8000 ppm	20000 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	1/49(2.0)	3/50(6.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	2.44	7.14	5.41	2.38
Terminal rates(c)	1/41(2.4)	2/41(4.9)	2/37(5.4)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.6489			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.6385			
Fisher Exact test(e)		P = 0.3312	P = 0.4851	P = 0.2426
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma,bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	2/49(4.1)	4/50(8.0)	4/50(8.0)	1/50(2.0)
Adjusted rates(b)	4.65	9.52	8.11	2.38
Terminal rates(c)	1/41(2.4)	3/41(7.3)	3/37(8.1)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3941			
Prevalence method(d)	P = 0.8039			
Combined analysis(d)	P = 0.7909			
Cochran-Armitage test(e)	P = 0.3815			
Fisher Exact test(e)		P = 0.3668	P = 0.3668	P = 0.5000
	SITE : lymph node			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	2/49(4.1)	4/50(8.0)	4/50(8.0)	3/50(6.0)
Adjusted rates(b)	4.88	4.88	8.11	4.76
Terminal rates(c)	2/41(4.9)	2/41(4.9)	3/37(8.1)	2/42(4.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4018			
Prevalence method(d)	P = 0.4925			
Combined analysis(d)	P = 0.4509			
Cochran-Armitage test(e)	P = 0.9131			
Fisher Exact test(e)		P = 0.3668	P = 0.3668	P = 0.4816

Group Name	Control	3200 ppm	8000 ppm	20000 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	4/49(8.2)	6/50(12.0)	1/50(2.0)	5/50(10.0)
Adjusted rates(b)	9.76	14.63	2.70	11.90
Terminal rates(c)	4/41(9.8)	6/41(14.6)	1/37(2.7)	5/42(11.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4730			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.9515			
Fisher Exact test(e)		P = 0.4066	P = 0.1936	P = 0.4763
	SITE : liver			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	2/49(4.1)	4/50(8.0)	5/50(10.0)	3/50(6.0)
Adjusted rates(b)	0.0	2.44	0.0	0.0
Terminal rates(c)	0/41(0.0)	1/41(2.4)	0/37(0.0)	0/42(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4006			
Prevalence method(d)	P = 0.5459			
Combined analysis(d)	P = 0.4660			
Cochran-Armitage test(e)	P = 0.9113			
Fisher Exact test(e)		P = 0.3668	P = 0.2510	P = 0.4816
	SITE : liver			
	TUMOR : hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	1/49(2.0)	3/50(6.0)	0/50(0.0)	0/50(0.0)
Adjusted rates(b)	2.44	4.88	0.0	0.0
Terminal rates(c)	1/41(2.4)	2/41(4.9)	0/37(0.0)	0/42(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5565			
Prevalence method(d)	P = 0.9107			
Combined analysis(d)	P = 0.9354			
Cochran-Armitage test(e)	P = 0.1480			
Fisher Exact test(e)		P = 0.3312	P = 0.5000	P = 0.5000

Group Name	Control	3200 ppm	8000 ppm	20000 ppm
	SITE : liver TUMOR : hepatocellular adenoma,hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	5/49(10.2)	9/50(18.0)	1/50(2.0)	5/50(10.0)
Adjusted rates(b)	12.20	19.51	2.70	11.90
Terminal rates(c)	5/41(12.2)	8/41(19.5)	1/37(2.7)	5/42(11.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5565			
Prevalence method(d)	P = 0.6847			
Combined analysis(d)	P = 0.7323			
Cochran-Armitage test(e)	P = 0.5351			
Fisher Exact test(e)		P = 0.2494	P = 0.1163	P = 0.3592
	SITE : Harderian gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	0/49(0.0)	1/50(2.0)	2/50(4.0)	3/50(6.0)
Adjusted rates(b)	0.0	2.44	5.41	7.14
Terminal rates(c)	0/41(0.0)	1/41(2.4)	2/37(5.4)	3/42(7.1)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0517			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0792			
Fisher Exact test(e)		P = 0.4900	P = 0.2626	P = 0.1364

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01

STUDY No. : 0243
ANIMAL : MOUSE Crj:BDF1
SEX : MALE

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS

Group Name	Control	3200 ppm	8000 ppm	20000 ppm
	SITE : ALL SITE TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	5/49(10.2)	7/50(14.0)	7/50(14.0)	7/50(14.0)
Adjusted rates(b)	7.32	9.76	2.70	4.76
Terminal rates(c)	3/41(7.3)	4/41(9.8)	1/37(2.7)	2/42(4.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1637			
Prevalence method(d)	P = 0.7660			
Combined analysis(d)	P = 0.3667			
Cochran-Armitage test(e)	P = 0.6864			
Fisher Exact test(e)		P = 0.4195	P = 0.4195	P = 0.4195
	SITE : ALL SITE TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	3/49(6.1)	6/50(12.0)	4/50(8.0)	5/50(10.0)
Adjusted rates(b)	7.32	9.76	8.11	9.52
Terminal rates(c)	3/41(7.3)	4/41(9.8)	3/37(8.1)	4/42(9.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4018			
Prevalence method(d)	P = 0.3970			
Combined analysis(d)	P = 0.3735			
Cochran-Armitage test(e)	P = 0.7426			
Fisher Exact test(e)		P = 0.2829	P = 0.4788	P = 0.3899

(HPT360A)

BAIS3

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
——— : There is no data which should be statistical analysis.
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01

APPENDIX N 4

NEOPLASTIC LESIONS - INCIDENCE AND STATISTICAL ANIMALS

MOSUE :FEMALE

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : lung TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	2/50(4.0)	4/50(8.0)	0/50(0.0)
Adjusted rates(b)	2.86	6.25	10.53	0.0
Terminal rates(c)	1/35(2.9)	1/31(3.2)	3/34(8.8)	0/34(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7895			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4120			
Fisher Exact test(e)		P = 0.4926	P = 0.1998	P = 0.4950
	SITE : lung TUMOR : bronchiolar-alveolar adenoma,bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	4/50(8.0)	6/50(12.0)	1/50(2.0)
Adjusted rates(b)	8.57	9.38	15.79	0.0
Terminal rates(c)	3/35(8.6)	2/31(6.5)	4/34(11.8)	0/34(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2547			
Prevalence method(d)	P = 0.9307			
Combined analysis(d)	P = 0.8548			
Cochran-Armitage test(e)	P = 0.3002			
Fisher Exact test(e)		P = 0.4895	P = 0.2728	P = 0.3235
	SITE : lymph node TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	11/50(22.0)	13/50(26.0)	7/50(14.0)	7/50(14.0)
Adjusted rates(b)	20.00	16.13	8.82	5.88
Terminal rates(c)	7/35(20.0)	5/31(16.1)	3/34(8.8)	2/34(5.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5802			
Prevalence method(d)	P = 0.9690			
Combined analysis(d)	P = 0.9127			
Cochran-Armitage test(e)	P = 0.1630			
Fisher Exact test(e)		P = 0.4450	P = 0.2711	P = 0.2711

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : spleen			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	4/50(8.0)	0/49(0.0)
Adjusted rates(b)	11.43	3.23	8.82	0.0
Terminal rates(c)	4/35(11.4)	1/31(3.2)	3/34(8.8)	0/33(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3828			
Prevalence method(d)	P = 0.9606			
Combined analysis(d)	P = 0.9471			
Cochran-Armitage test(e)	P = 0.1204			
Fisher Exact test(e)		P = 0.1998	P = 0.3579	P = 0.0715
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	3/50(6.0)	6/50(12.0)	20/50(40.0)
Adjusted rates(b)	5.71	9.68	15.79	58.82
Terminal rates(c)	2/35(5.7)	3/31(9.7)	5/34(14.7)	20/34(58.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P < 0.0001**			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P < 0.0001**			
Fisher Exact test(e)		P = 0.4909	P = 0.1606	P = 0.0003**
	SITE : liver			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	4/50(8.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	2.56	0.0
Terminal rates(c)	0/35(0.0)	0/31(0.0)	0/34(0.0)	0/34(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1645			
Prevalence method(d)	P = 0.4029			
Combined analysis(d)	P = 0.1764			
Cochran-Armitage test(e)	P = 0.3135			
Fisher Exact test(e)		P = 0.1325	P = 0.0688	P = 0.1325

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : liver			
	TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	5.71	3.23	0.0	2.94
Terminal rates(c)	2/35(5.7)	1/31(3.2)	0/34(0.0)	1/34(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7236			
Prevalence method(d)	P = 0.6784			
Combined analysis(d)	P = 0.7963			
Cochran-Armitage test(e)	P = 0.3947			
Fisher Exact test(e)		P = 0.3235	P = 0.3235	P = 0.3235
	SITE : liver			
	TUMOR : hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	2/50(4.0)	5/50(10.0)	12/50(24.0)
Adjusted rates(b)	0.0	6.45	8.82	29.41
Terminal rates(c)	0/35(0.0)	2/31(6.5)	3/34(8.8)	10/34(29.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1852			
Prevalence method(d)	P < 0.0001**			
Combined analysis(d)	P < 0.0001**			
Cochran-Armitage test(e)	P < 0.0001**			
Fisher Exact test(e)		P = 0.2574	P = 0.0360*	P = 0.0005**
	SITE : liver			
	TUMOR : hepatocellular adenoma,hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	5/50(10.0)	11/50(22.0)	26/50(52.0)
Adjusted rates(b)	5.71	16.13	25.00	70.59
Terminal rates(c)	2/35(5.7)	5/31(16.1)	8/34(23.5)	24/34(70.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1852			
Prevalence method(d)	P < 0.0001**?			
Combined analysis(d)	P < 0.0001**?			
Cochran-Armitage test(e)	P < 0.0001**			
Fisher Exact test(e)		P = 0.2425	P = 0.0170*	P < 0.0001**

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : uterus TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	12/50(24.0)	7/50(14.0)	7/50(14.0)
Adjusted rates(b)	2.86	19.35	5.88	11.63
Terminal rates(c)	1/35(2.9)	6/31(19.4)	2/34(5.9)	3/34(8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8854			
Prevalence method(d)	P = 0.2838			
Combined analysis(d)	P = 0.6873			
Cochran-Armitage test(e)	P = 0.6996			
Fisher Exact test(e)		P = 0.1474	P = 0.4863	P = 0.4863
	SITE : Harderian gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	2/50(4.0)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	2.86	5.13	7.32	8.33
Terminal rates(c)	1/35(2.9)	1/31(3.2)	2/34(5.9)	2/34(5.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1766			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3645			
Fisher Exact test(e)		P = 0.4926	P = 0.3235	P = 0.3235

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01

Group Name	Control	8000 ppm	20000 ppm	50000 ppm
	SITE : ALL SITE TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	18/50(36.0)	11/50(22.0)	11/50(22.0)
Adjusted rates(b)	2.86	25.81	7.69	14.63
Terminal rates(c)	1/35(2.9)	8/31(25.8)	2/34(5.9)	4/34(11.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6823			
Prevalence method(d)	P = 0.2553			
Combined analysis(d)	P = 0.4854			
Cochran-Armitage test(e)	P = 0.8805			
Fisher Exact test(e)		P = 0.0222*	P = 0.1955	P = 0.1955
	SITE : ALL SITE TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	15/50(30.0)	14/50(28.0)	11/50(22.0)	7/50(14.0)
Adjusted rates(b)	31.43	19.35	17.65	5.88
Terminal rates(c)	11/35(31.4)	6/31(19.4)	6/34(17.6)	2/34(5.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5762			
Prevalence method(d)	P = 0.9965			
Combined analysis(d)	P = 0.9770			
Cochran-Armitage test(e)	P = 0.0395*			
Fisher Exact test(e)		P = 0.4810	P = 0.3167	P = 0.0941

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01

APPENDIX O 1

HISTOLOGICAL FINDINGS :METASTASIS OF TUMOR (2-YEAR STUDY: SUMMARY)

RAT: MALE : ALL ANIMALS

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : METASTASIS OF TUMOR (SUMMARY)
ALL ANIMALS (0-105W)

