

Table 15 Histopathological findings
Male, Female, 13w

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				10				10				9						
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	
Digestive system																					
Tongue		NR (10)				(0)				(0)				NR (9)							
Esophagus		(10)				(0)				(0)				(9)							
Fibrosis, muscular layer		9	1	0	0	1					9	0	0	0	0						
Stomach		NR (10)				(0)				(0)				NR (9)							
Duodenum		NR (10)				(0)				(0)				NR (9)							
Jejunum		NR (10)				(0)				(0)				NR (9)							
Ileum		NR (10)				(0)				(0)				NR (9)							
Cecum		NR (10)				(0)				(0)				NR (9)							
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		NR (10)				(0)				(0)				NR (9)							
Liver		(10)				(10)				(10)				(9)							
Degeneration, hepatocyte, fatty, midzonal		10	0	0	0	0	9	1	0	0	1	10	0	0	0	0	9	0	0	0	0
Degeneration, hepatocyte, fatty, periportal		10	0	0	0	0	10	0	0	0	0	10	0	0	0	0	9	0	0	0	0
Necrosis, hepatocyte, focal		9	1	0	0	1	10	0	0	0	0	9	1	0	0	1	7	2	0	0	2
Hypertrophy, hepatocyte ¹⁾ , centrilobular		10	0	0	0	0	10	0	0	0	0	7	3	0	0	3	0	6	3	0	9**
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		(10)				(0)				(0)				(9)							
Atrophy, acinus, focal		10	0	0	0	0					9	0	0	0	0						
Respiratory system																					
Trachea		NR (10)				(0)				(0)				NR (9)							
Lung		(10)				(0)				(0)				(9)							
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		(10)				(0)				(0)				(9)							
Hemorrhage		10	0	0	0	0					9	0	0	0	0						
Submaxillary lymph node		NR (10)				(0)				(0)				NR (9)							
Mesenteric lymph node		NR (10)				(0)				(0)				NR (9)							

** : 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.

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				
			10					10					10					9				
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Hematopoietic system																						
Spleen																						
Cardiovascular system																						
Heart																						
Aorta																						
Urinary system																						
Kidney																						
Urinary bladder																						
Genital system																						
Testis																						
Epididymis																						
Prostate																						
Endocrine system																						
Pituitary																						
Thyroid																						

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	Female																	
			Control				0.5 mg/kg				2.5 mg/kg				12.5 mg/kg					
			10				10				10				10					
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++
Digestive system																				
Tongue																				
Esophagus																				
Fibrosis, muscular layer		10	0	0	0	0										9	1	0	0	1
Stomach																				
Duodenum																				
Jejunum																				
Ileum																				
Cecum																				
Colon																				
Rectum																				
Submaxillary gland																				
Sublingual gland																				
Parotid gland																				
Liver																				
Degeneration, hepatocyte, fatty, midzonal		10	0	0	0	0										10	0	0	0	0
Degeneration, hepatocyte, fatty, periportal		9	1	0	0	1										10	0	0	0	0
Necrosis, hepatocyte, focal		10	0	0	0	0										10	0	0	0	0
Hypertrophy, hepatocyte ¹⁾ , centrilobular		10	0	0	0	0										4	6	0	0	6**
Cellular infiltration, mononuclear cell		7	3	0	0	3										8	2	0	0	2
Pancreas																				
Atrophy, acinus, focal		9	1	0	0	1														
Respiratory system																				
Trachea																				
Lung																				
Accumulation, foam cell, alveolus		9	1	0	0	1										9	1	0	0	1
Mineralization, artery		9	1	0	0	1										8	2	0	0	2
Hematopoietic system																				
Thymus																				
Hemorrhage		9	1	0	0	1														
Submaxillary lymph node																				
Mesenteric lymph node																				

