

Table 14 Histopathological findings
Male, Female, 13w

Study No. P030098

Organs and findings	Sex	Group and dose	Male														
			Control					4 mg/kg					20 mg/kg				
			Number of animals					9					10				
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system																	
Tongue					NR (10)					(0)					(0)		
Esophagus					NR (10)					(0)					(0)		
Stomach					NR (10)					(0)					(0)		
Duodenum					NR (10)					(0)					(0)		
Jejunum					NR (10)					(0)					(0)		
Ileum					NR (10)					(0)					(0)		
Cecum					NR (10)					(0)					(0)		
Colon					NR (10)					(0)					(0)		
Rectum					NR (10)					(0)					(0)		
Submaxillary gland					NR (10)					(0)					(0)		
Sublingual gland					NR (10)					(0)					(0)		
Parotid gland					NR (10)					(0)					(0)		
Liver					NR (10)					(9)					(10)		
Degeneration, hepatocyte, fatty, centrilobular					10	0	0	0	0	9	0	0	0	0	8	2	0
Degeneration, hepatocyte, fatty, periportal					7	3	0	0	3	6	3	0	0	3	5	5	0
Necrosis, hepatocyte, focal					10	0	0	0	0	9	0	0	0	0	10	0	0
Hypertrophy, hepatocyte, centrilobular					10	0	0	0	0	9	0	0	0	0	10	0	0
Cellular infiltration, mononuclear cell					10	0	0	0	0	9	0	0	0	0	10	0	0
Fibrosis					9	1	0	0	1	9	0	0	0	0	10	0	0
Pancreas															(0)	0	
Atrophy, acinus, focal					8	2	0	0	2						(0)	0	
Cellular infiltration, mixed					9	1	0	0	1							0	
Respiratory system																	
Trachea										NR (10)					(0)		
Lung										(10)					(0)		
Metaplasia, osseous					7	3	0	0	3						(0)		
Accumulation, foam cell, alveolus					9	1	0	0	1								
Mineralization, artery					9	1	0	0	1								
Hematopoietic system																	
Thymus										NR (10)					(0)		
Submaxillary lymph node										NR (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.

One male in the 4 mg/kg group was imminently sacrificed when moribund.

Table 14 - continued

Histopathological findings
Male, Female, 13w

Study No. P030098

Organs and findings	Sex Group and dose Number of animals	Male														
		Control					4 mg/kg					20 mg/kg				
		10					9					10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Hematopoietic system																
Mesenteric lymph node																
				(10)					(0)					(10)		
		10	0	0	0	0								10	0	0
Spleen																
				NR (10)					(0)					(0)		0
Bone marrow (sternum)																
				NR (10)					(0)					(0)		
Bone marrow (femur)																
				NR (10)					(0)					(0)		
Cardiovascular system																
Heart																
				(10)					(0)					(0)		
		8	2	0	0	2										
				0	0											
Fibrosis, myocardium																
		9	1	0	0	1								(0)		
				NR (10)					(0)					(0)		
Aorta																
Urinary system																
Kidney																
				(10)					(9)					(10)		
		6	4	0	0	4			6	3	0	0	3	8	2	0
Tubule, basophilic																
		10	0	0	0	0			9	0	0	0	3	7	3	0
Droplet, epithelial cell, proximal tubule, hyaline																
		10	0	0	0	0			9	0	0	0	0	8	0	0
Cast, proteinaceous																
		10	0	0	0	0			9	0	0	0	0	10	0	0
Cyst, medulla																
		10	0	0	0	0			8	1	0	0	1	10	0	0
Cellular infiltration, mononuclear cell, pelvis																
		10	0	0	0	0			9	0	0	0	0	10	0	0
Fibrosis, medulla																
		10	0	0	0	0			9	0	0	0	0	9	1	0
Mineralization, cortex																
		9	1	0	0	1			9	0	0	0	0	10	0	0
Mineralization, medulla																
		9	1	0	0	1			8	1	0	0	1	9	1	0
Urinary bladder																
				(10)					(0)					(0)		
		10	0	0	0	0										1
Granuloma, adventitia																
Genital system																
Testis																
				NR (10)					(0)					(0)		
Epididymis																
				NR (10)					(0)					(0)		
Prostate																
				(10)					(0)					(0)		
		7	3	0	0	3										
Cellular infiltration, mononuclear cell																
				NR (10)					(0)					(0)		
Seminal vesicle																
				NA					NA					NA		
Ovary																
				NA					NA					NA		
Uterus																
				NA					NA					NA		

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.