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Respiratory system]						
nasal cavit			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
	metastasis:pancreas tumor		0	0	0	1
lung			<50>	<50>	<50>	<50>
	leukemic cell infiltration		4	1	1	0
	metastasis:thyroid tumor		1	1	0	0
	metastasis:pancreas tumor		0	0	0	1
	metastasis:bone tumor		0	0	1	1
	metastasis:preputial/clitoral gland tumor		1	0	0	0
[Hematopoietic system]						
bone marrow			<50>	<50>	<50>	<50>
	leukemic cell infiltration		4	1	1	1
lymph node			<50>	<50>	<50>	<50>
	leukemic cell infiltration		3	0	0	0
[Circulatory system]						
heart			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	1
	metastasis:thyroid tumor		1	0	0	0
[Digestive system]						
salivary gl			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Digestive system]						
stomach			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
small intes			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
large intes			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
liver			<50>	<50>	<50>	<50>
	leukemic cell infiltration		5	1	1	1
pancreas			<50>	<50>	<50>	<50>
	leukemic cell infiltration		2	0	0	0
[Urinary system]						
kidney			<50>	<50>	<50>	<50>
	leukemic cell infiltration		3	1	1	0
	metastasis:pancreas tumor		0	0	0	1
urin bladd			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
[Endocrine system]						
pituitary			<49>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
	metastasis:pancreas tumor		0	0	0	1
thyroid			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Endocrine system]						
adrenal			<50>	<50>	<50>	<50>
	leukemic cell infiltration		2	1	1	1
	metastasis:pancreas tumor		0	0	0	1
[Reproductive system]						
prostate			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
[Nervous system]						
brain			<50>	<50>	<50>	<50>
	leukemic cell infiltration		2	1	1	0
[Musculoskeletal system]						
muscle			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	0	0
	metastasis:pancreas tumor		0	0	0	1
[Body cavities]						
pleura			<50>	<50>	<50>	<50>
	metastasis:bone tumor		0	0	0	1
retroperit			<50>	<50>	<50>	<50>
	metastasis:preputial/clitoral gland tumor		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

APPENDIX O 2

HISTOLOGICAL FINDINGS :METASTASIS OF TUMOR (2-YEAR STUDY: SUMMARY)

RAT: FEMALE : ALL ANIMALS

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS : METASTASIS OF TUMOR (SUMMARY)
ALL ANIMALS (0-105W)

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Respiratory system]						
nasal cavit			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	0	1
lung			<50>	<50>	<50>	<50>
	leukemic cell infiltration		4	6	1	4
	metastasis:bone tumor		0	0	1	0
	metastasis:mammary gland tumor		0	0	1	0
	metastasis:mediastinum tumor		1	0	0	0
[Hematopoietic system]						
bone marrow			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	3	0	3
lymph node			<50>	<50>	<50>	<50>
	leukemic cell infiltration		3	0	0	3
	metastasis:uterus tumor		0	0	0	1
[Circulatory system]						
heart			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	0	1
	metastasis:mediastinum tumor		1	0	0	0
[Digestive system]						
tongue			<50>	<50>	<50>	<50>
	metastasis:subcutis tumor		0	1	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Digestive system]						
salivary gl			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
stomach			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
	metastasis:uterus tumor		0	0	1	0
small intes			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
large intes			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
liver			<50>	<50>	<50>	<50>
	leukemic cell infiltration		5	7	1	6
	metastasis:uterus tumor		0	0	1	1
pancreas			<50>	<50>	<50>	<50>
	leukemic cell infiltration		2	0	0	1
[Urinary system]						
kidney			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	3	2	3
	metastasis:mediastinum tumor		1	0	0	0
[Endocrine system]						
pituitary			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	1

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Endocrine system]						
adrenal			<50>	<50>	<50>	<50>
	leukemic cell infiltration		3	3	1	3
[Reproductive system]						
ovary			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	2	0	0
[Nervous system]						
brain			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	3	0	2
	metastasis:pituitary tumor		0	0	1	0
spinal cord			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	3	0	1
[Musculoskeletal system]						
muscle			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	1
[Body cavities]						
pleura			<50>	<50>	<50>	<50>
	metastasis:mediastinum tumor		1	0	0	0
peritoneum			<50>	<50>	<50>	<50>
	metastasis:uterus tumor		0	0	0	1
retroperit			<50>	<50>	<50>	<50>
	metastasis:uterus tumor		0	0	1	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

APPENDIX O 3

HISTOLOGICAL FINDINGS :METASTASIS OF TUMOR (2-YEAR STUDY: SUMMARY)

RAT: MALE : SACRIFICED ANIMALS

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS : METASTASIS OF TUMOR (SUMMARY)
SACRIFICED ANIMALS (105W)

Organ	Findings	Group Name / No. of Animals on Study	Control 40	8000 ppm 40	20000 ppm 40	50000 ppm 37
[Respiratory system]						
lung			<40>	<40>	<40>	<37>
	leukemic cell infiltration		2	1	1	2
[Hematopoietic system]						
bone marrow			<40>	<40>	<40>	<37>
	leukemic cell infiltration		0	0	0	1
lymph node			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	0	1
[Digestive system]						
salivary gl			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	0	0
stomach			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	0	0
small intes			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	0	0
large intes			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	0	0
liver			<40>	<40>	<40>	<37>
	leukemic cell infiltration		3	2	1	3
pancreas			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	0	0
[Urinary system]						
kidney			<40>	<40>	<40>	<37>
	leukemic cell infiltration		0	0	2	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 40	8000 ppm 40	20000 ppm 40	50000 ppm 37
[Endocrine system]						
pituitary			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	0	0
adrenal			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	1	1
[Nervous system]						
brain			<40>	<40>	<40>	<37>
	leukemic cell infiltration		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

APPENDIX O 4

HISTOLOGICAL FINDINGS :METASTASIS OF TUMOR (2-YEAR STUDY: SUMMARY)

RAT: FEMALE : SACRIFICED ANIMALS

STUDY NO. : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : METASTASIS OF TUMOR (SUMMARY)
SACRIFICED ANIMALS (105W)

Organ	Findings	Group Name / No. of Animals on Study	Control	8000 ppm	20000 ppm	50000 ppm
			33	43	43	38
[Respiratory system]						
nasal cavit			<33>	<43>	<43>	<38>
	metastasis:pancreas tumor		0	0	0	1
lung			<33>	<43>	<43>	<38>
	metastasis:thyroid tumor		1	1	0	0
	metastasis:pancreas tumor		0	0	0	1
[Hematopoietic system]						
bone marrow			<33>	<43>	<43>	<38>
	leukemic cell infiltration		0	0	0	1
[Circulatory system]						
heart			<33>	<43>	<43>	<38>
	leukemic cell infiltration		0	0	0	1
	metastasis:thyroid tumor		1	0	0	0
[Digestive system]						
liver			<33>	<43>	<43>	<38>
	leukemic cell infiltration		0	0	0	1
[Urinary system]						
kidney			<33>	<43>	<43>	<38>
	metastasis:pancreas tumor		0	0	0	1
[Endocrine system]						
pituitary			<32>	<43>	<43>	<38>
	metastasis:pancreas tumor		0	0	0	1

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 33	8000 ppm 43	20000 ppm 43	50000 ppm 38
[Endocrine system]						
adrenal			<33>	<43>	<43>	<38>
	leukemic cell infiltration		0	0	0	1
	metastasis:pancreas tumor		0	0	0	1
[Musculoskeletal system]						
muscle			<33>	<43>	<43>	<38>
	metastasis:pancreas tumor		0	0	0	1

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

APPENDIX O 5

HISTOLOGICAL FINDINGS :METASTASIS OF TUMOR (2-YEAR STUDY: SUMMARY)

MOUSE: MALE : ALL ANIMALS

STUDY NO. : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : METASTASIS OF TUMOR (SUMMARY)
ALL ANIMALS (0-105W)

Organ	Findings	Group Name / No. of Animals on Study	Control	3200 ppm	8000 ppm	20000 ppm
			49	50	50	50
[Respiratory system]						
nasal cavit			<49>	<50>	<50>	<50>
	metastasis:liver tumor		0	0	0	1
	metastasis:subcutis tumor		0	0	1	0
	metastasis:spleen tumor		0	0	0	1
	metastasis:urinary bladder tumor		0	0	0	1
lung			<49>	<50>	<50>	<50>
	leukemic cell infiltration		1	2	1	1
	metastasis:liver tumor		1	1	2	1
	metastasis:spleen tumor		0	0	0	1
	metastasis:urinary bladder tumor		0	0	0	1
[Hematopoietic system]						
bone marrow			<49>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	0	0
	metastasis:subcutis tumor		0	0	1	0
lymph node			<49>	<50>	<50>	<50>
	metastasis:liver tumor		0	0	0	1
	metastasis:subcutis tumor		0	1	0	0
spleen			<49>	<50>	<50>	<50>
	leukemic cell infiltration		2	3	2	2
	metastasis:liver tumor		0	0	0	1

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 49	3200 ppm 50	8000 ppm 50	20000 ppm 50
[Hematopoietic system]						
spleen			<49>	<50>	<50>	<50>
	metastasis:lympho node tumor		1	0	0	0
[Circulatory system]						
heart			<49>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	1	1
	metastasis:liver tumor		0	1	2	0
[Digestive system]						
tongue			<49>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	0	0
salivary gl			<49>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	1	0
	metastasis:liver tumor		0	1	1	0
	metastasis:subcutis tumor		0	1	0	0
stomach			<49>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	1	0
	metastasis:liver tumor		1	0	1	0
	metastasis:lympho node tumor		1	0	0	0
small intes			<49>	<50>	<50>	<50>
	metastasis:liver tumor		1	0	0	0
	metastasis:epididymis tumor		0	0	0	1

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 49	3200 ppm 50	8000 ppm 50	20000 ppm 50
[Digestive system]						
large intes			<49>	<50>	<50>	<50>
	metastasis:epididymis tumor		0	0	0	1
liver			<49>	<50>	<50>	<50>
	leukemic cell infiltration		1	1	2	1
	metastasis:subcutis tumor		0	0	1	0
	metastasis:spleen tumor		0	0	0	1
	metastasis:urinary bladder tumor		0	0	0	1
	metastasis:epididymis tumor		0	0	0	1
	metastasis:lympho node tumor		1	0	0	1
pancreas			<49>	<50>	<50>	<50>
	leukemic cell infiltration		1	2	0	0
	metastasis:liver tumor		1	0	0	0
	metastasis:urinary bladder tumor		0	0	0	1
[Urinary system]						
kidney			<49>	<50>	<50>	<50>
	leukemic cell infiltration		1	1	2	1
	metastasis:liver tumor		1	1	1	2
	metastasis:spleen tumor		0	0	0	1
	metastasis:salivary gland tumor		0	0	0	1
	metastasis:lympho node tumor		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 49	3200 ppm 50	8000 ppm 50	20000 ppm 50
[Urinary system]						
urin bladd			<49>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	0	0
	metastasis:epididymis tumor		1	0	0	0
[Endocrine system]						
panc islet			<49>	<50>	<50>	<50>
	metastasis:lympho node tumor		1	0	0	0
adrenal			<49>	<50>	<50>	<50>
	metastasis:spleen tumor		0	0	0	1
[Reproductive system]						
testis			<49>	<50>	<50>	<50>
	metastasis:liver tumor		0	1	0	0
	metastasis:subcutis tumor		0	0	1	0
	metastasis:epididymis tumor		0	0	0	1
	metastasis:salivary gland tumor		0	1	0	0
epididymis			<49>	<50>	<50>	<50>
	leukemic cell infiltration		1	0	1	0
	metastasis:subcutis tumor		0	0	1	0
semin ves			<49>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	1	0
	metastasis:liver tumor		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 49	3200 ppm 50	8000 ppm 50	20000 ppm 50
[Reproductive system]						
prostate			<49>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	1	0
[Musculoskeletal system]						
muscle			<49>	<50>	<50>	<50>
	metastasis:liver tumor		0	0	0	1
[Body cavities]						
mediastinum			<49>	<50>	<50>	<50>
	metastasis:liver tumor		0	0	1	0
	metastasis:lung tumor		0	0	1	0
peritoneum			<49>	<50>	<50>	<50>
	metastasis:liver tumor		0	0	1	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

APPENDIX O 6

HISTOLOGICAL FINDINGS :METASTASIS OF TUMOR (2-YEAR STUDY : SUMMARY)