** : 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		Female																	
	Group and dose		Control				0.5 mg/kg				2.5 mg/kg				12.5 mg/kg					
	Number of animals		10				10				10				10					
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Hematopoietic system																				
Spleen		NR (10)				(0)				(0)				NR (10)						
Bone marrow (sternum)		NR (10)				(0)				(0)				NR (10)						
Bone marrow (femur)		NR (10)				(0)				(0)				NR (10)						
Cardiovascular system																				
Heart		(10)				(0)				(0)				(10)						
Cellular infiltration, mononuclear cell		10	0	0	0	0										10	0	0	0	0
Aorta		NR (10)				(0)				(0)				NR (10)						
Urinary system																				
Kidney		(10)				(0)				(0)				(10)						
Tubule, basophilic		10	0	0	0	0										10	0	0	0	0
Cast, proteinaceous		10	0	0	0	0										10	0	0	0	0
Cellular infiltration, pelvis, neutrophil		10	0	0	0	0										10	0	0	0	0
Mineralization, corticomedullary		9	1	0	0	1										10	0	0	0	0
Nephroblastoma		9	1	0	0	1										10	0	0	0	0
Urinary bladder		NR (10)				(0)				(0)				NR (10)						
Genital system																				
Testis		NA				NA				NA				NA						
Epididymis		NA				NA				NA				NA						
Prostate		NA				NA				NA				NA						
Cellular infiltration, mononuclear cell		NA				NA				NA				NA						
Seminal vesicle		NA				NA				NA				NA						
Ovary		NR (10)				(0)				(0)				NR (10)						
Uterus		NR (10)				(0)				(0)				NR (10)						
Vagina		NR (10)				(0)				(0)				NR (10)						
Mammary gland		NR (10)				(0)				(0)				NR (10)						
Endocrine system																				
Pituitary		NR (10)				(0)				(0)				NR (10)						
Thyroid		(10)				(0)				(0)				(10)						
Remnant, ultimobranchial body		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					12.5 mg/kg				
			10					10					10					10				
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Endocrine system																						
Parathyroid																						
Adrenal																						
Hypertrophy, cortical cell, focal																						
Hypertrophy, cortical cell, focal																						
Nervous system																						
Cerebrum																						
Dilatation, lateral ventricle																						
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																						

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	Male																			
			Control					0.1 mg/kg					0.5 mg/kg					2.5 mg/kg				
			Number of animals																			
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system																						
Tongue																						
Esophagus																						
Stomach																						
Dilatation, glandular space, glandular stomach																						
Cellular infiltration, mucosa, glandular stomach, neutrophil																						
Duodenum																						
Jejunum																						
Ileum																						
Cecum																						
Fibrosis, muscular layer																						
Colon																						
Rectum																						
Submaxillary gland																						
Sublingual gland																						
Parotid gland																						
Cellular infiltration, lymphocyte																						
Liver																						
Degeneration, hepatocyte, fatty, periportal																						
Degeneration, cystic																						
Necrosis, hepatocyte, focal																						
Hypertrophy, hepatocyte ¹⁾ , centrilobular																						
Hematopoiesis, extramedullary																						
Focus, altered cell, basophilic																						
Focus, altered cell, clear																						
Deposit, lipofuscin ²⁾ , hepatocyte																						
Angiectasis																						
Cellular infiltration, mononuclear cell																						
Adenoma, hepatocellular																						