One male in the 4 mg/kg group was imminently sacrificed when moribund.

Table 14 - continued Histopathological findings
Male, Female, 13w

Study No. P030098

Organs and findings	Sex	Group and dose	Male														
			Control					4 mg/kg					20 mg/kg				
			10					9					10				
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Genital system																	
Vagina					NA					NA						NA	
Degeneration, epithelium, mucous																	
Mammary gland					NR(10)					(0)						(0)	
Endocrine system																	
Pituitary					(10)					(0)							(0)
Cyst, anterior lobe						10	0	0	0	0							
Thyroid					(10)					(0)							(0)
Remnant, ultimobranchial body						9	1	0	0	1							
Parathyroid					NR(10)					(0)							(0)
Adrenal					(10)					(0)							(0)
Hypertrophy, cortical cell, focal						9	1	0	0	1							
Nervous system																	
Cerebrum					NR(10)					(0)							(0)
Cerebellum					NR(10)					(0)							(0)
Medulla oblongata					NR(10)					(0)							(0)
Spinal cord					NR(10)					(0)							(0)
Optic nerve					NR(10)					(0)							(0)
Sciatic nerve					NR(10)					(0)							(0)
Special sense organs																	
Eye					(10)					(0)							(0)
Dysplasia, retina						9	1	0	0	1							
Harderian gland					NR(10)					(0)							(0)
Musculoskeletal system																	
M. biceps femoris					NR(10)					(0)							(0)
Sternum					NR(10)					(0)							(0)
Femur					NR(10)					(0)							(0)
Integumentary system																	
Integument					NR(10)					(0)							(0)

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.

One male in the 4 mg/kg group was imminently sacrificed when moribund.

Table 14 - continued

Histopathological findings
Male, Female, 13w

Study No. P030098

Organs and findings	Sex		Male					Female									
	Group and dose		100 mg/kg					Control					4 mg/kg				
	Number of animals		9					10					10				
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
Digestive system																	
Tongue																	
Esophagus																	
Stomach																	
Duodenum																	
Jejunum																	
Ileum																	
Cecum																	
Colon																	
Rectum																	
Submaxillary gland																	
Sublingual gland																	
Parotid gland																	
Liver																	
Degeneration, hepatocyte, fatty, centrilobular	9	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Degeneration, hepatocyte, fatty, periportal	6	3	0	0	3	9	1	0	0	1	9	1	0	0	1		
Necrosis, hepatocyte, focal	9	0	0	0	0	10	0	0	0	0	9	1	0	0	1		
Hypertrophy, hepatocyte, centrilobular	7	2	0	0	2	10	0	0	0	0	10	0	0	0	0		
Cellular infiltration, mononuclear cell	9	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Fibrosis	9	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Pancreas																	
Atrophy, acinus, focal	9	0	0	0	0	9	1	0	0	1							
Cellular infiltration, mixed	9	0	0	0	0	10	0	0	0	0							
Respiratory system																	
Trachea																	
Lung																	
Metaplasia, osseous	7	2	0	0	2	10	0	0	0	0							
Accumulation, foam cell, alveolus	8	1	0	0	1	10	0	0	0	0							
Mineralization, artery	5	4	0	0	4	8	2	0	0	2							
Hematopoietic system																	
Thymus																	
Submaxillary lymph node																	

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 100 mg/kg group died.

