

Table 15 Histopathological findings  
Male, Female, 13w

Organs and findings	Sex	Group and dose	Male																			
			Control				0.1 mg/kg				0.5 mg/kg				2.5 mg/kg							
			Number of animals			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system																						
Tongue																						
Esophagus																						
Fibrosis, muscular layer			9	1	0	0	1											9	0	0	0	0
Stomach																						
Duodenum																						
Jejunum																						
Ileum																						
Cecum																						
Colon																						
Rectum																						
Submaxillary gland																						
Sublingual gland																						
Parotid gland																						
Liver																						
Degeneration, hepatocyte, fatty, midzonal			10	0	0	0	0	0	9	1	0	0	1	10	0	0	0	0	9	0	0	0
Degeneration, hepatocyte, fatty, periportal			10	0	0	0	0	0	10	0	0	0	0	10	0	0	0	0	9	0	0	0
Necrosis, hepatocyte, focal			9	1	0	0	1	10	0	0	0	0	0	9	1	0	0	1	7	2	0	0
Hyper trophy, hepatocyte <sup>1)</sup> , centrilobular			10	0	0	0	0	10	0	0	0	0	0	7	3	0	0	3	0	6	3	0
Cellular infiltration, mononuclear cell			9	1	0	0	1	7	3	0	0	3	8	2	0	0	2	9	0	0	0	0
Pancreas																						
Atrophy, acinus, focal			10	0	0	0	0											9	0	0	0	0
Respiratory system																						
Trachea																						
Lung																						
Accumulation, foam cell, alveolus			9	1	0	0	1											6	3	0	0	3
Mineralization, artery			9	1	0	0	1											8	1	0	0	1
Hematopoietic system																						
Thymus																						
Hemorrhage			10	0	0	0	0											9	0	0	0	0
Submaxillary lymph node																						
Mesenteric lymph node																						

\*\*: P&lt;0.01 (significantly different from control).

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

1) with eosinophilic granular cytoplasm.

Figures in parentheses are number of animals with tissues examined histopathologically.

One male in the 2.5 mg/kg group died.

Table 15 - continued

Histopathological findings  
Male, Female, 13w

Organs and findings	Sex Group and dose Number of animals	Male																			
		Control				0.1 mg/kg				0.5 mg/kg											
		10		10		10		10		9											
Hematopoietic system	Spleen	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
						NR(10)					(0)				(0)					NR(9)	
						NR(10)					(0)				(0)					NR(9)	
	Bone marrow (sternum)					NR(10)					(0)				(0)					NR(9)	
	Bone marrow (femur)					NR(10)					(0)				(0)					NR(9)	
Cardiovascular system	Heart					(10)					(0)				(0)						
		8	2	0	0	NR(10)	2				(0)				(0)						
	Aorta										(0)				(0)						
Urinary system	Kidney					(10)					(0)				(0)						
		10	0	0	0	0					(0)				(0)						
	Tubule, basophilic																				
		9	1	0	0	1															
	Cast, proteinaceous																				
		10	0	0	0	0															
	Cellular infiltration, pelvis, neutrophil																				
		10	0	0	0	0															
	Mineralization, corticomedullary																				
		10	0	0	0	0															
	Nephroblastoma																				
Genital system	Urinary bladder					NR(10)					(0)				(0)					NR(9)	
	Testis					NR(10)					(0)				(0)					NR(9)	
																				NR(9)	
	Epididymis					NR(10)					(0)				(0)						
																				(9)	
	Prostate					(10)					(0)				(0)						
		8	2	0	0	2					(0)				(0)						
	Cellular infiltration, mononuclear cell					NR(10)					(0)				(0)						
Endocrine system	Seminal vesicle					NR(10)					(0)				(0)					NR(9)	
		8	2	0	0	2					(0)				(0)						
	Ovary					NA					NA				NA					NA	
	Uterus					NA					NA				NA					NA	
	Vagina					NA					NA				NA					NA	
	Mammary gland					NR(10)					(0)				(0)					NR(9)	
	Pituitary					NR(10)					(0)				(0)					NR(9)	
Thyroid					(10)					(0)				(0)					(9)		
	Remnant, ultimobranchial body	10	0	0	0	0					(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 male in the 2.5 mg/kg group died.

