Table 16 - continued Histopathological findings
Male, Female, 52w

Organs and findings	Sex	Male															
	Group and dose	Control					0.1 mg/kg					0.5 mg/kg					2.5 mg/kg
	Number of animals	10					8					10					10
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Musculoskeletal system																	
Sternum				NR(10)					(0)					(0)					NR(10)		
Femur				NR(10)					(0)					(0)					NR(10)		
Integumentary system																	
Integument				NR(10)					(0)					(0)					NR(10)		
Others																	
Extremity				(5)					(0)					(0)					(1)		
Ulcer, hindlimb		0	4	1	0	5											0	0	1	0	1

Not significantly different from control.
Grade sign: -, none; +, mild; ++, moderate; +++, marked.
NR: no remarkable changes.
Figures in parentheses are number of animals with tissues examined histopathologically.
Two males in the 0.1 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

Organs and findings	Sex	Female																			
	Group and dose	Control					0.5 mg/kg					2.5 mg/kg					12.5 mg/kg				
	Number of animals	10					10					10					9				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system																					
Tongue				NR(10)					(0)					(0)					NR(9)		
Esophagus				NR(10)					(0)					(0)					NR(9)		
Stomach				(10)					(0)					(0)					(9)		
Dilatation, glandular space, glandular stomach	10	0	0	0	0												9	0	0	0	0
Cellular infiltration, mucosa, glandular stomach, neutrophil	10	0	0	0	0												8	1	0	0	1
Duodenum				NR(10)					(0)					(0)					NR(9)		
Jejunum				NR(10)					(0)					(0)					NR(9)		
Ileum				NR(10)					(0)					(0)					NR(9)		
Cecum				(10)					(0)					(0)					(9)		
Fibrosis, muscular layer	10	0	0	0	0												8	1	0	0	1
Colon				NR(10)					(0)					(0)					NR(9)		
Rectum				NR(10)					(0)					(0)					NR(9)		
Submaxillary gland				NR(10)					(0)					(0)					NR(9)		
Sublingual gland				NR(10)					(0)					(0)					NR(9)		
Parotid gland				(10)					(0)					(0)					(9)		
Cellular infiltration, lymphocyte	10	0	0	0	0												8	1	0	0	1
Liver				(10)					(0)					(10)					(9)		
Degeneration, hepatocyte, fatty, periportal	8	2	0	0	2							10	0	0	0	0	9	0	0	0	0
Degeneration, cystic	10	0	0	0	0							10	0	0	0	0	9	0	0	0	0
Necrosis, hepatocyte, focal	8	2	0	0	2							10	0	0	0	0	9	0	0	0	0
Hypertrophy, hepatocyte[1], centrilobular	10	0	0	0	0							10	0	0	0	0	5	4	0	0	4*
Hematopoiesis, extramedullary	8	2	0	0	2							10	0	0	0	0	9	0	0	0	0
Focus, altered cell, basophilic	6	4	0	0	4							8	2	0	0	2	7	2	0	0	2
Focus, altered cell, clear	10	0	0	0	0							10	0	0	0	0	9	0	0	0	0
Deposit, lipofuscin[2], hepatocyte	10	0	0	0	0							10	0	0	0	0	7	2	0	0	2
Angiectasis	10	0	0	0	0							10	0	0	0	0	9	0	0	0	0
Cellular infiltration, mononuclear cell	10	0	0	0	0							10	0	0	0	0	8	1	0	0	1
Adenoma, hepatocellular	10	0	0	0	0							10	0	0	0	0	8	1	0	0	1

*: $P<0.05$ (significantly different from control).
Grade sign: -, none; +, mild(existent of tumor); ++, moderate; +++, marked.
NR: no remarkable changes.
1) with eosinophilic granular cytoplasm.
2) identified by Schmorl method, Berlin blue staining and Hall method.
Figures in parentheses are number of animals with tissues examined histopathologically.
One female in the 12.5 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

Study No. P030097

Organs and findings	Sex	Female														
	Group and dose	Control					0.5 mg/kg					2.5 mg/kg				
	Number of animals	10					10					10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system																
Pancreas				(10)					(0)					(0)		
Atrophy, acinus, focal		9	1	0	0	1										
Hyperplasia, acinar cell, focal		10	0	0	0	0										
Cellular infiltration, lymphocyte		10	0	0	0	0										
Fibrosis, islet		10	0	0	0	0										
Respiratory system																
Trachea				(10)					(0)					(0)		
Cellular infiltration, lamina propria, neutrophil		10	0	0	0	0										
Lung				(10)					(0)					(0)		
Accumulation, foam cell, alveolus		6	4	0	0	4										
Pneumonia, aspiration		10	0	0	0	0										
Mineralization, artery		9	1	0	0	1										
Hematopoietic system																
Thymus				(10)					(0)					(0)		
Atrophy		1	8	1	0	9										
Submaxillary lymph node				NR(10)					(0)					(0)		
Popliteal lymph node				(0)					(0)					(0)		
Proliferation, plasma cell																
Mesenteric lymph node				NR(10)					(0)					(0)		
Spleen				(10)					(0)					(0)		
Thickening, capsule		10	0	0	0	0										
Hematopoiesis, extramedullary		8	2	0	0	2										
Deposit, pigment, red pulp, brown		9	1	0	0	1										
Bone marrow (sternum)				(10)					(0)					(0)		
Atrophy, focal		10	0	0	0	0										