Table 14 - continued

Histopathological findings
Male, Female, 13w

Study No. P030098

Organs and findings	Sex		Histopathological findings														
	Group and dose	Number of animals	Male					Female									
			100 mg/kg					Control					4 mg/kg				
			9					10					10				
-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total			
Hematopoietic system																	
Mesenteric lymph node																	
			(9)					(10)						(0)			
	7	2	0	0	2	10	0	0	0	0							
Spleen																	
			NR (9)					NR (10)						(0)			
Bone marrow (sternum)																	
			NR (9)					NR (10)						(0)			
Bone marrow (femur)																	
			NR (9)					NR (10)						(0)			
Cardiovascular system																	
Heart																	
			(9)					(10)						(0)			
	5	4	0	0	4	10	0	0	0	0							
Fibrosis, myocardium																	
	7	2	0	0	2	10	0	0	0	0							
Aorta																	
			NR (9)					NR (10)						(0)			
Urinary system																	
Kidney																	
			(9)					(10)						(10)			
	5	4	0	0	4	10	0	0	0	0	10	0	0	0	0		
Droplet, epithelial cell, proximal tubule, hyaline																	
	4	5	0	0	5**	10	0	0	0	0	10	0	0	0	0		
Cast, proteinaceous																	
	9	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Cyst, medulla																	
	9	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Cellular infiltration, mononuclear cell, pelvis																	
	8	1	0	0	1	10	0	0	0	0	10	0	0	0	0		
Fibrosis, medulla																	
	9	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Mineralization, cortex																	
	6	3	0	0	3	10	0	0	0	0	10	0	0	0	0		
Mineralization, medulla																	
	9	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Urinary bladder																	
	9	0	(9)					(10)			9	1	0	0	1		
Granuloma, adventitia																	
	9	0	0	0	0	9	1	0	0	1			(0)				
Genital system																	
Testis																	
			NR (9)					NA						NA			
Epididymis																	
			NR (9)					NA						NA			
Prostate																	
			(9)					NA						NA			
Cellular infiltration, mononuclear cell																	
	7	2	0	0	2												
Seminal vesicle																	
			NR (9)					NA						NA			
Ovary																	
			NA					NR (10)						(0)			
Uterus																	
			NA					NR (10)						(0)			

** : P<0.01 (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.

One male in the 100 mg/kg group died.

Table 14 - continued
Histopathological findings
Male, Female, 13w

Organs and findings	Sex		Male					Female									
	Group and dose		100 mg/kg					Control					4 mg/kg				
	Number of animals		9					10					10				
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
Genital system																	
Vagina			NA							(10)					(0)		
Degeneration, epithelium, mucous						10	0	0	0	0							
Mammary gland			NR (9)							NR (10)					(0)		
Endocrine system																	
Pituitary			(9)							(10)					(0)		
Cyst, anterior lobe	9	0	0	0	0	10	0	0	0	0							
Thyroid			(9)							(10)					(0)		
Remnant, ultimobranchial body	6	3	0	0	3	6	4	0	0	4							
Parathyroid			NR (9)							NR (10)					(0)		
Adrenal			(9)							(10)					(0)		
Hypertrophy, cortical cell, focal	9	0	0	0	0	10	0	0	0	0							
Nervous system																	
Cerebrum			NR (9)							NR (10)					(0)		
Cerebellum			NR (9)							NR (10)					(0)		
Medulla oblongata			NR (9)							NR (10)					(0)		
Spinal cord			NR (9)							NR (10)					(0)		
Optic nerve			NR (9)							NR (10)					(0)		
Sciatic nerve			NR (9)							NR (10)					(0)		
Special sense organs																	
Eye			(9)							(10)					(0)		
Dysplasia, retina	9	0	0	0	0	10	0	0	0	0							
Harderian gland			NR (9)							NR (10)					(0)		
Musculoskeletal system																	
M. biceps femoris			NR (9)							NR (10)					(0)		
Sternum			NR (9)							NR (10)					(0)		
Femur			NR (9)							NR (10)					(0)		
Integumentary system																	
Integument			NR (9)							NR (10)					(0)		

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.

One male in the 100 mg/kg group died.