Table 15 - continued

Histopathological findings  
Male, Female, 13w

Organs and findings	Sex Group and dose	Male															
		Control				0.1 mg/kg				0.5 mg/kg				2.5 mg/kg			
		Number of animals			Total	10			Total	10			Total	9			Total
		-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++
Endocrine system																	
Parathyroid																	
Adrenal																	
Hypertrophy, cortical cell, focal		9	1	0	0	1				(0)			(0)				NR(9)
Nervous system																	
Cerebrum																	
Dilatation, lateral ventricle		9	1	(10)	0	0	1			(0)			(0)				9
Cerebellum																	0
Medulla oblongata																	NR(9)
Spinal cord																	NR(9)
Optic nerve																	NR(9)
Sciatic nerve																	NR(9)
Special sense organs																	
Eye																	NR(9)
Harderian gland																	NR(9)
Musculoskeletal system																	
M. biceps femoris																	NR(9)
Sternum																	NR(9)
Femur																	NR(9)
Integumentary system																	
Integument																	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 male in the 2.5 mg/kg group died.

Table 15 - continued      Histopathological findings  
Male, Female, 13w

Organs and findings	Sex	Female														
		Control				0.5 mg/kg				2.5 mg/kg						
	Number of animals	10		10		10		10		10		10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system																
Tongue						NR(10)				(0)					NR(10)	
Esophagus						(10)				(0)					(10)	
Fibrosis, muscular layer		10	0	0	0	0				(0)					9	
Stomach						NR(10)				(0)					NR(10)	
Duodenum						NR(10)				(0)					NR(10)	
Jejunum						NR(10)				(0)					NR(10)	
Ileum						NR(10)				(0)					NR(10)	
Cecum						NR(10)				(0)					NR(10)	
Colon						NR(10)				(0)					NR(10)	
Rectum						NR(10)				(0)					NR(10)	
Submaxillary gland						NR(10)				(0)					NR(10)	
Sublingual gland						NR(10)				(0)					NR(10)	
Parotid gland						NR(10)				(0)					NR(10)	
Liver						(10)				(0)					(10)	
Degeneration, hepatocyte, fatty, midzonal		10	0	0	0	0									0	
Degeneration, hepatocyte, fatty, periportal		9	1	0	0	1									0	
Necrosis, hepatocyte, focal		10	0	0	0	0									0	
Hyper trophy, hepatocyte <sup>1)</sup> , centrilobular		10	0	0	0	0									0	
Cellular infiltration, mononuclear cell		7	3	0	0	3									6**	
Pancreas						(10)				(0)					(10)	
Atrophy, acinus, focal		9	1	0	0	1				(0)					0	
Respiratory system																
Trachea						NR(10)				(0)					NR(10)	
Lung						(10)				(0)					(10)	
Accumulation, foam cell, alveolus		9	1	0	0	1				(0)					9	
Mineralization, artery		9	1	0	0	1				(0)					2	
Hematopoietic system																
Thymus						(10)				(0)					(10)	
Hemorrhage						0				(0)					0	
Submaxillary lymph node						NR(10)				(0)					NR(10)	
Mesenteric lymph node						NR(10)				(0)					NR(10)	

\*\*: P<0.01 (significantly different from control).

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

1) with eosinophilic granular cytoplasm.

Figures in parentheses are number of animals with tissues examined histopathologically.

Table 15 - continued      Histopathological findings  
Male, Female, 13w

Organs and findings	Sex	Group and dose	Female												
			Control				0.5 mg/kg				2.5 mg/kg				
	Number of animals		10		10		10		10		10		10		
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Hematopoietic system															
Spleen															
Bone marrow (sternum)															
Bone marrow (femur)															
Cardiovascular system															
Heart															
Cellular infiltration, mononuclear cell	10	0	(10)	0	0										
Aorta						NR(10)									
Urinary system															
Kidney						(10)									
Tubule, basophilic	10	0	0	0	0										
Cast, proteinaceous	10	0	0	0	0										
Cellular infiltration, pelvis, neutrophil	10	0	0	0	0										
Mineralization, corticomедullary	9	1	0	0	1										
Nephroblastoma	9	1	0	0	1										
Urinary bladder						NR(10)									
Genital system															
Testis						NA									
Epididymis						NA									
Prostate						NA									
Cellular infiltration, mononuclear cell															
Seminal vesicle						NA									
Ovary						NR(10)									
Uterus						NR(10)									
Vagina						NR(10)									
Mammary gland						NR(10)									
Endocrine system															
Pituitary						NR(10)									
Thyroid						(10)									
Remnant, ultimobranchial body						0	0	4							
	6	4	0	0	4										
	8	2	0	0	2										

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.