MOUSE: FEMALE : ALL ANIMALS

Organ	Findings	Group Name	Control	8000 ppm	20000 ppm	50000 ppm
		No. of Animals on Study	50	50	50	50
[Integumentary system/appandage]						
skin/app			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	0	3
[Respiratory system]						
nasal cavit			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	1	0
	metastasis:liver tumor		0	1	0	0
	metastasis:uterus tumor		0	1	1	0
larynx			<50>	<50>	<50>	<50>
	metastasis:thyroid tumor		0	1	0	0
lung			<50>	<50>	<50>	<50>
	leukemic cell infiltration		4	11	7	5
	metastasis:liver tumor		0	1	4	2
	metastasis:uterus tumor		3	2	2	0
	metastasis:subcutis tumor		0	1	0	0
	metastasis:bone tumor		1	0	0	0
[Hematopoietic system]						
bone marrow			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	3	2	0
	metastasis:liver tumor		0	0	0	1
	metastasis:uterus tumor		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Hematopoietic system]						
bone marrow			<50>	<50>	<50>	<50>
	metastasis:lympho node tumor		0	0	1	0
lymph node			<50>	<50>	<50>	<50>
	metastasis:liver tumor		0	0	1	0
spleen			<50>	<50>	<50>	<50>
	leukemic cell infiltration		6	9	5	7
	metastasis:liver tumor		0	0	1	2
	metastasis:lympho node tumor		0	0	1	0
[Circulatory system]						
heart			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	3	2	3
	metastasis:liver tumor		0	1	0	0
[Digestive system]						
tongue			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	0	0
salivary gl			<50>	<50>	<50>	<50>
	leukemic cell infiltration		2	5	3	2
stomach			<50>	<50>	<50>	<50>
	leukemic cell infiltration		2	3	2	1
	metastasis:liver tumor		0	1	0	0
	metastasis:uterus tumor		1	2	2	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Digestive system]						
small intes			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	1	0
	metastasis:uterus tumor		0	1	0	0
large intes			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	1	0
liver			<50>	<50>	<50>	<50>
	leukemic cell infiltration		8	10	6	5
	metastasis:uterus tumor		6	6	5	2
	metastasis:subcutis tumor		0	1	0	0
	metastasis:bone tumor		1	0	0	0
	metastasis:lympho node tumor		0	0	1	0
pancreas			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	2	2	0
	metastasis:uterus tumor		1	0	1	0
[Urinary system]						
kidney			<50>	<50>	<50>	<50>
	leukemic cell infiltration		4	8	6	3
	metastasis:liver tumor		0	0	1	1
	metastasis:uterus tumor		1	1	2	0
	metastasis:subcutis tumor		0	1	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Urinary system]						
kidney			<50>	<50>	<50>	<50>
	metastasis:stomach tumor		0	0	0	1
	metastasis:urinary bladder tumor		0	1	0	0
	metastasis:lympho node tumor		0	0	1	0
urin bladd			<50>	<50>	<50>	<50>
	leukemic cell infiltration		3	7	4	1
	metastasis:liver tumor		0	1	0	0
	metastasis:subcutis tumor		0	1	0	0
[Endocrine system]						
thyroid			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	0	1
adrenal			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	3	1	1
[Reproductive system]						
ovary			<50>	<50>	<50>	<50>
	leukemic cell infiltration		4	10	2	4
	metastasis:liver tumor		0	1	1	0
	metastasis:uterus tumor		3	3	5	2
	metastasis:subcutis tumor		0	1	0	0
uterus			<50>	<50>	<50>	<50>
	leukemic cell infiltration		1	5	2	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Reproductive system]						
vagina			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	4	0	0
	metastasis:subcutis tumor		0	1	0	1
[Nervous system]						
brain			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	3	1	0
	metastasis:liver tumor		0	1	0	0
periph nerv			<50>	<50>	<50>	<50>
	metastasis:liver tumor		0	1	0	0
[Special sense organs/appandage]						
eye			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	1	0
Harder gl			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	1	1	1
[Musculoskeletal system]						
muscle			<50>	<50>	<50>	<50>
	leukemic cell infiltration		0	0	2	0
[Body cavities]						
mediastinum			<50>	<50>	<50>	<50>
	metastasis:bone tumor		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 50	8000 ppm 50	20000 ppm 50	50000 ppm 50
[Body cavities]						
mediastinum			<50>	<50>	<50>	<50>
	metastasis:lympho node tumor		0	0	1	0
peritoneum			<50>	<50>	<50>	<50>
	leukemic cell infiltration		4	5	1	2
	metastasis:liver tumor		0	0	1	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

APPENDIX O 7

HISTOLOGICAL FINDINGS :METASTASIS OF TUMOR (2-YEAR STUDY: SUMMARY)

MOUSE: MALE : SACRIFICED ANIMALS

STUDY NO. : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
SEX : MALE

HISTOLOGICAL FINDINGS : METASTASIS OF TUMOR (SUMMARY)
SACRIFICED ANIMALS (105W)

Organ	Findings	Group Name / No. of Animals on Study	Control 41	3200 ppm 41	8000 ppm 37	20000 ppm 42
[Respiratory system]						
nasal cavit			<41>	<41>	<37>	<42>
	metastasis:spleen tumor		0	0	0	1
lung			<41>	<41>	<37>	<42>
	leukemic cell infiltration		1	1	1	0
	metastasis:spleen tumor		0	0	0	1
[Hematopoietic system]						
bone marrow			<41>	<41>	<37>	<42>
	leukemic cell infiltration		0	1	0	0
lymph node			<41>	<41>	<37>	<42>
	metastasis:subcutis tumor		0	1	0	0
spleen			<41>	<41>	<37>	<42>
	leukemic cell infiltration		2	2	2	2
	metastasis:lympho node tumor		1	0	0	0
[Circulatory system]						
heart			<41>	<41>	<37>	<42>
	leukemic cell infiltration		0	1	1	0
	metastasis:liver tumor		0	1	0	0
[Digestive system]						
tongue			<41>	<41>	<37>	<42>
	leukemic cell infiltration		0	1	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control	3200 ppm	8000 ppm	20000 ppm
			41	41	37	42
[Digestive system]						
salivary gl			<41>	<41>	<37>	<42>
	leukemic cell infiltration		0	1	1	0
	metastasis:subcutis tumor		0	1	0	0
stomach			<41>	<41>	<37>	<42>
	leukemic cell infiltration		0	0	1	0
	metastasis:lympho node tumor		1	0	0	0
liver			<41>	<41>	<37>	<42>
	leukemic cell infiltration		1	1	1	0
	metastasis:spleen tumor		0	0	0	1
	metastasis:lympho node tumor		1	0	0	0
pancreas			<41>	<41>	<37>	<42>
	leukemic cell infiltration		1	1	0	0
[Urinary system]						
kidney			<41>	<41>	<37>	<42>
	leukemic cell infiltration		1	1	1	0
	metastasis:spleen tumor		0	0	0	1
	metastasis:salivary gland tumor		0	0	0	1
	metastasis:lympho node tumor		1	0	0	0
urin bladd			<41>	<41>	<37>	<42>
	leukemic cell infiltration		1	0	0	0
	metastasis:epididymis tumor		1	0	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 41	3200 ppm 41	8000 ppm 37	20000 ppm 42
[Endocrine system]						
panc islet			<41>	<41>	<37>	<42>
	metastasis:lympho node tumor		1	0	0	0
adrenal			<41>	<41>	<37>	<42>
	metastasis:spleen tumor		0	0	0	1
[Reproductive system]						
testis			<41>	<41>	<37>	<42>
	metastasis:salivary gland tumor		0	1	0	0
epididymis			<41>	<41>	<37>	<42>
	leukemic cell infiltration		1	0	1	0
semin ves			<41>	<41>	<37>	<42>
	leukemic cell infiltration		0	1	1	0
prostate			<41>	<41>	<37>	<42>
	leukemic cell infiltration		0	0	1	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

APPENDIX O 8

HISTOLOGICAL FINDINGS :METASTASIS OF TUMOR (2-YEAR STUDY: SUMMARY)

MOUSE: FEMALE : SACRIFICED ANIMALS

STUDY NO. : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
SEX : FEMALE

HISTOLOGICAL FINDINGS : METASTASIS OF TUMOR (SUMMARY)
SACRIFICED ANIMALS (105W)

Organ	Findings	Group Name / No. of Animals on Study	Control 35	8000 ppm 31	20000 ppm 34	50000 ppm 34
[Respiratory system]						
nasal cavit			<35>	<31>	<34>	<34>
	metastasis:uterus tumor		0	1	0	0
lung			<35>	<31>	<34>	<34>
	leukemic cell infiltration		1	6	3	0
	metastasis:liver tumor		0	0	1	0
[Hematopoietic system]						
bone marrow			<35>	<31>	<34>	<34>
	leukemic cell infiltration		0	2	0	0
	metastasis:lympho node tumor		0	0	1	0
spleen			<35>	<31>	<34>	<34>
	leukemic cell infiltration		4	5	3	2
	metastasis:lympho node tumor		0	0	1	0
[Circulatory system]						
heart			<35>	<31>	<34>	<34>
	leukemic cell infiltration		0	1	1	0
[Digestive system]						
salivary gl			<35>	<31>	<34>	<34>
	leukemic cell infiltration		1	2	2	0
stomach			<35>	<31>	<34>	<34>
	leukemic cell infiltration		0	1	1	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 35	8000 ppm 31	20000 ppm 34	50000 ppm 34
[Digestive system]						
stomach			<35>	<31>	<34>	<34>
	metastasis:uterus tumor		1	0	0	0
liver			<35>	<31>	<34>	<34>
	leukemic cell infiltration		5	5	3	1
	metastasis:uterus tumor		1	2	0	0
	metastasis:lympho node tumor		0	0	1	0
pancreas			<35>	<31>	<34>	<34>
	leukemic cell infiltration		0	1	1	0
	metastasis:uterus tumor		1	0	0	0
[Urinary system]						
kidney			<35>	<31>	<34>	<34>
	leukemic cell infiltration		3	5	3	1
	metastasis:uterus tumor		0	1	0	0
	metastasis:urinary bladder tumor		0	1	0	0
	metastasis:lympho node tumor		0	0	1	0
urin bladd			<35>	<31>	<34>	<34>
	leukemic cell infiltration		2	4	3	0
[Endocrine system]						
adrenal			<35>	<31>	<34>	<34>
	leukemic cell infiltration		0	1	1	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

Organ	Findings	Group Name / No. of Animals on Study	Control 35	8000 ppm 31	20000 ppm 34	50000 ppm 34
[Reproductive system]						
ovary			<35>	<31>	<34>	<34>
	leukemic cell infiltration		2	2	0	0
	metastasis:uterus tumor		1	1	0	0
uterus			<35>	<31>	<34>	<34>
	leukemic cell infiltration		1	2	0	0
vagina			<35>	<31>	<34>	<34>
	leukemic cell infiltration		0	2	0	0
	metastasis:subcutis tumor		0	0	0	1
[Nervous system]						
brain			<35>	<31>	<34>	<34>
	leukemic cell infiltration		0	1	0	0
[Musculoskeletal system]						
muscle			<35>	<31>	<34>	<34>
	leukemic cell infiltration		0	0	2	0
[Body cavities]						
mediastinum			<35>	<31>	<34>	<34>
	metastasis:lympho node tumor		0	0	1	0
peritoneum			<35>	<31>	<34>	<34>
	leukemic cell infiltration		1	1	0	0

< a > a : Number of animals examined at the site
b b : Number of animals with lesion