Table 14 - continued

Histopathological findings
Male, Female, 13w

Study No. P030098

Organs and findings	Sex		Female									
	Group and dose		20 mg/kg					100 mg/kg				
	Number of animals		10					10				
	-	+	++	+++	Total	-	+	++	+++	Total		
Digestive system												
Tongue												
Esophagus			(0)					NR (10)				
Stomach			(0)					NR (10)				
Duodenum			(0)					NR (10)				
Jejunum			(0)					NR (10)				
Ileum			(0)					NR (10)				
Cecum			(0)					NR (10)				
Colon			(0)					NR (10)				
Rectum			(0)					NR (10)				
Submaxillary gland			(0)					NR (10)				
Sublingual gland			(0)					NR (10)				
Parotid gland			(0)					NR (10)				
Liver			(0)					NR (10)				
Degeneration, hepatocyte, fatty, centrilobular	10	0	0	0	0	10	0	0	0	0		
Degeneration, hepatocyte, fatty, periportal	8	2	0	0	2	6	4	0	0	4		
Necrosis, hepatocyte, focal	9	1	0	0	1	10	0	0	0	0		
Hypertrophy, hepatocyte, centrilobular	8	2	0	0	2	1	8	1	0	9**		
Cellular infiltration, mononuclear cell	9	1	0	0	1	10	0	0	0	0		
Fibrosis	10	0	0	0	0	10	0	0	0	0		
Pancreas			(0)					(10)				
Atrophy, acinus, focal						10	0	0	0	0		
Cellular infiltration, mixed						10	0	0	0	0		
Respiratory system												
Trachea			(0)					NR (10)				
Lung			(0)					(10)				
Metaplasia, osseous						10	0	0	0	0		
Accumulation, foam cell, alveolus						10	0	0	0	0		
Mineralization, artery						8	2	0	0	2		
Hematopoietic system												
Thymus			(0)					NR (10)				
Submaxillary lymph node			(0)					NR (10)				

** : P < 0.01 (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 14 - continued

Histopathological findings
Male, Female, 13w

Study No. P030098

Organs and findings	Sex	Female										
		Group and dose	20 mg/kg					100 mg/kg				
			Number of animals					10				
			-	+	++	+++	Total	-	+	++	+++	Total
Hematopoietic system												
Mesenteric lymph node				(10)								
Accumulation, foam cell	10	0	0	0	0	9	1	0	0	1		
Spleen			(0)					NR	(10)			
Bone marrow (sternum)			(0)					NR	(10)			
Bone marrow (femur)			(0)					NR	(10)			
Cardiovascular system												
Heart												
Cellular infiltration, mononuclear cell			(0)			10	0	0	0	0		
Fibrosis, myocardium						10	0	0	0	0		
Aorta												
			(0)					NR	(10)			
Urinary system												
Kidney												
Tubule, basophilic			(10)					(10)				
Droplet, epithelial cell, proximal tubule, hyaline	10	0	0	0	0	8	2	0	0	2		
Cast, proteinaceous	10	0	0	0	0	10	0	0	0	0		
Cyst, medulla	10	0	0	0	0	9	1	0	0	1		
Cellular infiltration, mononuclear cell, pelvis	10	0	0	0	0	10	0	0	0	0		
Fibrosis, medulla	10	0	0	0	0	10	0	0	0	0		
Mineralization, cortex	10	0	0	0	0	10	0	0	0	0		
Mineralization, medulla	10	0	0	0	0	10	0	0	0	0		
Urinary bladder	8	2	0	0	2	10	0	0	0	0		
Granuloma, adventitia			(0)					(10)				
						10	0	0	0	0		
Genital system												
Testis			NA					NA				
Epididymis			NA					NA				
Prostate			NA					NA				
Cellular infiltration, mononuclear cell												
Seminal vesicle			NA					NA				
Ovary			(0)					NR	(10)			
Uterus			(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.