Table 15 - continued

Histopathological findings  
Male, Female, 13w

Organs and findings	Sex	Group and dose	Female																
			Control				0.5 mg/kg				2.5 mg/kg								
	Number of animals			10				10			10		10						
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
Endocrine system																			
Parathyroid																			
Adrenal																			
Hypertrophy, cortical cell, focal			10	0	0	0	0	NR(10) (10)			(0)		(0)			NR(10) (10)			
Nervous system																			
Cerebrum																			
Dilatation, lateral ventricle			10	0	0	0	0	(10)			(0)		(0)			10	0	0	0
Cerebellum																			
Medulla oblongata																			
Spinal cord																			
Optic nerve																			
Sciatic nerve																			
Special sense organs																			
Eye																			
Harderian gland																			
Musculoskeletal system																			
M. biceps femoris																			
Sternum																			
Femur																			
Integumentary system																			
Integument																			
								NR(10)			(0)		(0)			NR(10)			

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.

Table 16 Histopathological findings  
Male, Female, 52w

Organs and findings	Sex Group and dose Number of animals	Male															
		Control				0.1 mg/kg				0.5 mg/kg				2.5 mg/kg			
		-	+	++	+++ Total	-	+	++	+++ Total	-	+	++	+++ Total	-	+	++	+++ Total
Digestive system																	
Tongue					NR(10)				(0)				(0)				NR(10)
Esophagus					NR(10)				(0)				(0)				NR(10)
Stomach					(10)				(0)				(0)				(10)
Dilatation, glandular space, glandular stomach	9	1	0	0	1												8
Cellular infiltration, mucosa, glandular stomach, neutrophil	10	0	0	0	0												10
Duodenum					NR(10)				(0)				(0)				NR(10)
Jejunum					NR(10)				(0)				(0)				NR(10)
Ileum					NR(10)				(0)				(0)				NR(10)
Cecum					(10)				(0)				(0)				(10)
Fibrosis, muscular layer	10	0	0	0	0												10
Colon					NR(10)				(0)				(0)				NR(10)
Rectum					NR(10)				(0)				(0)				NR(10)
Submaxillary gland					NR(10)				(0)				(0)				NR(10)
Sublingual gland					NR(10)				(0)				(0)				NR(10)
Parotid gland					(10)				(0)				(0)				(10)
Cellular infiltration, lymphocyte	10	0	0	0	0												10
Liver					(10)												(10)
Degeneration, hepatocyte, fatty, periportal	8	1	1	0	2	6	0	2	0	2	10	0	0	0	0	10	0
Degeneration, cystic	10	0	0	0	0	6	2	0	0	2	8	2	0	0	2	6	4
Necrosis, hepatocyte, focal	9	1	0	0	1	8	0	0	0	0	7	3	0	0	3	6	4
Hypertrophy, hepatocyte <sup>1)</sup> , centrilobular	10	0	0	0	0	8	0	0	0	0	5	5	0	0	5*	2	7
Hematopoiesis, extramedullary	10	0	0	0	0	8	0	0	0	0	10	0	0	0	0	10	0
Focus, altered cell, basophilic	10	0	0	0	0	8	0	0	0	0	10	0	0	0	0	10	0
Focus, altered cell, clear	10	0	0	0	0	7	1	0	0	1	3	7	0	0	7**	3	6
Deposit, lipofuscin <sup>2)</sup> , hepatocyte	10	0	0	0	0	8	0	0	0	0	10	0	0	0	0	4	6
Angiectasis	10	0	0	0	0	8	0	0	0	0	10	0	0	0	0	9	1
Cellular infiltration, mononuclear cell	8	2	0	0	2	6	2	0	0	2	10	0	0	0	0	7	3
Adenoma, hepatocellular	10	0	0	0	0	8	0	0	0	0	10	0	0	0	0	10	0

\*: P&lt;0.05, \*\*: P&lt;0.01 (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.

Two males in the 0.1 mg/kg group died.