APPENDIX P 1

IDENTITY AND IMPURITY OF ANTHRACENE IN THE 2-YEAR FEED STUDIES

Identity and Impurity of Anthracene in the 2-Year Feed Studies

A.Lot No.507E4208

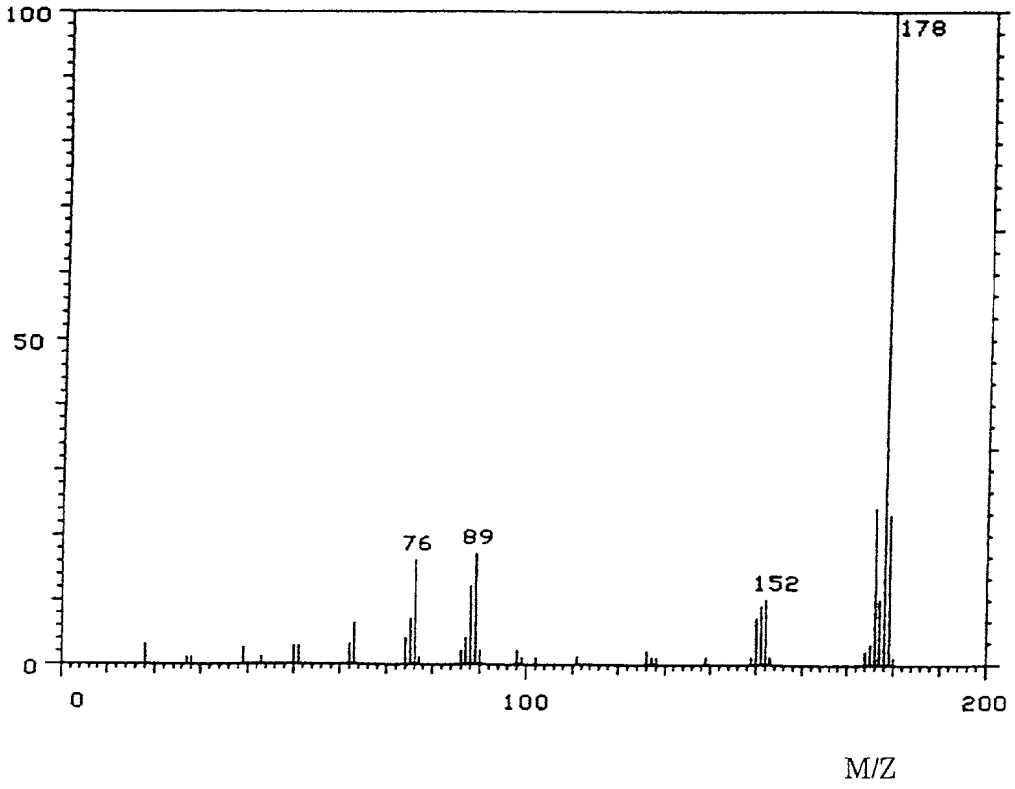
1. Identity(Spectral data)

(1) Mass Spectrometry

Instrument ; Hitachi M-80B Mass Spectrometer

Ionization ; EI(Electron Ionization)

Ionization Voltage ; 70eV



Mass Spectrum of Test Substance

Results; The mass spectrum was consistent with literature spectrum.

Determined Molecular and Fragment Peak(M/Z)	Literature Value* Molecular and Fragment Peak(M/Z)
178[M]$^+$	178[M]$^+$
152	152
89	89
76	76

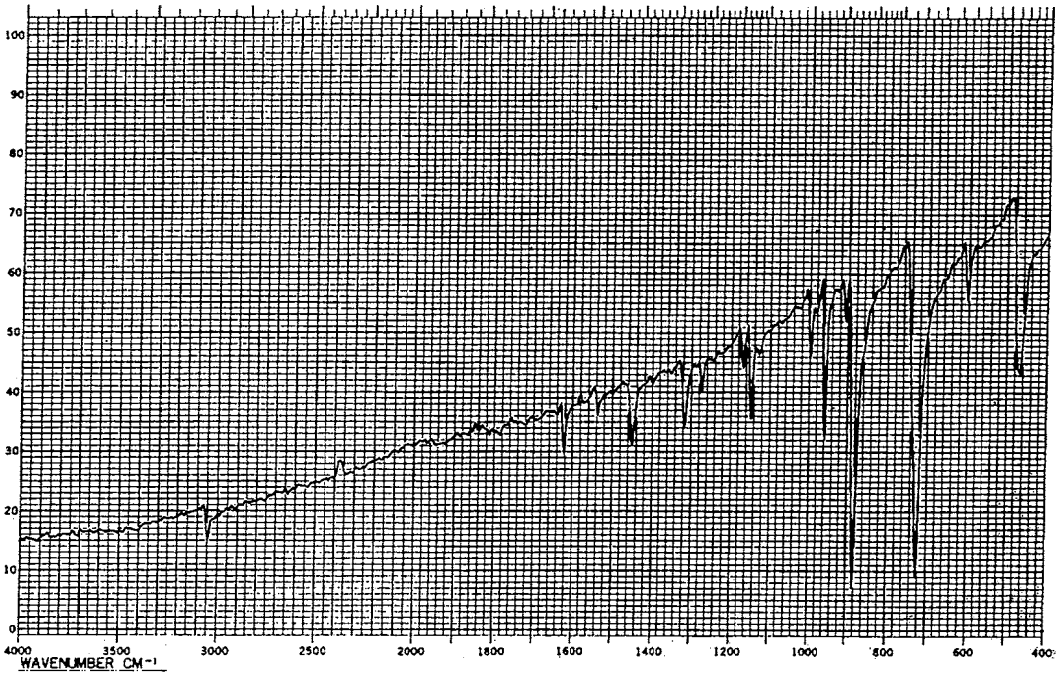
(* EPA/NIH Mass Spectral Data Base(1978) Vol.1, p. 882.)

(2) Infrared Spectrometry

Instrument ; Hitachi 270-30 Infrared Spectrometer

Cell ; KBr

Slit ; Medium



Infrared Spectrum of Test Substance

Results; The infrared spectrum was consistent with literature spectrum.

Determines Wave Number(cm^{-1})	Literature Values* Wave Number(cm^{-1})
460～ 490	460～ 490
700～ 750	700～ 750
860～ 900	860～ 900
940～ 970	940～ 970
990～1010	990～1010
1130～1160	1130～1160
1300～1330	1300～1330
1440～1470	1440～1470
	1530～1550
1610～1640	1610～1640
3030～3080	3010～3050

(Sadtler Handbook by Sadtler Research Laboratories, Inc. (1978) p. 78.)

2. Impurity(Gas Chromatography)

Instrument ; Hewlett Packard 5890A Gas Chromatograph

Column ; METHYL SILICONE(0.2mmϕ×30m)

Column Temperature ; 170°C

Flow Rate ; 1 ml/min

Detector ; FID(Flame Ionization Detector)

Injection Volume ; 1 μl

Results; Gas chromatography indicated one major peak(peak No.1) and two impurities. It was identified only by comparing its gas chromatograph with that of the Carbazole(peak No.3) in the Anthracene,the amount in the test substance was 0.0857% by standard sample(Carbazole).

Sample Name	Peak No.	Retention Time(min)	Peak Name
Test sabstance	1	16.477	Anthracene
	2	16.9	Not Identity
	3	17.867	Carbazole
Carbazole (standard sample)		17.925	

3. Conclusions; The result of the mass spectrum and the infrared spectrum agreed with the literature values.Consequently,the test substance was identified as Anthracene.
Gas chromatography indicated one major peak and two impurities, it was identified only by comparing its gas chromatograph with that of the Carbazole, the amount in the test substance was 0.0857%.

B.Lot No.507E4209

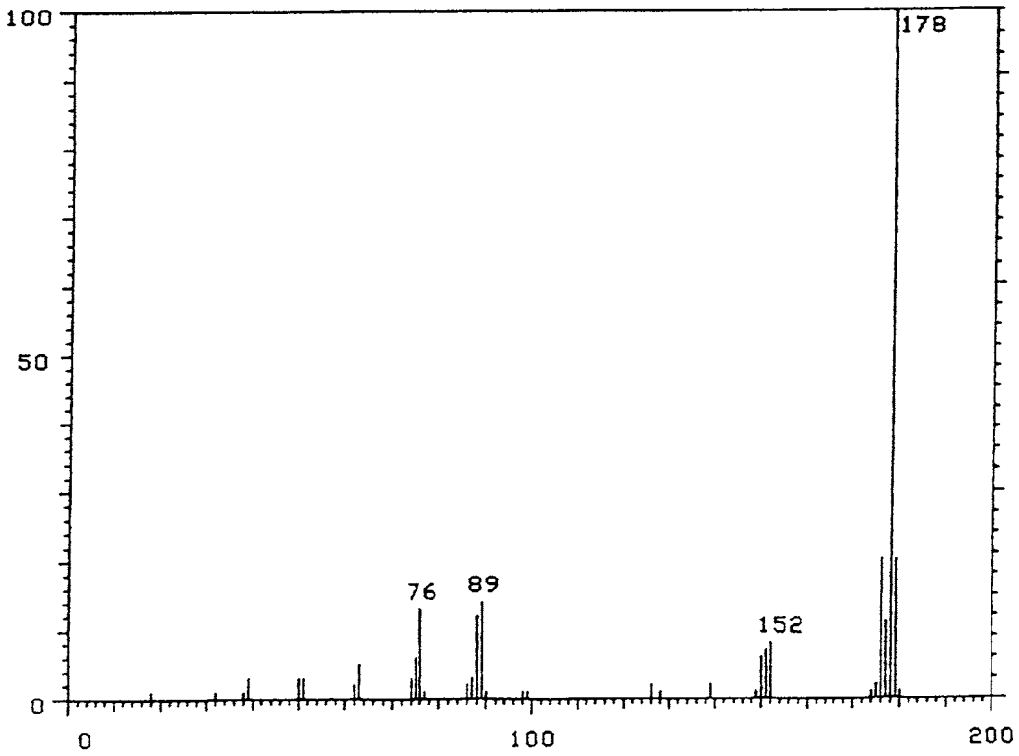
1. Identity(Spectral data)

(1) Mass Spectrometry

Instrument ; Hitachi M-80B Mass Spectrometer

Ionization ; EI(Electron Ionization)

Ionization Voltage ; 70eV



Mass Spectrum of Test Substance

Results; The mass spectrum was consistent with literature spectrum.

Determined Molecular and Fragment Peak(M/Z)	Literature Value* Molecular and Fragment Peak(M/Z)
$178[M]^+$	$178[M]^+$
152	152
89	89
76	76

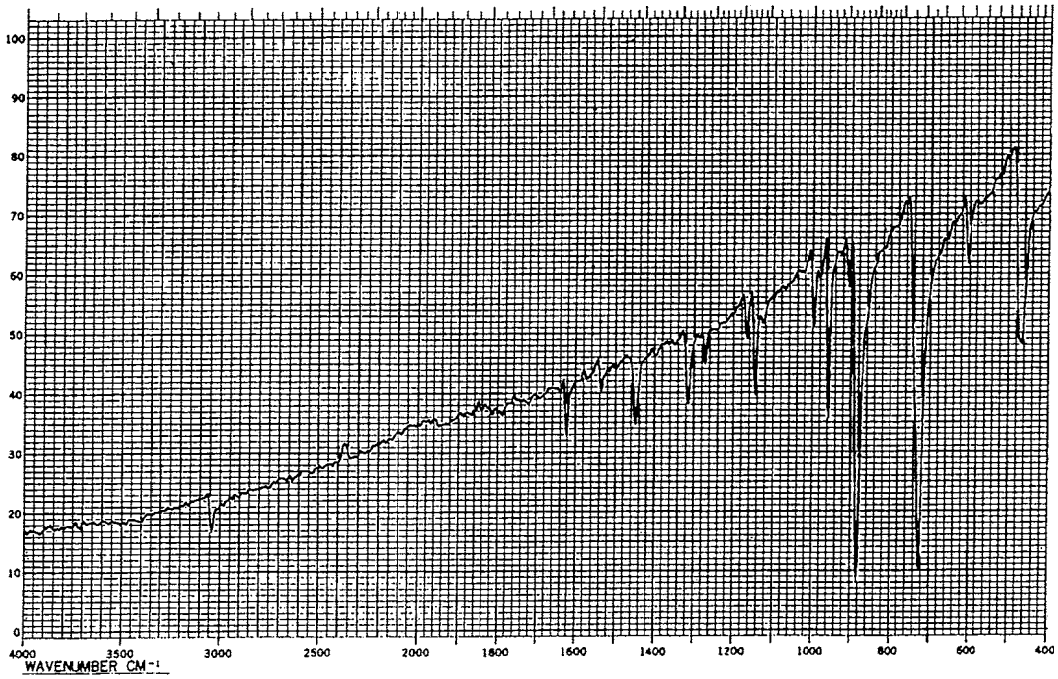
(* EPA/NIH Mass Spectral Data Base(1978) Vol.1, p. 882.)

(2) Infrared Spectrometry

Instrument ; Hitachi 270-30 Infrared Spectrometer

Cell ; KBr

Slit ; Medium



Infrared Spectrum of Test Substance

Results; The infrared spectrum was consistent with literature spectrum.