Table 14 - continued

Histopathological findings
Male, Female, 13w

Study No. P030098

Organs and findings	Sex	Female									
	Group and dose	20 mg/kg					100 mg/kg				
	Number of animals	10					10				
		-	+	++	+++	Total	-	+	++	+++	Total
Genital system											
Vagina				(0)					(10)		
Degeneration, epithelium, mucous						9	1	0	0	1	
Mammary gland				(0)					NR(10)		
Endocrine system											
Pituitary				(0)					(10)		
Cyst, anterior lobe						9	1	0	0	1	
Thyroid				(0)					(10)		
Remnant, ultimobranchial body						9	1	0	0	1	
Parathyroid				(0)					NR(10)		
Adrenal				(0)					(10)		
Hypertrophy, cortical cell, focal						10	0	0	0	0	
Nervous system											
Cerebrum				(0)					NR(10)		
Cerebellum				(0)					NR(10)		
Medulla oblongata				(0)					NR(10)		
Spinal cord				(0)					NR(10)		
Optic nerve				(0)					NR(10)		
Sciatic nerve				(0)					NR(10)		
Special sense organs											
Eye				(0)					(10)		
Dysplasia, retina						10	0	0	0	0	
Harderian gland				(0)					NR(10)		
Musculoskeletal system											
M. biceps femoris				(0)					NR(10)		
Sternum				(0)					NR(10)		
Femur				(0)					NR(10)		
Integumentary system											
Integument				(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 15 Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex Group and dose Number of animals	Male															
		Control					4 mg/kg					20 mg/kg					
		10					8					8					
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	
Digestive system																	
Tongue																	
Esophagus																	
Stomach																	
Dilatation, glandular space, glandular stomach		5	5		0	5											
Duodenum																	
Accumulation, foam cell, lamina propria		10	0		0	0											
Jejunum																	
Accumulation, foam cell, lamina propria		10	0		0	0						8	0		0	0	
Ileum																	
Accumulation, foam cell, lamina propria		10	0		0	0						8	0		0	0	
Accumulation, foam cell, peyer's patch		10	0		0	0						8	0		0	0	
Cecum																	
Colon																	
Rectum																	
Submaxillary gland																	
Sublingual gland																	
Parotid gland																	
Liver																	
Degeneration, hepatocyte, fatty, centrilobular		9	1		0	1											
Degeneration, hepatocyte, fatty, periportal		4	5		1	6	7	7	1	0	0	1	8	0		0	0
Necrosis, hepatocyte, focal		10	0		0	0	5	2	1	0	0	1*	4	3	1	0	4
Hypertrophy, hepatocyte, centrilobular		10	0		0	0	8	0	0	0	0	3*	8	0	0	0	0
Hyperplasia, bile duct		9	1		0	1	8	0	0	0	0	0	8	0	0	0	0
Hematopoiesis, extramedullary		10	0		0	0	8	0	0	0	0	0	6	2	0	0	2
Focus, altered cell, basophilic		10	0		0	0	8	0	0	0	0	0	8	0	0	0	0
Focus, altered cell, clear		10	0		0	0	8	0	0	0	0	0	8	0	0	0	0
Angiectasis		10	0		0	0	8	0	0	0	0	0	8	0	0	0	0
Hemorrhage		10	0		0	0	8	0	0	0	0	0	8	0	0	0	0
Cellular infiltration, mononuclear cell		8	2		0	2	8	0	0	0	0	0	8	0	0	0	0
Accumulation, foam cell, sinusoid ^{a)}		10	0		0	0	8	0	0	0	0	0	5	3	0	0	3
Cholangioma		9	1		0	1	8	0	0	0	0	0	6	2	0	0	2

*: P<0.05 (significantly different from control).

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

a) with lymphocyte infiltration.

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

One male in the 4 mg/kg group died and one male in the 4 mg/kg group was imminently sacrificed when moribund.

Two males in the 20 mg/kg group died.

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex	Group and dose	Male														
			Control					4 mg/kg					20 mg/kg				
			10					8					8				
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system																	
Pancreas																	
			(10)					(0)					(0)				
			10	0	0	0	0										
			8	2	0	0	0										
			8	2	0	0	0										
			10	0	0	0	0										
			9	1	0	0	0										
			10	0	0	0	0										
Respiratory system																	
Trachea																	
			NR(10)					(0)					(0)				
Lung																	
			(10)					(0)					(0)				
			8	2	0	0	2										
			9	1	0	0	1										
			6	4	0	0	4										
Hematopoietic system																	
Thymus																	
			(10)					(0)					(0)				
			0	7	3	0	10										
Submaxillary lymph node																	
			NR(10)					(0)					(0)				
Mesenteric lymph node																	
			(10)					(8)					(8)				
			10	0	0	0	0	8	0	0	0	0	3	5	0	0	5**
Spleen																	
			(10)					(8)					(8)				
			10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
			10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
			10	0	0	0	0	8	0	0	0	0	7	1	0	0	1
			10	0	0	0	0	8	0	0	0	0	7	1	0	0	1
Bone marrow (sternum)																	
			NR(10)					(0)					(0)				
Bone marrow (femur)																	
			NR(10)					(0)					(0)				
Cardiovascular system																	
Heart																	
			(10)					(0)					(0)				
			4	6	0	0	6										
			5	5	0	0	5										

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

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

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

One male in the 4 mg/kg group died and one male in the 4 mg/kg group was imminently sacrificed when moribund.