Organs and findings	Sex	Female					
	Group and dose	12.5 mg/kg					
	Number of animals	9					
		-	+	++	+++	Total	
Digestive system							
Pancreas				(9)			
Atrophy, acinus, focal		9	0	0	0	0	
Hyperplasia, acinar cell, focal		9	0	0	0	0	
Cellular infiltration, lymphocyte		8	1	0	0	1	
Fibrosis, islet		9	0	0	0	0	
Respiratory system							
Trachea				(9)			
Cellular infiltration, lamina propria, neutrophil		8	1	0	0	1	
Lung				(9)			
Accumulation, foam cell, alveolus		5	4	0	0	4	
Pneumonia, aspiration		9	0	0	0	0	
Mineralization, artery		7	2	0	0	2	
Hematopoietic system							
Thymus				(9)			
Atrophy		0	7	2	0	9	
Submaxillary lymph node				NR(9)			
Popliteal lymph node				(0)			
Proliferation, plasma cell							
Mesenteric lymph node				NR(9)			
Spleen				(9)			
Thickening, capsule		9	0	0	0	0	
Hematopoiesis, extramedullary		8	1	0	0	1	
Deposit, pigment, red pulp, brown		7	2	0	0	2	
Bone marrow (sternum)				(9)			
Atrophy, focal		8	1	0	0	1	

Not significantly different from control.
Grade sign: -, none; +, mild; ++, moderate; +++, marked.
NR: no remarkable changes.
Figures in parentheses are number of animals with tissues examined histopathologically.
One female in the 12.5 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

Study No. P030097

Organs and findings	Sex	Female														
	Group and dose	Control					0.5 mg/kg					2.5 mg/kg				
	Number of animals	10					10					10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Hematopoietic system																
Bone marrow (femur)				(10)					(0)					(0)		
Atrophy, focal		10	0	0	0	0										
Hematopoiesis, increased		9	1	0	0	1										
Cardiovascular system																
Heart				(10)					(0)					(0)		
Cellular infiltration, mononuclear cell		9	1	0	0	1										
Fibrosis, myocardium		10	0	0	0	0										
Aorta				NR(10)					(0)					(0)		
Urinary system																
Kidney				(10)					(0)					(0)		
Hyperplasia, epithelial cell, tubule		10	0	0	0	0										
Hyperplasia, transitional cell, pelvis		10	0	0	0	0										
Tubule, basophilic		10	0	0	0	0										
Cast, proteinaceous		10	0	0	0	0										
Hemorrhage, pelvis		10	0	0	0	0										
Cellular infiltration, mononuclear cell, pelvis		9	1	0	0	1										
Cellular infiltration, mononuclear cell, cortex		10	0	0	0	0										
Cellular infiltration, pelvis, neutrophil		10	0	0	0	0										
Cellular infiltration, cortex, neutrophil		9	1	0	0	1										
Cellular exudation, pelvic cavity, neutrophil		9	1	0	0	1										
Mineralization, papilla		7	3	0	0	3										
Mineralization, pelvis		7	3	0	0	3										
Urinary bladder				(10)					(0)					(0)		
Cellular infiltration, muscular layer, neutrophil		10	0	0	0	0										

Organs and findings	Sex	Female					
	Group and dose	12.5 mg/kg					
	Number of animals	9					
		-	+	++	+++	Total	
Hematopoietic system							
Bone marrow (femur)				(9)			
Atrophy, focal		8	1	0	0	1	
Hematopoiesis, increased		9	0	0	0	0	
Cardiovascular system							
Heart				(9)			
Cellular infiltration, mononuclear cell		7	2	0	0	2	
Fibrosis, myocardium		8	1	0	0	1	
Aorta				NR(9)			
Urinary system							
Kidney				(9)			
Hyperplasia, epithelial cell, tubule		8	1	0	0	1	
Hyperplasia, transitional cell, pelvis		8	1	0	0	1	
Tubule, basophilic		7	2	0	0	2	
Cast, proteinaceous		8	1	0	0	1	
Hemorrhage, pelvis		9	0	0	0	0	
Cellular infiltration, mononuclear cell, pelvis		9	0	0	0	0	
Cellular infiltration, mononuclear cell, cortex		8	1	0	0	1	
Cellular infiltration, pelvis, neutrophil		8	1	0	0	1	
Cellular infiltration, cortex, neutrophil		9	0	0	0	0	
Cellular exudation, pelvic cavity, neutrophil		8	1	0	0	1	
Mineralization, papilla		8	1	0	0	1	
Mineralization, pelvis		8	1	0	0	1	
Urinary bladder				(9)			
Cellular infiltration, muscular layer, neutrophil		9	0	0	0	0	