Table 16 - continued

Histopathological findings  
Male, Female, 52w

Study No. P030097

Organs and findings	Sex	Group and dose	Male												
			Control				0.1 mg/kg				0.5 mg/kg				
			Number of animals			Total	-			Total	-			Total	
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system															
Pancreas															
Atrophy, acinus, focal	10	0	0	0	0	(10)				(0)					
Hyperplasia, acinar cell, focal	8	2	0	0	2										
Cellular infiltration, lymphocyte	10	0	0	0	0										
Fibrosis, islet	9	1	0	0	1										
Respiratory system															
Trachea															
Cellular infiltration, lamina propria, neutrophil	10	0	0	0	0	(10)				(0)					
Lung															
Accumulation, foam cell, alveolus	7	3	0	0	3	(10)				(0)					
Pneumonia, aspiration	10	0	0	0	0										
Mineralization, artery	6	4	0	0	4										
Hematopoietic system															
Thymus															
Atrophy	1	8	1	0	9	(10)				(0)					
Submaxillary lymph node						NR(10)				(0)					
Popliteal lymph node						(1)				(0)					
Proliferation, plasma cell	0	1	0	0	1										
Mesenteric lymph node						NR(10)				(0)					
Spleen						(10)				(0)					
Thickening, capsule	9	1	0	0	1										
Hematopoiesis, extramedullary	10	0	0	0	0										
Deposit, pigment, red pulp, brown	10	0	0	0	0										
Bone marrow (sternum)															
Atrophy, focal	10	0	0	0	0	(10)				(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.

Two males in the 0.1 mg/kg group died.

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

Organs and findings	Sex	Group and dose	Male																
			Control				0.1 mg/kg				0.5 mg/kg				2.5 mg/kg				
			Number of animals		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
Hematopoietic system																			
Bone marrow (femur)			10	0	0	0	0	(10)				(0)							
Atrophy, focal			9	1	0	0	1												
Hematopoiesis, increased																			
Cardiovascular system																			
Heart																			
Cellular infiltration, mononuclear cell			7	3	0	0	3	(10)				(0)							
Fibrosis, myocardium			6	4	0	0	4												
Aorta								NR(10)											
Urinary system																			
Kidney																			
Hyperplasia, epithelial cell, tubule			10	0	0	0	0	(10)				(0)							
Hyperplasia, transitional cell, pelvis			10	0	0	0	0												
Tubule, basophilic			6	4	0	0	4												
Cast, proteinaceous			6	4	0	0	4												
Hemorrhage, pelvis			9	1	0	0	1												
Cellular infiltration, mononuclear cell, pelvis			8	2	0	0	2												
Cellular infiltration, mononuclear cell, cortex			8	2	0	0	2												
Cellular infiltration, pelvis, neutrophil			9	1	0	0	1												
Cellular infiltration, cortex, neutrophil			10	0	0	0	0												
Cellular exudation, pelvic cavity, neutrophil			9	1	0	0	1												
Mineralization, papilla			10	0	0	0	0												
Mineralization, pelvis			9	1	0	0	1												
Urinary bladder																			
Cellular infiltration, muscular layer, neutrophil			9	1	0	0	1	(10)				(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.

Two males in the 0.1 mg/kg group died.

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

Organs and findings	Sex	Male																				
		Control				0.1 mg/kg				0.5 mg/kg				2.5 mg/kg								
		Number of animals				10				8				10								
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	
Genital system																						
Testis																						
Atrophy, seminiferous tubule		10	0	0	0	(10)					(0)						8	0	1	1	(10)	2
Hyperplasia, leydig cell, focal		10	0	0	0	0					(0)						9	1	0	0	(10)	1
Epididymis																						
Decrease, sperm, lumen		10	0	0	0	0					(0)						9	0	0	1	(10)	1
Cellular infiltration, mononuclear cell		9	1	0	0	1					(0)						10	0	0	0	(10)	0
Prostate																						
Atrophy		6	4	0	0	4					(0)						5	3	2	0	(10)	5
Hemorrhage		10	0	0	0	0					(0)						9	1	0	0	(10)	1
Cellular infiltration, mononuclear cell		9	1	0	0	1					(0)						8	2	0	0	(10)	2
Seminal vesicle							NR(10)				(0)						NR(10)					
Ovary							NA				NA						NA					
Dilatation, ovarian bursa																						
Cyst																						
Uterus							NA				NA						NA					
Metaplasia, epithelial cell, gland, squamous																						
Polyp, endometrial stromal																						
Vagina							NA				NA						NA					
Degeneration, epithelium, mucous																						
Mammary gland							(10)				(0)						(0)				(10)	
Hyperplasia, lobular		10	0	0	0	0					(0)						10	0	0	0	(10)	0
Ectasia, alveolus/duct		10	0	0	0	0					(0)						10	0	0	0	(10)	0
Adenoma		10	0	0	0	0					(0)						10	0	0	0	(10)	0
Fibroadenoma		10	0	0	0	0					(0)						10	0	0	0	(10)	0
Adenocarcinoma		10	0	0	0	0					(0)						10	0	0	0	(10)	0

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.