Two males in the 20 mg/kg group died.

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex		Male														
	Group and dose		Control					4 mg/kg					20 mg/kg				
	Number of animals		10					8					8				
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
Cardiovascular system																	
Aorta					NR(10)					(0)						(0)	
Urinary system																	
Kidney					(10)					(8)						(8)	
Hyperplasia, transitional epithelium, pelvis	9	1	0	0	1	6	2	0	0	2	8	0	0	0	0	0	
Tubule, basophilic	5	4	1	0	5	3	4	1	0	5	3	5	0	0	0	5	
Karyomegaly, epithelial cell, proximal tubule	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0	0	
Droplet, epithelial cell, proximal tubule, hyaline	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0	0	
Cast, proteinaceous	8	2	0	0	2	6	2	0	0	2	4	4	0	0	0	4	
Dilatation, distal tubule	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0	0	
Dilatation, pelvic cavity	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0	0	
Cyst, medulla	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0	0	
Hemorrhage, pelvis	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0	0	
Cellular infiltration, mononuclear cell, pelvis	9	1	0	0	1	5	3	0	0	3	5	3	0	0	0	3	
Cellular infiltration, mononuclear cell, cortex	9	1	0	0	1	6	2	0	0	2	7	1	0	0	0	1	
Cellular exudation, pelvic cavity, neutrophil	9	1	0	0	1	6	2	0	0	2	5	3	0	0	0	3	
Mineralization, pelvis	9	1	0	0	1	8	0	0	0	0	8	0	0	0	0	0	
Mineralization, cortex	10	0	0	0	0	7	1	0	0	1	4	4	0	0	0	4*	
Mineralization, medulla	10	0	0	0	0	8	0	0	0	0	7	1	0	0	0	1	
Urinary bladder					NR(10)					(0)					(0)		
Genital system																	
Testis					(10)					(0)						(0)	
Atrophy, seminiferous tubule	9	0	0	1	1												
Edema, interstitium	9	0	0	1	1												
Epididymis					(10)					(0)						(0)	
Decrease, sperm, lumen	9	0	1	0	1												
Prostate					(10)					(0)						(0)	
Cellular infiltration, mononuclear cell	9	1	0	0	1												
Fibrosis, interstitium	10	0	0	0	0												
Seminal vesicle					NR(10)					(0)						(0)	
Ovary					NA					NA						NA	

*: P<0.05 (significantly different from control).

Grade sign: -, none; +, mild (existence 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 4 mg/kg group died and one male in the 4 mg/kg group was imminently sacrificed when moribund.

Two males in the 20 mg/kg group died.

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex Group and dose Number of animals	Male														
		Control					4 mg/kg					20 mg/kg				
		10					8					8				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Genital system																
Uterus																
Metaplasia, epithelial cell, gland, squamous					NA					NA					NA	
Cyst, endometrium																
Vagina																
Degeneration, epithelium, mucous					NA					NA					NA	
Mammary gland					(10)					(0)					(0)	
Ectasia, alveolus/duct		10	0	0	0	0										
Adenoma		10	0	0	0	0										
Endocrine system																
Pituitary					(10)					(0)					(0)	
Hyperplasia, anterior lobe, focal		9	1	0	0	1										
Cyst, anterior lobe		10	0	0	0	0										
Hemorrhage, Rathke's pouch		10	0	0	0	0										
Gliosis, posterior lobe		9	1	0	0	1										
Ectopic tissue, posterior lobe		10	0	0	0	0										
Adenoma, anterior lobe		10	0	0	0	0										
Thyroid					(10)					(0)					(0)	
Hyperplasia, C cell, focal		9	1	0	0	1										
Remnant, ultimobranchial body		8	2	0	0	2										
Parathyroid					NR (10)					(0)					(0)	
Adrenal					(10)					(0)					(0)	
Hypertrophy, cortical cell, focal		9	1	0	0	1										
Hyperplasia, cortical cell, focal		10	0	0	0	0										
Angiectasis		10	0	0	0	0										
Nervous system																
Cerebrum					NR (10)					(0)					(0)	
Cerebellum					NR (10)					(0)					(0)	
Medulla oblongata					NR (10)					(0)					(0)	
Spinal cord					NR (10)					(0)					(0)	
Optic nerve					NR (10)					(0)					(0)	
Sciatic nerve					NR (10)					(0)					(0)	