*: P<0.05, **: P<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

Organs and findings	Sex	Group and dose	Male																	
			Control				0.1 mg/kg				0.5 mg/kg				2.5 mg/kg					
			10				8				10				10					
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++
Digestive system																				
Pancreas																				
			(10)				(0)				(0)				(10)					
			10	0	0	0	0									9	1	0	0	1
			8	2	0	0	2									7	3	0	0	3
			10	0	0	0	0									10	0	0	0	0
			9	1	0	0	1									10	0	0	0	0
Respiratory system																				
Trachea																				
			(10)				(0)				(0)				(10)					
			10	0	0	0	0								10	0	0	0	0	
Lung																				
			(10)				(0)				(0)				(10)					
			7	3	0	0	3								4	5	1	0	6	
			10	0	0	0	0								9	1	0	0	1	
			6	4	0	0	4								5	5	0	0	5	
Hematopoietic system																				
Thymus																				
			(10)				(0)				(0)				(10)					
			1	8	1	0	9								1	9	0	0	9	
			NR (10)				(0)				(0)				NR (10)					
			(1)				(0)				(0)				(1)					
			0	1	0	0	1								0	1	0	0	1	
			NR (10)				(0)				(0)				NR (10)					
			(10)				(0)				(0)				(10)					
			9	1	0	0	1								10	0	0	0	0	
			10	0	0	0	0								10	0	0	0	0	
			10	0	0	0	0								10	0	0	0	0	
			(10)				(0)				(0)				(10)					
			10	0	0	0	0								10	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.

Two males in the 0.1 mg/kg group died.

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
Hematopoietic system																				
Bone marrow (femur)																				
Atrophy, focal																				
Hematopoiesis, increased																				
Cardiovascular system																				
Heart																				
Cellular infiltration, mononuclear cell																				
Fibrosis, myocardium																				
Aorta																				
Urinary system																				
Kidney																				
Hyperplasia, epithelial cell, tubule																				
Hyperplasia, transitional cell, pelvis																				
Tubule, basophilic																				
Cast, proteinaceous																				
Hemorrhage, pelvis																				
Cellular infiltration, mononuclear cell, pelvis																				
Cellular infiltration, mononuclear cell, cortex																				
Cellular infiltration, pelvis, neutrophil																				
Cellular infiltration, cortex, neutrophil																				
Cellular exudation, pelvic cavity, neutrophil																				
Mineralization, papilla																				
Mineralization, pelvis																				
Urinary bladder																				
Cellular infiltration, muscular layer, neutrophil																				

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.

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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				
		10					8					10					10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Genital system																					
Testis																					
Atrophy, seminiferous tubule		10	0	(10)	0	0	(0)			(0)					8	0	1	1	2		
Hyperplasia, leydig cell, focal		10	0	(10)	0	0	(0)			(0)					9	1	0	0	1		
Epididymis																					
Decrease, sperm, lumen		10	0	(10)	0	0	(0)			(0)					9	0	0	1	1		
Cellular infiltration, mononuclear cell		9	1	(10)	0	0	(0)			(0)					10	0	0	0	0		
Prostate																					
Atrophy		6	4	(10)	0	0	(0)			(0)					5	3	2	0	5		
Hemorrhage		10	0	(10)	0	0	(0)			(0)					9	1	0	0	1		
Cellular infiltration, mononuclear cell		9	1	(10)	0	0	(0)			(0)					8	2	0	0	2		
Seminal vesicle		NR (10)																			
Ovary		NA																			
Dilatation, ovarian bursa		NA																			
Cyst		NA																			
Uterus		NA																			
Metaplasia, epithelial cell, gland, squamous		NA																			
Polyp, endometrial stromal		NA																			
Vagina		NA																			
Degeneration, epithelium, mucous		NA																			
Mammary gland																					
Hyperplasia, lobular		10	0	(10)	0	0	(0)			(0)					10	0	0	0	0		
Ectasia, alveolus/duct		10	0	(10)	0	0	(0)			(0)					10	0	0	0	0		
Adenoma		10	0	(10)	0	0	(0)			(0)					10	0	0	0	0		
Fibroadenoma		10	0	(10)	0	0	(0)			(0)					10	0	0	0	0		
Adenocarcinoma		10	0	(10)	0	0	(0)			(0)					10	0	0	0	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						
		10				8				10				10						
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++
Endocrine system																				
Pituitary																				
Hyperplasia, anterior lobe																				
		7	3	0	0	3														
Cyst, anterior lobe																				
		10	0	0	0	0														
Thyroid																				
Hyperplasia, C cell																				
		10	0	0	0	0														
Deposit, material, interstitium, eosinophilic																				
		10	0	0	0	0														
Remnant, ultimobranchial body																				
		9	1	0	0	1														
Parathyroid																				
Adrenal																				
Hypertrophy, cortical cell, focal																				
		8	2	0	0	2														
Hyperplasia, cortical cell, focal																				
		9	1	0	0	1														
Angiectasis																				
		10	0	0	0	0														
Nervous system																				
Cerebrum																				
Cerebellum																				
Medulla oblongata																				
Spinal cord																				
Optic nerve																				
Sciatic nerve																				
Special sense organs																				
Eye																				
Harderian gland																				
Cellular infiltration, lymphocyte																				
		10	0	0	0	0														
Musculoskeletal system																				
M. biceps femoris																				