Determines Wave Number(cm^{-1})	Literature Values* Wave Number(cm^{-1})
460～ 490	460～ 490
700～ 750	700～ 750
860～ 900	860～ 900
940～ 970	940～ 970
990～1010	990～1010
1130～1160	1130～1160
1300～1330	1300～1330
1440～1470	1440～1470
	1530～1550
1610～1640	1610～1640
3030～3080	3010～3050

(Sadtler Handbook by Sadtler Research Laboratories,Inc. (1978) p. 78.)

2. Impurity(Gas Chromatography)

Instrument ; Hewlett Packard 5890A Gas Chromatograph

Column ; METHYL SILICONE(0.2mmϕ×30m)

Column Temperature ; 170°C

Flow Rate ; 1 ml/min

Detector ; FID(Flame Ionization Detector)

Injection Volume ; 1 μl

Results; Gas chromatography indicated one major peak(peak No.1) and two impurities. It was identified only by comparing its gas chromatograph with that of the Carbazole(peak No.3) in the Anthracene,the amount in the test substance was 0.0841% by standard sample(Carbazole).

Sample Name	Peak No.	Retention Time(min)	Peak Name
Test sabstance	1	16.472	Anthracene
	2	16.89	Not Identity
	3	17.848	Carbazole
Carbazole (standard sample)		17.925	

3. Conclusions; The result of the mass spectrum and the infrared spectrum agreed with the literature values.Consequently,the test substance was identified as Anthracene.
Gas chromatography indicated one major peak and two impurities, it was identified only by comparing its gas chromatograph with that of the Carbazole, the amount in the test substance was 0.0841%.

C.Lot No.507E4210

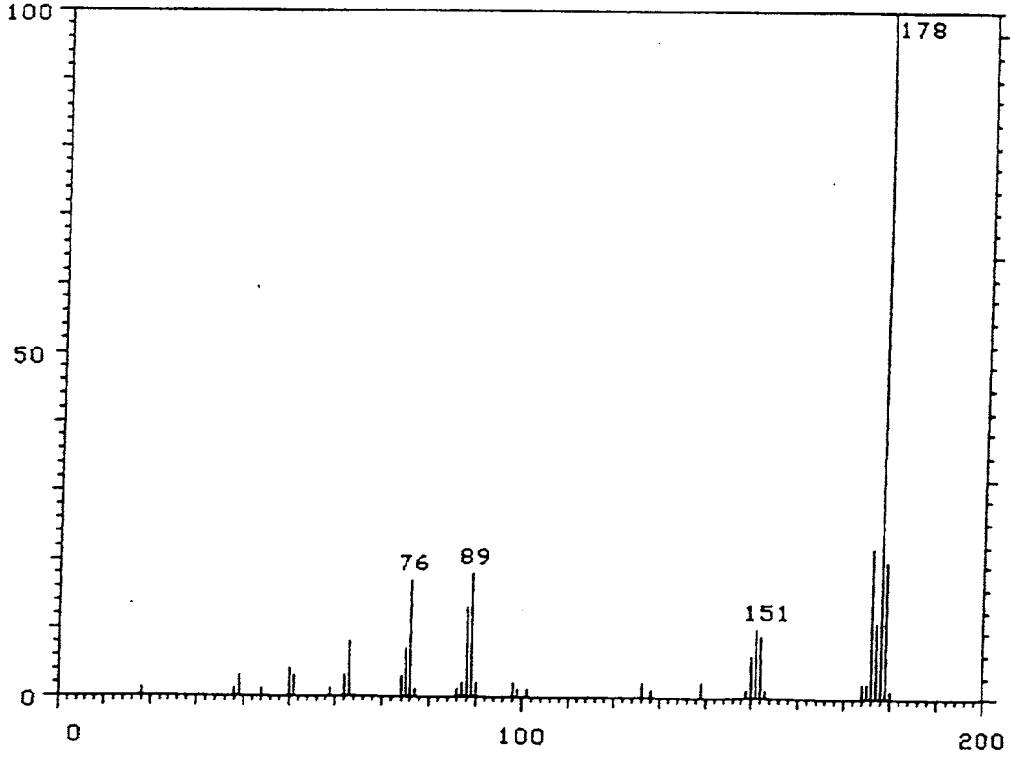
1. Identity(Spectral data)

(1) Mass Spectrometry

Instrument ; Hitachi M-80B Mass Spectrometer

Ionization ; EI(Electron Ionization)

Ionization Voltage ; 70eV



Mass Spectrum of Test Substance

Results; The mass spectrum was consistent with literature spectrum.

Determined Molecular and Fragment Peak(M/Z)	Literature Value* Molecular and Fragment Peak(M/Z)
$178[M]^+$	$178[M]^+$
152	152
89	89
76	76

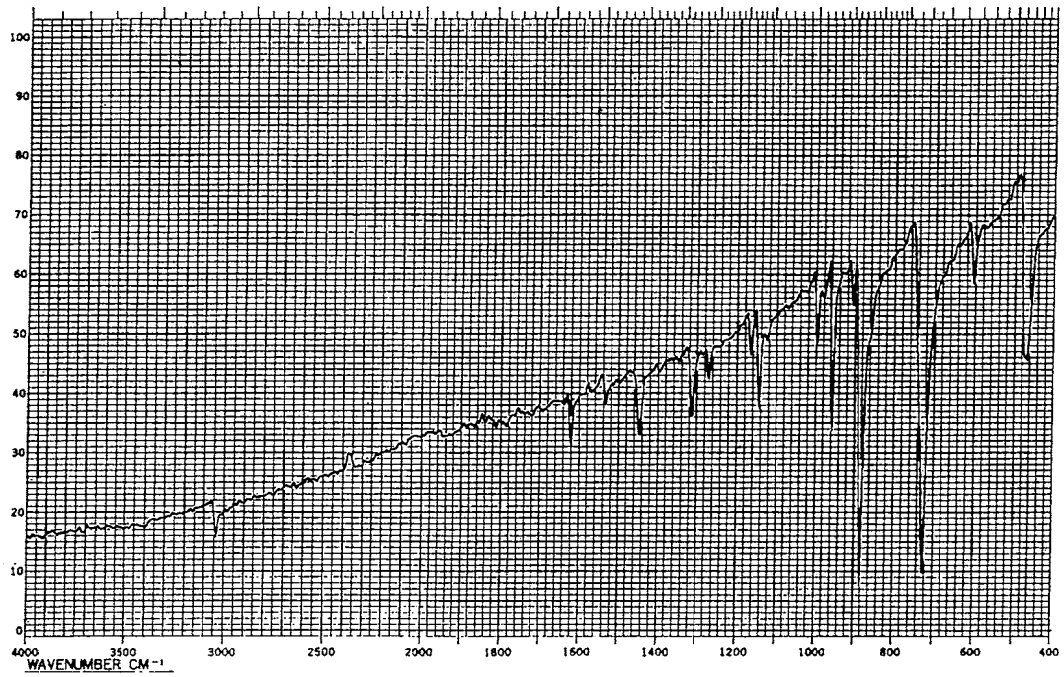
(* EPA/NIH Mass Spectral Data Base(1978) Vol.1, p. 882.)

(2) Infrared Spectrometry

Instrument ; Hitachi 270-30 Infrared Spectrometer

Cell ; KBr

Slit ; Medium



Infrared Spectrum of Test Substance

Results; The infrared spectrum was consistent with literature spectrum.

Determines Wave Number(cm^{-1})	Literature Values* Wave Number(cm^{-1})
460～ 490	460～ 490
700～ 750	700～ 750
860～ 900	860～ 900
940～ 970	940～ 970
990～1010	990～1010
1130～1160	1130～1160
1300～1330	1300～1330
1440～1470	1440～1470
	1530～1550
1610～1640	1610～1640
3030～3080	3010～3050

(Sadtler Handbook by Sadtler Research Laboratories, Inc. (1978) p. 78.)

2. Impurity(Gas Chromatography)

Instrument ; Hewlett Packard 5890A Gas Chromatograph

Column ; METHYL SILICONE(0.2mmϕ×30m)

Column Temperature ; 170°C

Flow Rate ; 1 ml/min

Detector ; FID(Flame Ionization Detector)

Injection Volume ; 1 μl

Results; Gas chromatography indicated one major peak(peak No.1) and two impurities. It was identified only by comparing its gas chromatograph with that of the Carbazole(peak No.3) in the Anthracene,the amount in the test substance was 0.0594% by standard sample(Carbazole).

Sample Name	Peak No.	Retention Time(min)	Peak Name
Test sabstance	1	16.458	Anthracene
	2	16.882	Not Identity
	3	17.842	Carbazole
Carbazole (standard sample)		17.925	

3. Conclusions; The result of the mass spectrum and the infrared spectrum agreed with the literature values.Consequently,the test substance was identified as Anthracene.
Gas chromatography indicated one major peak and two impurities, it was identified only by comparing its gas chromatograph with that of the Carbazole, the amount in the test substance was 0.0594%.

APPENDIX P 2

STABILITY OF ANTHRACENE IN THE 2-YEAR FEED STUDIES

Stability of Anthracene in the 2-Year Feed Studies

A.Lot No.507E4208

1.Sample storage; This lot was used from 1993.9.9 to 1994.6.16. Test substance was stored at room temperature.

2. Infrared Spectrometry

Instrument ; Hitachi 270-30 Infrared Spectrometer

Cell ; KBr

Slit ; Medium

Results; The result of infrared spectrum did not change when the term of administration.

1993.08.04. Wave Number(cm^{-1})	1994.06.23. Wave Number(cm^{-1})
460～ 490	460～ 490
700～ 750	700～ 750
860～ 900	860～ 900
940～ 970	940～ 970
990～1010	990～1010
1130～1160	1130～1160
1300～1330	1300～1330
1440～1470	1440～1470
1610～1640	1610～1640
3030～3080	3030～3080

3. Gas Chromatography

Instrument ; Hewlett Packard 5890A Gas Chromatograph

Column ; METHYL SILICONE(0.2mmϕ×30m)

Column Temperature ; 170°C

Flow Rate ; 1 ml/min

Detector ; FID(Flame Ionization Detector)

Injection Volume ; 1 μl

Results; Gas chromatography indicated one major peak(peak No.1) and two impurities(peak No.2,3 < 0.3% of total area) analyzed at 1993.8.4 and one major peak(peak No.1) and two impurities(peak No.2,3 < 0.3% of total area) analyzed at 1994.6.23. No new treace impurity peak in the test substance analyzed at 1994.6.23 was detected.

Date	Peak No.	Retention Time(min)	(percent of total peak)
1993.08.04	1	16.477	99.7771
(date analyzed)	2	16.9	0.1414
	3	17.867	0.0816
1994.06.23	1	16.458	99.7837
(date analyzed)	2	16.882	0.1345
	3	17.84	0.0818

4. Conclusions; The results indicated that the test substance did not change when stored in the dark at room temperature during this period(for about 11 months).

B.Lot No.507E4209

1.Sample storage; This lot was used from 1994.6.16 to 1995.6.1. Test substance was stored at room temperature.

2. Infrared Spectrometry

Instrument ; Hitachi 270-30 Infrared Spectrometer

Cell ; KBr

Slit ; Medium

Results; The result of infrared spectrum did not change when the term of administration.

1993.08.04. Wave Number(cm^{-1})	1995.06.08. Wave Number(cm^{-1})
460～ 490	460～ 490
700～ 750	700～ 750
860～ 900	860～ 900
940～ 970	940～ 970
990～1010	990～1010
1130～1160	1130～1160
1300～1330	1300～1330
1440～1470	1440～1470
1610～1640	1610～1640
3030～3080	3030～3080

3. Gas Chromatography

Instrument ; Hewlett Packard 5890A Gas Chromatograph

Column ; METHYL SILICONE(0.2mmϕ×30m)

Column Temperature ; 170°C

Flow Rate ; 1 ml/min

Detector ; FID(Flame Ionization Detector)

Injection Volume ; 1 μl

Results; Gas chromatography indicated one major peak(peak No.1) and two impurities(peak No.2,3 < 0.3% of total area) analyzed at 1993.8.4 and one major peak(peak No.1) and two impurities(peak No.2,3 < 0.3% of total area) analyzed at 1995.6.8. No new treace impurity peak in the test substance analyzed at 1995.6.8 was detected.

Date	Peak No.	Retention Time(min)	(percent of total peak)
1993.08.04	1	16.472	99.7795
(date analyzed)	2	16.89	0.1345
	3	17.848	0.0860
1995.06.08	1	16.447	99.7854
(date analyzed)	2	16.877	0.1358
	3	17.832	0.0788

4. Conclusions; The results indicated that the test substance did not change when stored in the dark at room temperature during this period(for about 22 months).