Not significantly different from control.

Grade sign: -, none; +, mild (existence 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 4 mg/kg group died and one male in the 4 mg/kg group was imminently sacrificed when moribund.

Two males in the 20 mg/kg group died.

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex		Male														
	Group and dose		Control					4 mg/kg					20 mg/kg				
	Number of animals		10					8					8				
			-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Special sense organs																	
Eye																	
	Atrophy, retina, focal		(10)					(0)					(0)				
	Dysplasia, retina		10	0	0	0	0										
	Mineralization, cornea		10	0	0	0	0										
	Harderian gland		NR(10)					(0)					(0)				
Musculoskeletal system																	
	M. biceps femoris		NR(10)					(0)					(0)				
	Sternum		NR(10)					(0)					(0)				
	Femur		NR(10)					(0)					(0)				
Integumentary system																	
	Integument		(10)					(0)					(0)				
	Cellular infiltration, mononuclear cell, subcutis		10	0	0	0	0										
	Keratoacanthoma		9	1	0	0	1										
Others																	
	Extremity		(4)					(0)					(0)				
	Formation, callus, hindlimb		4	0	0	0	0										
	Ulcer, hindlimb		0	4	0	0	4										

Not significantly different from control.

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

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

One male in the 4 mg/kg group died and one male in the 4 mg/kg group was imminently sacrificed when moribund.

Two males in the 20 mg/kg group died.

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex		Male					Female									
	Group and dose		100 mg/kg					Control					4 mg/kg				
	Number of animals		10					10					10				
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
Digestive system																	
Tongue					NR(10)					NR(10)					(0)		
Esophagus					NR(10)					NR(10)					(0)		
Stomach					(10)					(10)					(0)		
Dilatation, glandular space, glandular stomach	7	3	0	0	3	8	2	0	0	2							
Duodenum					(10)					(10)					(0)		
Accumulation, foam cell, lamina propria	9	1	0	0	1	10	0	0	0	0							
Jejunum					(10)					(10)					(0)		
Accumulation, foam cell, lamina propria	2	8	0	0	8**	10	0	0	0	0							
Ileum					(10)					(10)					(0)		
Accumulation, foam cell, lamina propria	4	6	0	0	6**	10	0	0	0	0							
Accumulation, foam cell, peyer's patch	7	3	0	0	3	10	0	0	0	0							
Cecum					NR(10)					NR(10)					(0)		
Colon					NR(10)					NR(10)					(0)		
Rectum					NR(10)					NR(10)					(0)		
Submaxillary gland					NR(10)					NR(10)					(0)		
Sublingual gland					NR(10)					NR(10)					(0)		
Parotid gland					NR(10)					NR(10)					(0)		
Liver					(10)					(10)					(10)		
Degeneration, hepatocyte, fatty, centrilobular	10	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Degeneration, hepatocyte, fatty, periportal	5	3	2	0	5	7	3	0	0	3	9	1	0	0	1		
Necrosis, hepatocyte, focal	8	2	0	0	2	9	1	0	0	1	9	1	0	0	1		
Hypertrophy, hepatocyte, centrilobular	8	2	0	0	2	10	0	0	0	0	10	0	0	0	0		
Hyperplasia, bile duct	3	5	2	0	7**	9	1	0	0	1	10	0	0	0	0		
Hematopoiesis, extramedullary	10	0	0	0	0	10	0	0	0	0	9	1	0	0	1		
Focus, altered cell, basophilic	10	0	0	0	0	9	1	0	0	1	9	1	0	0	1		
Focus, altered cell, clear	9	1	0	0	1	10	0	0	0	0	10	0	0	0	0		
Angiectasis	9	1	0	0	1	9	1	0	0	1	10	0	0	0	0		
Hemorrhage	10	0	0	0	0	10	0	0	0	0	8	2	0	0	2		
Cellular infiltration, mononuclear cell	10	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Accumulation, foam cell, sinusoid ^{a)}	0	2	8	0	10**	10	0	0	0	0	10	0	0	0	0		
Cholangioma	10	0	0	0	0	10	0	0	0	0	10	0	0	0	0		