Two males in the 0.1 mg/kg group died.

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

Organs and findings	Sex Group and dose Number of animals	Male																
		Control				0.1 mg/kg				0.5 mg/kg				2.5 mg/kg				
		-	+	++	+++ Total	-	+	++	+++ Total	-	+	++	+++ Total	-	+	++	+++ Total	
Endocrine system																		
Pituitary					(10)				(0)			(0)				(10)		
Hyperplasia, anterior lobe		7	3	0	0	3							10	0	0	0	0	
Cyst, anterior lobe		10	0	0	0	0							9	1	0	0	1	
Thyroid					(10)				(0)			(0)				(10)		
Hyperplasia, C cell		10	0	0	0	0							10	0	0	0	0	
Deposit, material, interstitium, eosinophilic		10	0	0	0	0							9	1	0	0	1	
Remnant, ultimobranchial body		9	1	0	0	1							9	1	0	0	1	
Parathyroid					NR(10)				(0)			(0)				NR(10)		
Adrenal					(10)				(0)			(0)				(10)		
Hyper trophy, cortical cell, focal		8	2	0	0	2							7	3	0	0	3	
Hyperplasia, cortical cell, focal		9	1	0	0	1							9	1	0	0	1	
Angiectasis		10	0	0	0	0							10	0	0	0	0	
Nervous system																		
Cerebrum					NR(10)				(0)			(0)				NR(10)		
Cerebellum					NR(10)				(0)			(0)				NR(10)		
Medulla oblongata					NR(10)				(0)			(0)				NR(10)		
Spinal cord					NR(10)				(0)			(0)				NR(10)		
Optic nerve					NR(10)				(0)			(0)				NR(10)		
Sciatic nerve					NR(10)				(0)			(0)				NR(10)		
Special sense organs																		
Eye					NR(10)				(0)			(0)				NR(10)		
Harderian gland					(10)				(0)			(0)				(10)		
Cellular infiltration, lymphocyte		10	0	0	0	0			(0)			(0)				10	0	0
Musculoskeletal system																		
M. biceps femoris					NR(10)				(0)			(0)				NR(10)		

Not significantly different from control.

Grade sign: -, none; +, mild; ++, moderate; +++, marked.

NR: no remarkable changes.

NA: not applicable.

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	Male														
		Control			0.1 mg/kg			0.5 mg/kg			2.5 mg/kg					
	Number of animals		10			8			10			10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Musculoskeletal system																
Sternum							NR(10)			(0)			(0)			NR(10)
Femur							NR(10)			(0)			(0)			NR(10)
Integumentary system							NR(10)			(0)			(0)			NR(10)
Integument																
Others																
Extremity																
Ulcer, hindlimb		0	4	1	0	5				(0)			(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	Group and dose	Female																				
			Control				0.5 mg/kg				2.5 mg/kg				12.5 mg/kg								
			Number of animals				10				10				10								
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	
Digestive system																							
Tongue																							
Esophagus																							
Stomach																							
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																							
Jejunum																							
Ileum																							
Cecum																							
Fibrosis, muscular layer			10	0	0	0	0												8	1	0	0	1
Colon																							
Rectum																							
Submaxillary gland																							
Sublingual gland																							
Parotid gland																							
Cellular infiltration, lymphocyte			10	0	0	0	0												8	1	0	0	1
Liver																							
Degeneration, hepatocyte, fatty, periportal			8	2	0	0	2												10	0	0	0	0
Degeneration, cystic			10	0	0	0	0											10	0	0	0	0	
Necrosis, hepatocyte, focal			8	2	0	0	2											10	0	0	0	0	
Hypertrophy, hepatocyte <sup>1)</sup> , centrilobular			10	0	0	0	0											10	0	0	0	0	
Hematopoiesis, extramedullary			8	2	0	0	2											10	0	0	0	0	
Focus, altered cell, basophilic			6	4	0	0	4											8	2	0	0	2	
Focus, altered cell, clear			10	0	0	0	0											10	0	0	0	0	
Deposit, lipofuscin <sup>2)</sup> , hepatocyte			10	0	0	0	0											10	0	0	0	0	
Angiectasis			10	0	0	0	0											10	0	0	0	0	
Cellular infiltration, mononuclear cell			10	0	0	0	0											10	0	0	0	1	
Adenoma, hepatocellular			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