C.Lot No.507E4210

1.Sample storage; This lot was used from 1995.2.2 to 1995.10.5. Test substance was stored at room temperature.

2. Infrared Spectrometry

Instrument ; Hitachi 270-30 Infrared Spectrometer

Cell ; KBr

Slit ; Medium

Results; The result of infrared spectrum did not change when the term of administration.

1993.08.04. Wave Number(cm^{-1})	1995.10.12. Wave Number(cm^{-1})
460～ 490	460～ 490
700～ 750	700～ 750
860～ 900	860～ 900
940～ 970	940～ 970
990～1010	990～1010
1130～1160	1130～1160
1300～1330	1300～1330
1440～1470	1440～1470
1610～1640	1610～1640
3030～3080	3030～3080

3. Gas Chromatography

Instrument ; Hewlett Packard 5890A Gas Chromatograph

Column ; METHYL SILICONE(0.2mmϕ×30m)

Column Temperature ; 170°C

Flow Rate ; 1 ml/min

Detector ; FID(Flame Ionization Detector)

Injection Volume ; 1 μl

Results; Gas chromatography indicated one major peak(peak No.1) and two impurities(peak No.2,3 < 0.2% of total area) analyzed at 1993.8.4 and one major peak(peak No.1) and two impurities(peak No.2,3 < 0.2% of total area) analyzed at 1995.10.12. No new treace impurity peak in the test substance analyzed at 1995.10.12 was detected.

Date	Peak No.	Retention Time(min)	(percent of total peak)
1993.08.04	1	16.458	99.8018
(date analyzed)	2	16.882	0.1388
	3	17.842	0.0595
1995.10.12	1	16.457	99.8043
(date analyzed)	2	16.875	0.1397
	3	17.833	0.0560

4. Conclusions; The results indicated that the test substance did not change when stored in the dark at room temperature during this period(for about 26 months).

APPENDIX P 3

CONCENTRATION OF ANTHRACENE IN FORMULATED DIETS OF RATS

IN THE 2-YEAR FEED STUDY

CONCENTRATION OF ANTHRACENE IN FORMULATED DIETS OF RATS IN THE 2-YEAR FEED STUDY
(Male)(Female)

	Target Concentration(ppm)		
Date analyzed	8000(*)	20000(*)	50000(*)
1993.09.08	7703(96.3)	21258(106.3)	50349(100.7)
1993.12.08	8138(101.7)	19846(99.2)	49275(98.5)
1994.03.09	7400(92.5)	22353(111.8)	49948(99.9)
1994.06.15	7438(93.0)	19992(100.0)	49721(99.4)
1994.08.22	7947(99.3)	21186(105.9)	51419(102.8)
1994.10.17	7811(97.6)	20300(101.5)	49976(100.0)
1995.02.01	7070(98.4)	22004(110.0)	52563(105.1)
1995.05.08	7816(97.7)	21068(105.3)	52609(105.2)
1995.08.02	7690(96.1)	21998(110.0)	52678(105.4)

(*) % of target concentration

Analytical method: The sample were analyzed by the GC.

Instrument : Hewlett Packard 5890A
Column : METHYL SILICONE(0.2mmϕ×30m)
Column Temperature: 260°C
Carrier : He
Flow Rate : 1ml/min
Detector : FID(Flame Ionization Detector)
Injection Volume : 1μl

APPENDIX P 4

CONCENTRATION OF ANTHRACENE IN FORMULATED DIETS IN MICE

IN THE 2-YEAR FEED STUDY

CONCENTRATION OF ANTHRACENE IN FORMULATED DIETS OF MALE MICE IN THE 2-YEAR FEED STUDY

(Male)

	Target Concentration(ppm)		
Date analyzed	3200(*)	8000	20000
1993.09.29	3052(95.4)	7291(91.1)	20321(97.1)
1993.12.08	3267(102.1)	8138(101.7)	19846(99.2)
1994.03.09	3154(98.6)	7400(92.5)	22353(111.8)
1994.06.15	2959(92.5)	7438(93.0)	19992(100.0)
1994.08.22	3129(97.8)	7947(99.3)	21186(105.9)
1994.10.17	3012(94.1)	7811(97.6)	20300(101.5)
1995.02.01	3328(104.0)	7870(98.4)	22004(110.0)
1995.05.08	3209(100.3)	7816(97.7)	21068(105.3)
1995.08.02	3235(101.1)	7690(96.1)	21998(110.0)

(*) % of target concentration

Analytical method: The sample were analyzed by the GC.

Instrument : Hewlett Packard 5890A
Column : METHYL SILICONE(0.2mmϕ×30m)
Column Temperature: 260°C
Carrier : He
Flow Rate : 1ml/min
Detector : FID(Flame Ionization Detector)
Injection Volume : 1μl

CONCENTRATION OF ANTHRACENE IN FORMULATED DIETS OF FEMALE MICE IN THE 2-YEAR FEED STUDY

(Female)

	Target Concentration(ppm)		
Date analyzed	8000	20000	50000
1993.09.29	7291(91.1)*	20321(101.6)	48526(97.1)
1993.12.08	8138(101.7)	19846(99.2)	49275(98.5)
1994.03.09	7400(92.5)	22353(111.8)	44948(99.9)
1994.06.15	7438(93.0)	19992(100.0)	49721(99.4)
1994.08.22	7947(99.3)	21186(105.9)	51419(102.8)
1994.10.17	7811(97.6)	20300(101.5)	49976(100.0)
1995.02.01	7870(98.4)	22004(110.0)	52563(105.1)
1995.05.08	7816(97.7)	21068(105.3)	52609(105.2)
1995.08.02	7690(96.1)	21998(110.0)	52678(105.4)

(*) % of target concentration

Analytical method: The sample were analyzed by the GC.

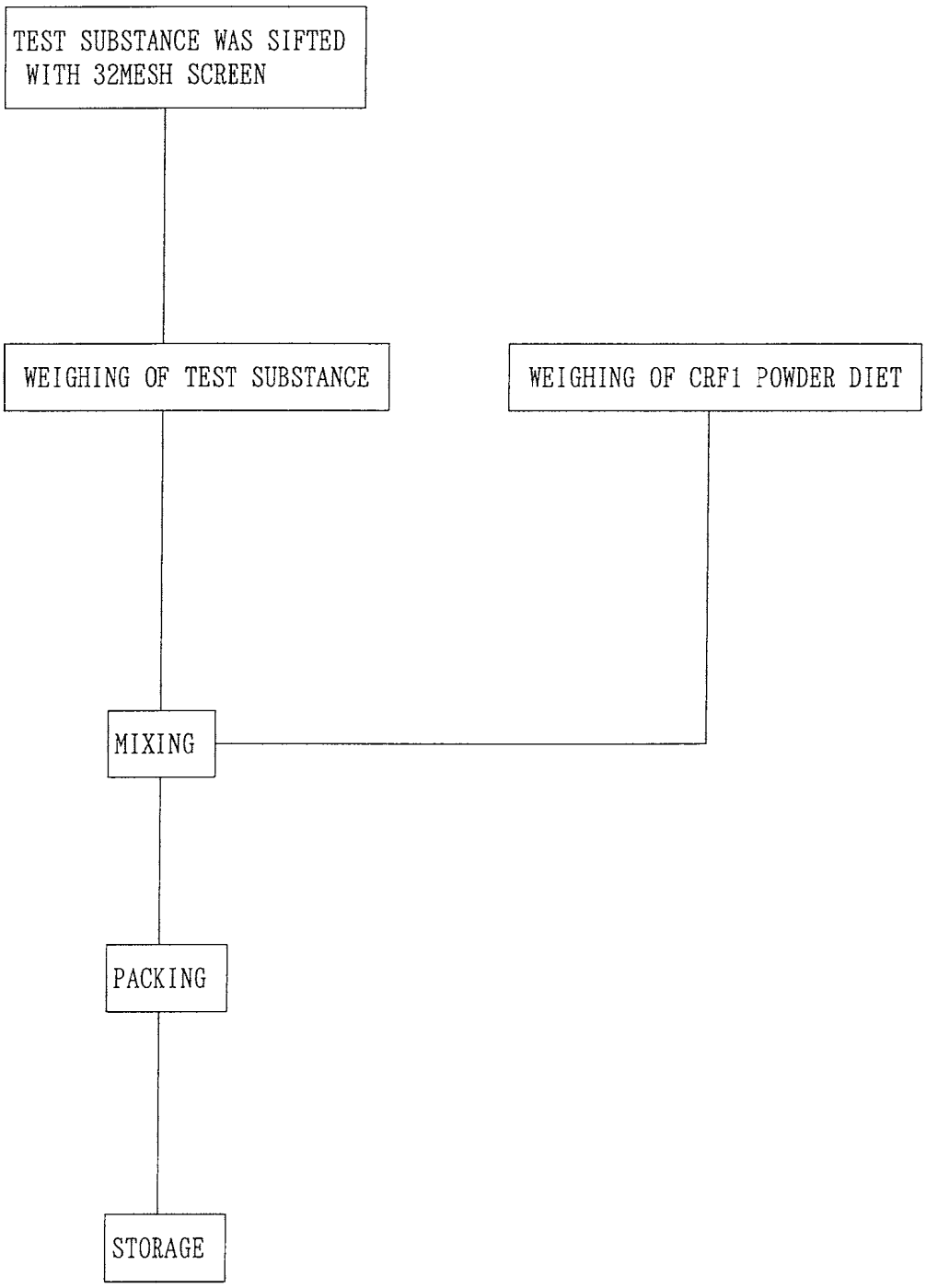
Instrument	: Hewlett Packard 5890A	Flow Rate	: 1ml/min
Column	: METHYL SILICONE(0.2mmϕ×30m)	Detector	: FID(Flame Ionization Detector)
Column Temperature	: 260°C	Injection Volume	: 1μl
Carrier	: He		

APPENDIX P 5

STABILITY OF ANTHRACENE IN FORMULATED DIETS

IN THE 2-YEAR FEED STUDY

Dose Formulations of Anthracene in the 2-Year Studies
(Prepared in Japan Bioassay Research Center)



APPENDIX Q 1

DOSE FORMULATIONS OF ANTHRACENE IN THE 2-YEAR FEED STUDIES

(PREPARED IN JAPAN BIOASSAY RESEARCH CENTER)

Stability of Anthracene in Formulated Diets in 2-Years Feed Studies

Term of stability	Target Concentration(ppm) 3200	50000
1993.08.12(a)	3178	49043
1993.08.27(b)	2879	49389
1993.09.08(c)	3150	49960
1993.10.13(d)	3222	49910
1993.11.15(e)	3104	48090
1993.12.08(f)	3193	50070

a ; Date of preparation
b ; The stability of Anthracene in formulated diets were established for 15 days when stored at animal room(24±2℃).
c ; The stability of Anthracene in formulated diets were established for about 1 months when stored at diet storage room(room temperature).
d ; The stability of Anthracene in formulated diets were established for about 2 months when stored at diet storage room(room temperature).
e ; The stability of Anthracene in formulated diets were established for about 3 months when stored at diet storage room(room temperature).
f ; The stability of Anthracene in formulated diets were established for about 4 months when stored at diet storage room(room temperature).

Analytical method; The samples were analyzed by the GC.

Instrument	: Hewlett Packard 5890A	Flow Rate	: 1ml/min
Column	: METHYL SILICONE(0.2mmφ×30m)	Detector	: FID(Flame Ionization Detector)
Column Temperature	: 260℃	Injection Volume	: 1μl
Carrier	: He		

Stability of Anthracene in Formulated Diets in 2-Years Feed Studies

	Target Concentration(ppm)	
Term of stability	3200	50000
1994.08.22(a)	3129	51419
1995.02.01(b)	3071	51804

a ; Date of preparation

b ; The stability of Anthracene in formulated diets were established for about 5 months when stored at diet storage room(room temperature).

Analytical method; The samples were analyzed by the GC.