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

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	0
Cellular infiltration, mucosa, glandular stomach, neutrophil		10	0	0	0	0									8	1	0	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	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	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

Organs and findings	Sex	Group and dose	Female																					
			Control					0.5 mg/kg					2.5 mg/kg					12.5 mg/kg						
			10					10					10					9						
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
Digestive system																								
Pancreas																								
			(10)					(0)					(0)					(9)						
			9	1	0	0	1																	
			10	0	0	0	0																	
			10	0	0	0	0																	
			10	0	0	0	0																	
Respiratory system																								
Trachea																								
					(10)					(0)					(0)					(9)				
			10	0	0	0	0	0																
Lung																								
					(10)					(0)					(0)					(9)				
			6	4	0	0	4																	
			10	0	0	0	0																	
			9	1	0	0	1																	
Hematopoietic system																								
Thymus																								
					(10)					(0)					(0)					(9)				
			1	8	1	0	9																	
					NR(10)					(0)					(0)					NR(9)				
					(0)					(0)					(0)					(0)				
					NR(10)					(0)					(0)					NR(9)				
					(10)					(0)					(0)					(9)				
			10	0	0	0	0																	
			8	2	0	0	2																	
			9	1	0	0	1																	
					(10)					(0)					(0)					(9)				
			10	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
Hematopoietic system																				
Bone marrow (femur)																				
Atrophy, focal																				
Hematopoiesis, increased																				
Cardiovascular system																				
Heart																				
Cellular infiltration, mononuclear cell																				
Fibrosis, myocardium																				
Aorta																				
Urinary system																				
Kidney																				
Hyperplasia, epithelial cell, tubule																				
Hyperplasia, transitional cell, pelvis																				
Tubule, basophilic																				
Cast, proteinaceous																				
Hemorrhage, pelvis																				
Cellular infiltration, mononuclear cell, pelvis																				
Cellular infiltration, mononuclear cell, cortex																				
Cellular infiltration, pelvis, neutrophil																				
Cellular infiltration, cortex, neutrophil																				
Cellular exudation, pelvic cavity, neutrophil																				
Mineralization, papilla																				
Mineralization, pelvis																				
Urinary bladder																				
Cellular infiltration, muscular layer, neutrophil																				

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					12.5 mg/kg				
			10					10					10					9				
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Genital system																						
Testis																						
Atrophy, seminiferous tubule																						
Hyperplasia, leydig cell, focal																						
Epididymis																						
Decrease, sperm, lumen																						
Cellular infiltration, mononuclear cell																						
Prostate																						
Atrophy																						
Hemorrhage																						
Cellular infiltration, mononuclear cell																						
Seminal vesicle																						
Ovary																						
Dilatation, ovarian bursa																						
Cyst																						
Uterus																						
Metaplasia, epithelial cell, gland, squamous																						
Polyp, endometrial stromal																						
Vagina																						
Degeneration, epithelium, mucous																						
Mammary gland																						
Hyperplasia, lobular																						
Ectasia, alveolus/duct																						
Adenoma																						
Fibroadenoma																						
Adenocarcinoma																						

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	Group and dose	Female																			
			Control					0.5 mg/kg					2.5 mg/kg					12.5 mg/kg				
			10					10					10					9				
Number of animals		-	+	++	+++	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																						
Exiremity						(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.