Organs and findings	Sex	Group and dose	Female												
			Control				0.5 mg/kg				2.5 mg/kg				
			Number of animals			Total	10			Total	10			Total	
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system															
Pancreas															
Atrophy, acinus, focal	9	1	0	0	1						(0)				
Hyperplasia, acinar cell, focal	10	0	0	0	0						(0)				
Cellular infiltration, lymphocyte	10	0	0	0	0						(0)				
Fibrosis, islet	10	0	0	0	0						(0)				
Respiratory system															
Trachea															
Cellular infiltration, lamina propria, neutrophil	10	0	0	0	0						(0)				
Lung															
Accumulation, foam cell, alveolus	6	4	0	0	4						(0)				
Pneumonia, aspiration	10	0	0	0	0						(0)				
Mineralization, artery	9	1	0	0	1						(0)				
Hematopoietic system															
Thymus															
Atrophy	1	8	1	0	9						(0)				
Submaxillary lymph node															
Popliteal lymph node															
Proliferation, plasma cell															
Mesenteric lymph node															
Spleen															
Thickening, capsule	10	0	0	0	0						(0)				
Hematopoiesis, extramedullary	8	2	0	0	2						(0)				
Deposit, pigment, red pulp, brown	9	1	0	0	1						(0)				
Bone marrow (sternum)															
Atrophy, focal	10	0	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	Group and dose	Female												
			Control				0.5 mg/kg				2.5 mg/kg				
			Number of animals			Total	10			Total	10			Total	
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Hematopoietic system															
Bone marrow (femur)															
Atrophy, focal	10	0	0	0	0		(0)			(0)		8	1	(9)	0
Hematopoiesis, increased	9	1	0	0	1							9	0	0	0
Cardiovascular system															
Heart															
Cellular infiltration, mononuclear cell	9	1	0	0	1		(0)			(0)		7	2	(9)	0
Fibrosis, myocardium	10	0	0	0	0							8	1	0	0
Aorta							NR(10)			(0)					NR(9)
Urinary system															
Kidney															
Hyperplasia, epithelial cell, tubule	10	0	0	0	0		(0)			(0)		8	1	(9)	0
Hyperplasia, transitional cell, pelvis	10	0	0	0	0							8	1	0	0
Tubule basophilic	10	0	0	0	0							7	2	0	0
Cast, proteinaceous	10	0	0	0	0							8	1	0	0
Hemorrhage, pelvis	10	0	0	0	0							9	0	0	0
Cellular infiltration, mononuclear cell, pelvis	9	1	0	0	1							9	0	0	0
Cellular infiltration, mononuclear cell, cortex	10	0	0	0	0							8	1	0	0
Cellular infiltration, pelvis, neutrophil	10	0	0	0	0							8	1	0	0
Cellular infiltration, cortex, neutrophil	9	1	0	0	1							9	0	0	0
Cellular exudation, pelvic cavity, neutrophil	9	1	0	0	1							8	1	0	0
Mineralization, papilla	7	3	0	0	3							8	1	0	0
Mineralization, pelvis	7	3	0	0	3							8	1	0	0
Urinary bladder															
Cellular infiltration, muscular layer, neutrophil	10	0	0	0	0		(0)			(0)		9	0	(9)	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

Study No. P030097

Organs and findings	Sex	Female											
		Control				0.5 mg/kg				2.5 mg/kg			
		Number of animals			Total	10			Total	10			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 (10)		NA (0)		NA (0)		NA (9)	
Ovary													
Dilatation, ovarian bursa		10	0	0	0	0				8	1	0	0
Cyst		8	2	0	0	2				7	2	0	0
Uterus						(10)		(0)		(0)		(9)	
Metaplasia, epithelial cell, gland, squamous		5	5	0	0	5					7	2	0
Polyp, endometrial stromal		10	0	0	0	0					8	1	0
Vagina						(10)		(0)		(0)		(9)	
Degeneration, epithelium, mucous		9	1	0	0	1					8	1	0
Mammary gland						(10)		(0)		(0)		(9)	
Hyperplasia, lobular		8	2	0	0	2					5	4	0
Ectasia, alveolus/duct		7	1	2	0	3					4	2	3
Adenoma						(9)		(0)			8	1	0
Fibroadenoma		8	2	0	0	2					8	1	0
Adenocarcinoma		9	1	0	0	1					8	1	0

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

Study No. P030097

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

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.