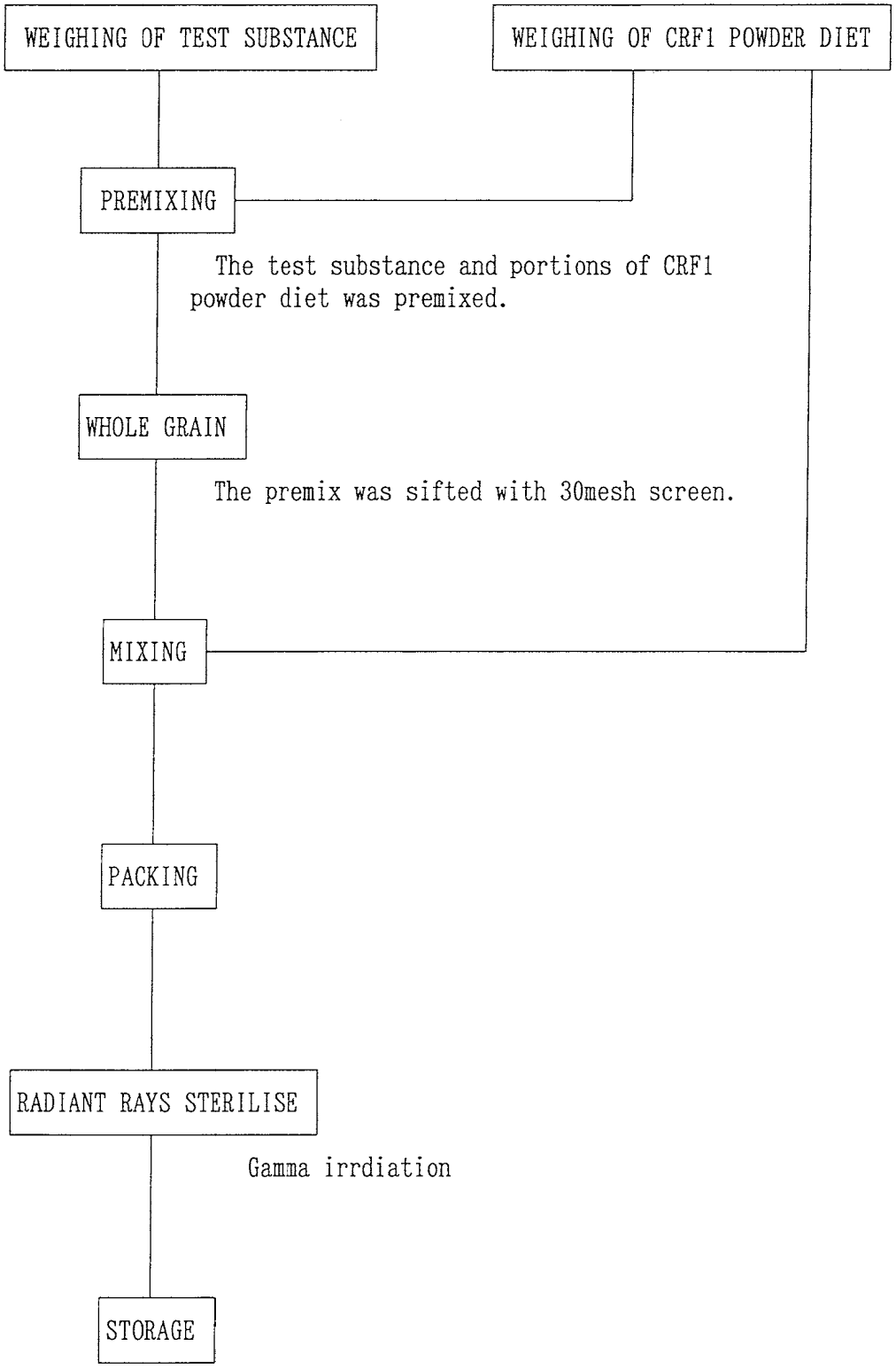
Instrument	: Hewlett Packard 5890A	Flow Rate	: 1ml/min
Column	: METHYL SILICONE(0.2mmϕ×30m)	Detector	: FID(Flame Ionization Detector)
Column Temperature	: 260℃	Injection Volume	: 1μl
Carrier	: He		

APPENDIX Q 2

DOSE FORMULATIONS OF ANTHRACENE IN THE 2-YEAR FEED STUDIES

(PREPARED BY ORIENTAL YEAST CO.,LTD.)

Dose Formulations of Anthracene in the 2-Year Studies
(Prepared by Oriental Yeast Co. LTD)



APPENDIX R 1

METHODS FOR HEMATOLOGY,BIOCHEMISTRY AND URINALYSIS

METHODS FOR HEMATOLOGY, BIOCHEMISTRY AND URINALYSIS

Item	Method	Unit
Hematology		
Red blood cell (RBC)	Light scattering method [1]	$\times 10^6/\mu l$
Hemoglobin (Hgb)	Cyanmethemoglobin method [1]	g/dl
Hematocrit (Hct)	Calculated as RBC×MCV/10 [1]	%
Mean corpuscular volume (MCV)	Light scattering method [1]	fl
Mean corpuscular hemoglobin (MCH)	Calculated as Hgb/RBC×10 [1]	pg
Mean corpuscular hemoglobin concentration (MCHC)	Calculated as Hgb/Hct×100 [1]	g/dl
Platelet	Light scattering method [1]	$\times 10^3/\mu l$
White blood cell (WBC)	Light scattering method [1]	$\times 10^3/\mu l$
Differential WBC	Pattern recognition method [2] (May-Grunwald-Giemsa staining)	%
Reticulocyte	Pattern recognition method [2] (New methyleneblue staining)	‰
Prothrombin time	Quick one stage method [3]	sec
Activated partial thromboplastin time (APTT)	Ellagic acid activated method [3]	sec
Biochemistry		
Total protein (TP)	Biuret method [4]	g/dl
Albumin (Alb)	BCG method [4]	g/dl
A/G ratio	Calculated as Alb/(TP-Alb) [4]	
T-bilirubin	Michaelson method [4]	mg/dl
Glucose	Enzymatic method (HK·G-6-PDH) [4]	mg/dl
T-cholesterol	Enzymatic method (CEH·COD·POD) [4]	mg/dl
Triglyceride	Enzymatic method (GK·GPO·POD) [4]	
Phospholipid	Enzymatic method (PLD·COD·POD) [4]	mg/dl
Glutamic oxaloacetic transaminase (GOT)	Karmen method [4]	IU/l
Glutamic pyruvic transaminase (GPT)	Karmen method [4]	IU/l
Lactate dehydrogenase (LDH)	Wroblewski-LaDue method [4]	IU/l
Alkaline phosphatase (ALP)	GSCC method [4]	
γ-Glutamyl transpeptidase (G-GTP)	L-γ-Glutamyl-p-nitroanilide substrate method [4]	IU/l
Creatine phosphokinase (CPK)	GSCC method [4]	IU/l
Urea nitrogen	Enzymatic method (Urease·GLDH) [4]	mg/dl
Creatinine	Jaffe method [4]	mg/dl
Sodium	Flame photometry [5]	mEq/l
Potassium	Flame photometry [5]	mEq/l
Chloride	Coulometric titration [5]	mEq/l
Calcium	OCPC method [4]	mg/dl
Inorganic phosphorus	Enzymatic method (SPL·PGM·G-6-PDH) [4]	mg/dl
Urinalysis		
PH, Protein, Glucose, Ketone body, Bilirubin, Occult blood, Urobilinogen	Urinalysis reagent paper method [6]	

1) Automatic blood cell analyzer (Technicon H·1 : Technicon Instruments Corporation, USA)
2) Automatic blood cell differential analyzer (Hitachi 8200 : Hitachi, Ltd., Japan)
3) Automatic coagulometer (Amelung KC-10 : Heinrich Amelung GmbH, Germany)
4) Automatic analyzer (Hitachi 705 : Hitachi, Ltd., Japan)
5) Flame photometer (Hitachi 750 : Hitachi, Ltd., Japan)
6) Ames reagent strips for urinalysis (Multistix, Uro-Labstix : Miles Sankyo Co., Ltd., Japan)

APPENDIX R 2

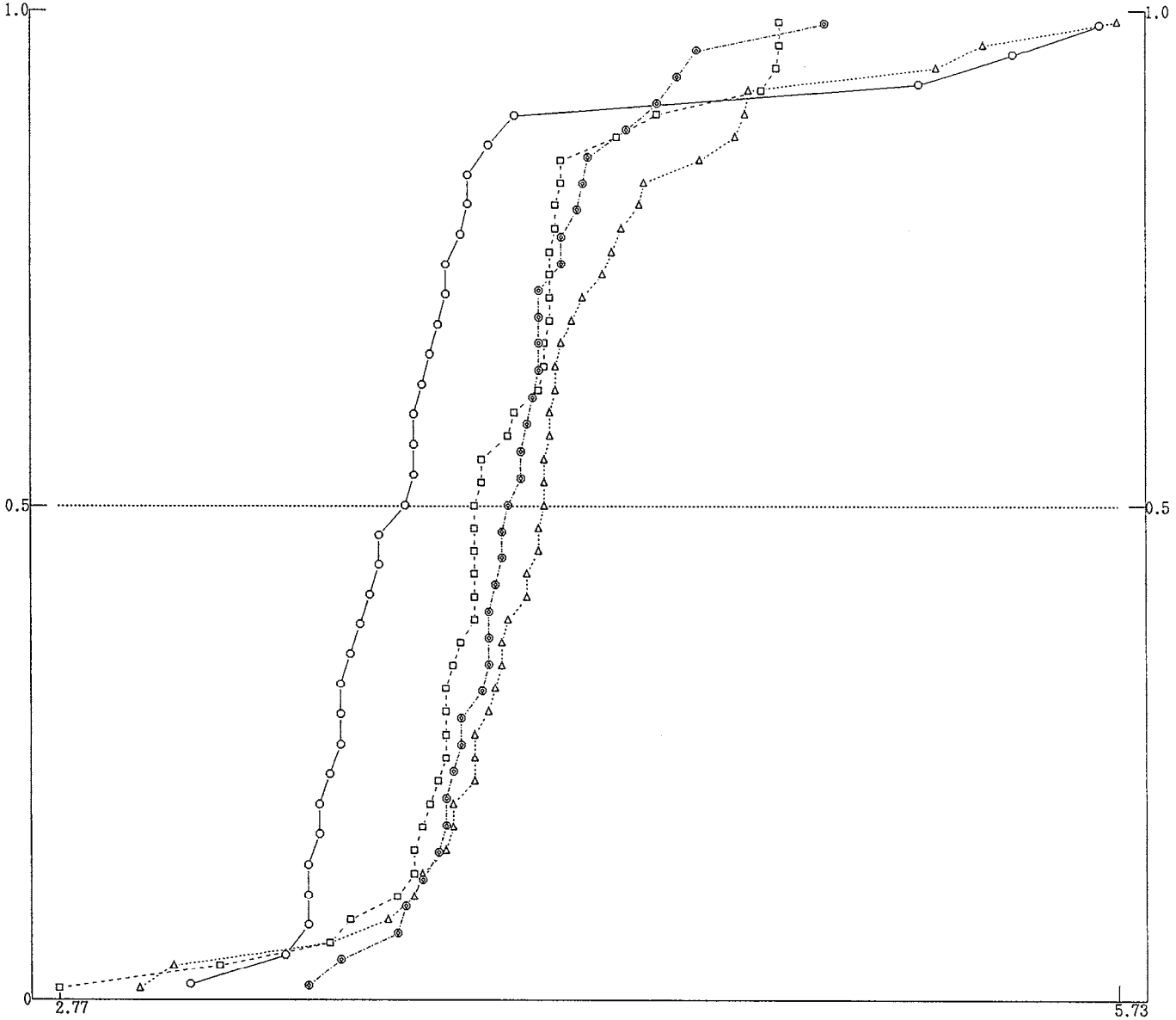
UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY

UNITS AND DECIMAL PLACE FOR HEMATOLOGY AND BIOCHEMISTRY

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

APPENDIX S 1

Q PLOT GRAPH FOR RETICULOCYTE OF MALE RATS IN THE 2-YEAR FEED STUDY OF ANTHRACENE



STUDY NO : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
OUTPUT TYPE : SURVIVAL ANIMALS
SEX : MALE

‰
(LN)