Not significantly different from control.
Grade sign: -, none; +, mild; ++, moderate; +++, marked.
NR: no remarkable changes.
Figures in parentheses are number of animals with tissues examined histopathologically.
One female in the 12.5 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

Organs and findings	Sex	Female															
	Group and dose	Control					0.5 mg/kg					2.5 mg/kg					12.5 mg/kg				
	Number of animals	10					10					10					9				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Genital system																					
Testis				NA					NA					NA					NA		
Atrophy, seminiferous tubule																					
Hyperplasia, leydig cell, focal																					
Epididymis				NA					NA					NA					NA		
Decrease, sperm, lumen																					
Cellular infiltration, mononuclear cell																					
Prostate				NA					NA					NA					NA		
Atrophy																					
Hemorrhage																					
Cellular infiltration, mononuclear cell																					
Seminal vesicle				NA					NA					NA					NA		
Ovary				(10)					(0)					(0)					(9)		
Dilatation, ovarian bursa		10	0	0	0	0											8	1	0	0	1
Cyst		8	2	0	0	2											7	2	0	0	2
Uterus				(10)					(0)					(0)					(9)		
Metaplasia, epithelial cell, gland, squamous		5	5	0	0	5											7	2	0	0	2
Polyp, endometrial stromal		10	0	0	0	0											8	1	0	0	1
Vagina				(10)					(0)					(0)					(9)		
Degeneration, epithelium, mucous		9	1	0	0	1											8	1	0	0	1
Mammary gland				(10)					(0)					(0)					(9)		
Hyperplasia, lobular		8	2	0	0	2											5	4	0	0	4
Ectasia, alveolus/duct		7	1	2	0	3											4	2	3	0	5
Adenoma		9	1	0	0	1											8	1	0	0	1
Fibroadenoma		8	2	0	0	2											8	1	0	0	1
Adenocarcinoma		9	1	0	0	1											8	1	0	0	1

Not significantly different from control.
Grade sign: -, none; +, mild(existent of tumor); ++, moderate; +++, marked.
NR: no remarkable changes.
NA: not applicable.
Figures in parentheses are number of animals with tissues examined histopathologically.
One female in the 12.5 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

Organs and findings	Sex	Female																	
	Group and dose	Control					0.5 mg/kg					2.5 mg/kg					12.5 mg/kg				
	Number of animals	10					10					10					9				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Endocrine system																					
Pituitary				(10)					(0)					(0)					(9)		
Hyperplasia, anterior lobe		7	3	0	0	3											6	3	0	0	3
Cyst, anterior lobe		10	0	0	0	0											9	0	0	0	0
Thyroid				(10)					(0)					(0)					(9)		
Hyperplasia, C cell		10	0	0	0	0											8	1	0	0	1
Deposit, material, interstitium, eosinophilic		10	0	0	0	0											9	0	0	0	0
Remnant, ultimobranchial body		8	2	0	0	2											8	1	0	0	1
Parathyroid				NR(10)					(0)					(0)					NR(9)		
Adrenal				(10)					(0)					(0)					(9)		
Hypertrophy, cortical cell, focal		8	2	0	0	2											7	2	0	0	2
Hyperplasia, cortical cell, focal		6	4	0	0	4											8	1	0	0	1
Angiectasis		6	4	0	0	4											8	1	0	0	1
Nervous system																					
Cerebrum				NR(10)					(0)					(0)					NR(9)		
Cerebellum				NR(10)					(0)					(0)					NR(9)		
Medulla oblongata				NR(10)					(0)					(0)					NR(9)		
Spinal cord				NR(10)					(0)					(0)					NR(9)		
Optic nerve				NR(10)					(0)					(0)					NR(9)		
Sciatic nerve				NR(10)					(0)					(0)					NR(9)		
Special sense organs																					
Eye				NR(10)					(0)					(0)					NR(9)		
Harderian gland				(10)					(0)					(0)					(9)		
Cellular infiltration, lymphocyte		10	0	0	0	0											8	1	0	0	1
Musculoskeletal system																					
M. biceps femoris				NR(10)					(0)					(0)					NR(9)		

Not significantly different from control.
Grade sign: -, none; +, mild; ++, moderate; +++, marked.
NR: no remarkable changes.
Figures in parentheses are number of animals with tissues examined histopathologically.
One female in the 12.5 mg/kg group died.

Table 16 - continued Histopathological findings
Male, Female, 52w

Organs and findings	Sex	Female															
	Group and dose	Control					0.5 mg/kg					2.5 mg/kg					12.5 mg/kg				
	Number of animals	10					10					10					9				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Musculoskeletal system																					
Sternum				NR(10)					(0)					(0)					NR(9)		
Femur				NR(10)					(0)					(0)					NR(9)		
Integumentary system																					
Integument				NR(10)					(0)					(0)					NR(9)		
Others																					
Extremity				(1)					(0)					(0)					(2)		
Ulcer, hindlimb		0	1	0	0	1											0	2	0	0	2

Not significantly different from control.
Grade sign: -, none; +, mild; ++, moderate; +++, marked.
NR: no remarkable changes.
Figures in parentheses are number of animals with tissues examined histopathologically.
One female in the 12.5 mg/kg group died.