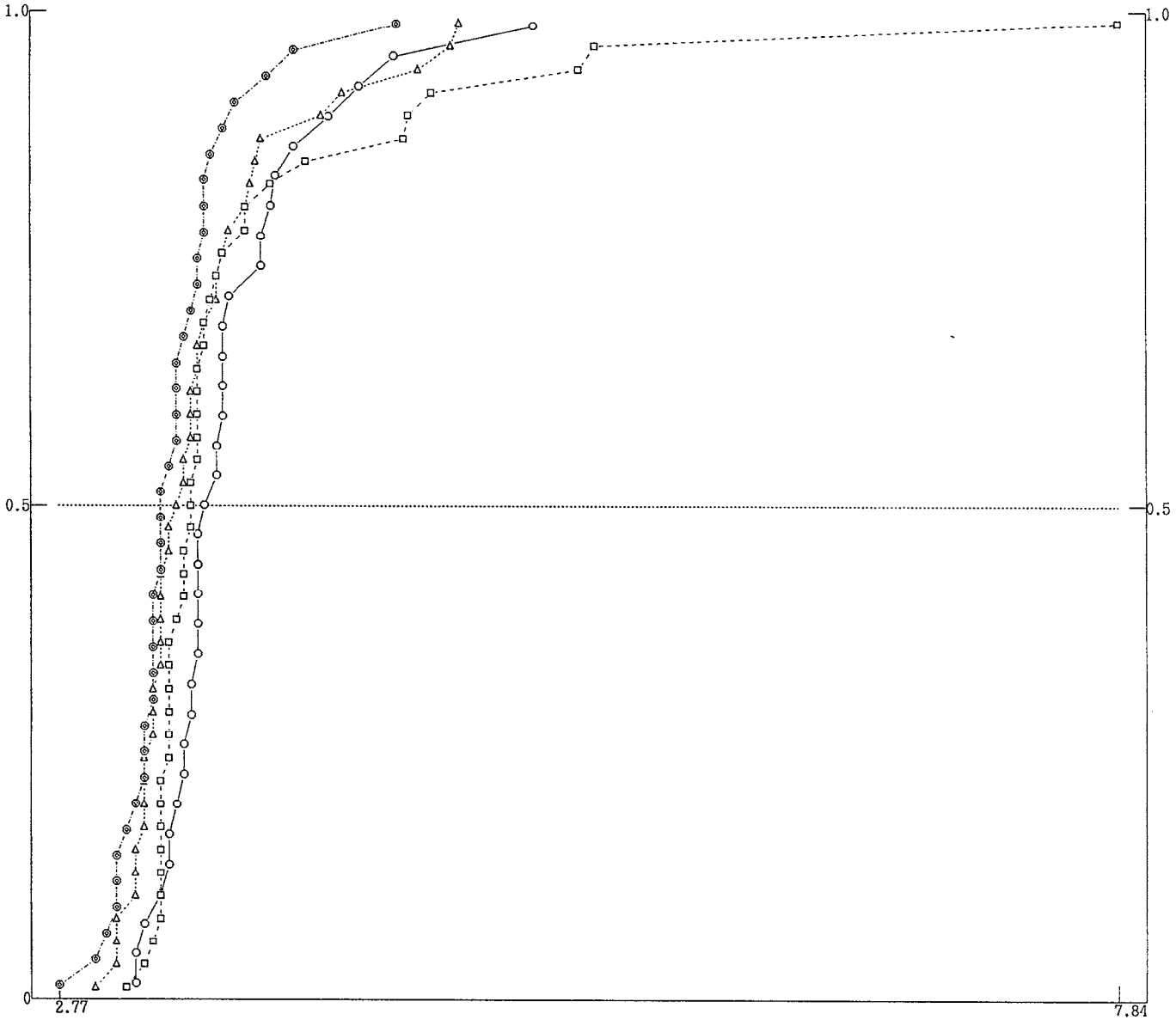
CONTROL
8000 PPM
20000 PPM
50000 PPM

RETICULOCYTE

APPENDIX S 2

Q PLOT GRAPH FOR GLUTAMIC PYRUVIC TRANSAMINASE (GPT)

OF MALE RATS IN THE 2-YEAR FEED STUDY OF ANTHRACENE



STUDY NO : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
OUTPUT TYPE : SURVIVAL ANIMALS
SEX : MALE

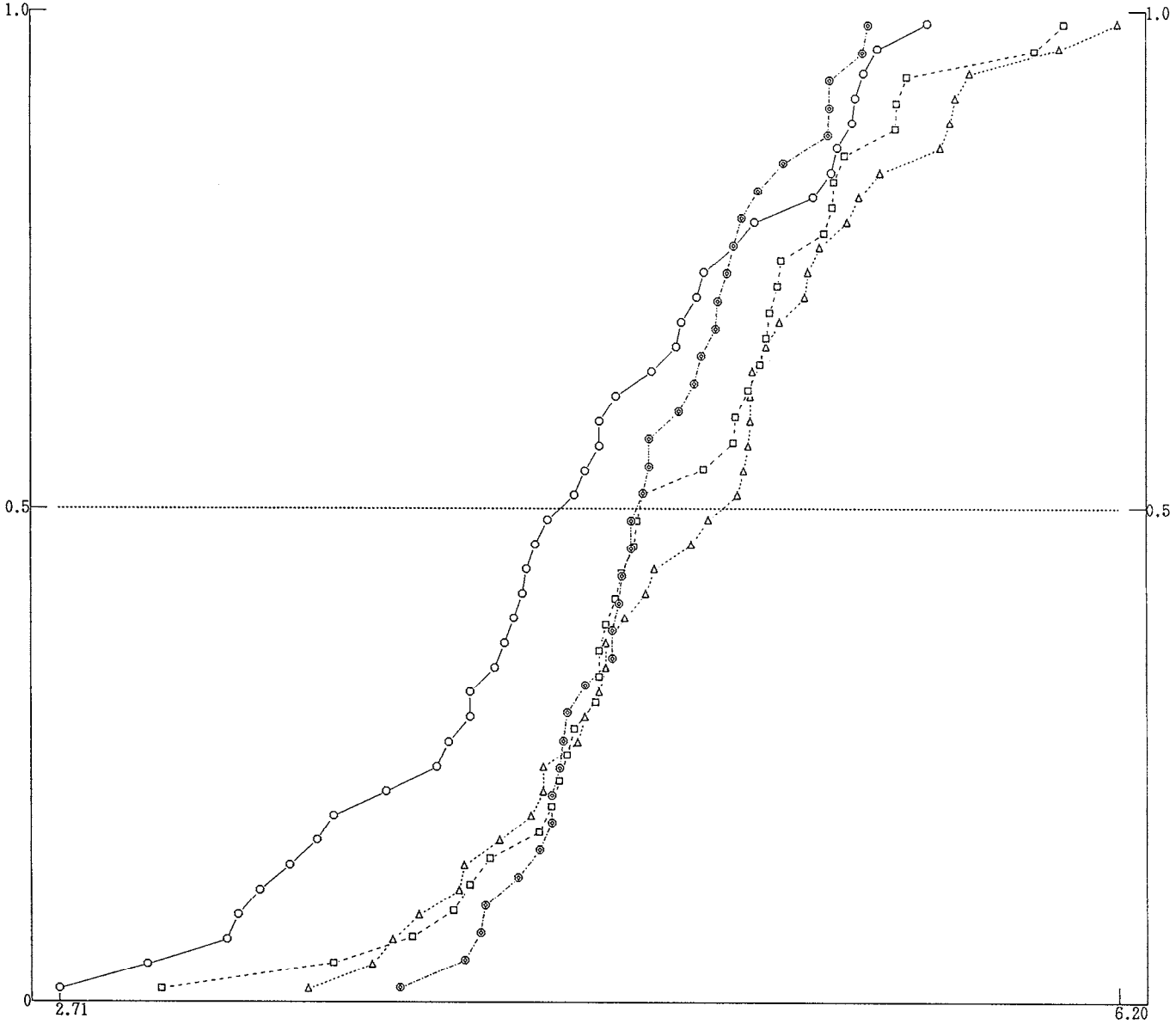
IU/ℓ
(LN)

GPT

CONTROL
8000 PPM
20000 PPM
50000 PPM

APPENDIX S 3

Q PLOT GRAPH FOR TRIGLYCERIDE OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF ANTHRACENE

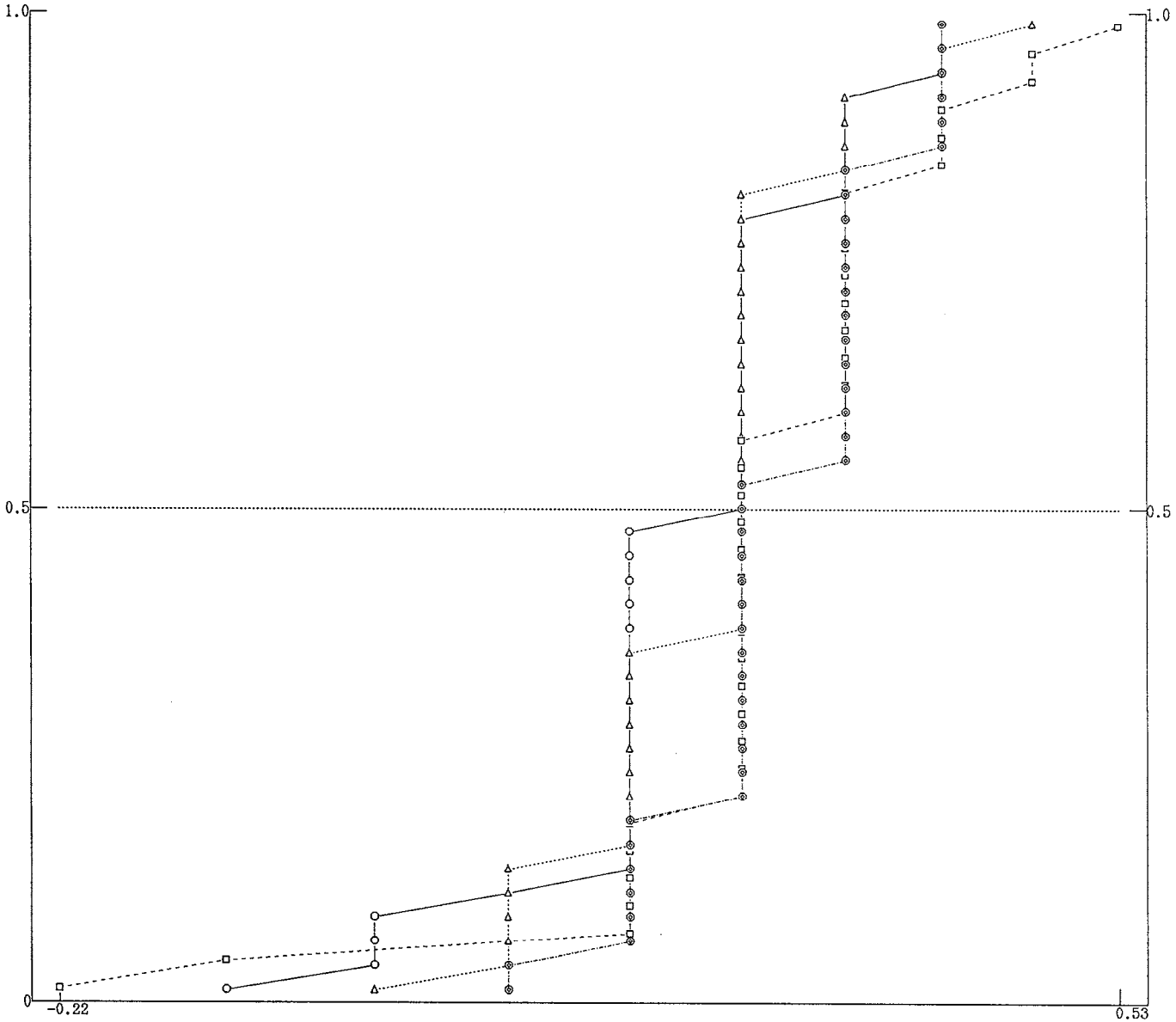


STUDY NO : 0242
ANIMAL : RAT F344/DuCrj
REPORT TYPE : A1
OUTPUT TYPE : SURVIVAL ANIMALS
SEX : FEMALE

TRIGLYCERIDE

APPENDIX S 4

Q PLOT GRAPH FOR A/G RATIO OF MALE MICE IN THE 2-YEAR FEED STUDY OF ANTHRACENE



STUDY NO : 0243
ANIMAL : MOUSE Crj:BDF1
REPORT TYPE : A1
OUTPUT TYPE : SURVIVAL ANIMALS
SEX : MALE

(LN)

A/G RATIO

CONTROL
3200 PPM
8000 PPM
20000 PPM