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

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

a) with lymphocyte infiltration.

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

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex		Histopathological findings														
	Group and dose	Number of animals	Male					Female									
			100 mg/kg					Control					4 mg/kg				
			10					10					10				
-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total			
Digestive system																	
Pancreas																	
Atrophy, acinus, focal			(10)					(10)						(0)			
Hyperplasia, acinar cell, focal	9	1	0	0	1	7	3	0	0	3							
Focus, acinar cell, basophilic	9	1	0	0	1	10	0	0	0	0							
Metaplasia, hepatocyte	10	0	0	0	0	10	0	0	0	0							
Hemorrhage	9	1	0	0	1	10	0	0	0	0							
Polyarteritis	10	0	0	0	0	10	0	0	0	0							
	10	0	0	0	0	9	1	0	0	1							
Respiratory system																	
Trachea																	
Lung																	
Metaplasia, osseous			NR (10)					NR (10)						(0)			
Accumulation, foam cell, alveolus	10	0	(10)	0	0	10	0	(10)	0	0				(0)			
Mineralization, artery	8	2	0	0	2	9	1	0	0	1							
	8	2	0	0	2	10	0	0	0	0							
Hematopoietic system																	
Thymus																	
Atrophy			(10)					(10)						(0)			
Submaxillary lymph node	0	6	4	0	10	1	8	1	0	9							
Mesenteric lymph node			NR (10)					NR (10)						(0)			
Accumulation, foam cell			(10)					(10)						(10)			
Spleen			(10)	1	10**	10	0	(10)	0	0	10	0		0	0		
Hematopoiesis, extramedullary	10	0	0	0	0	10	0	(10)	0	0				(10)			
Cyst, capsule	10	0	0	0	0	9	1	0	0	1	8	1	1	0	2		
Accumulation, foam cell, white pulp	6	3	1	0	4*	10	0	0	0	0	10	0	0	0	0		
Accumulation, foam cell, red pulp	6	3	1	0	4*	10	0	0	0	0	10	0	0	0	0		
Bone marrow (sternum)			NR (10)					NR (10)						(0)			
Bone marrow (femur)			NR (10)					NR (10)						(0)			
Cardiovascular system																	
Heart																	
Cellular infiltration, mononuclear cell			(10)					(10)						(0)			
Fibrosis, myocardium	5	5	0	0	5	9	1	0	0	1							
	5	4	1	0	5	10	0	0	0	0							

*: P<0.05, **: P<0.01 (significantly different from control).

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

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

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex		Male					Female									
	Group and dose		100 mg/kg					Control					4 mg/kg				
	Number of animals		10					10					10				
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total		
Cardiovascular system																	
Aorta	NR(10)					NR(10)					(0)						
Urinary system																	
Kidney	(10)					(10)					(10)						
Hyperplasia, transitional epithelium, pelvis	10	0	0	0	0	9	1	0	0	1	8	2	0	0	2		
Tubule, basophilic	1	7	2	0	9	10	0	0	0	0	7	3	0	0	3		
Karyomegaly, epithelial cell, proximal tubule	9	1	0	0	1	10	0	0	0	0	10	0	0	0	0		
Droplet, epithelial cell, proximal tubule, hyaline	7	3	0	0	3	10	0	0	0	0	10	0	0	0	0		
Cast, proteinaceous	7	3	0	0	3	9	1	0	0	1	8	2	0	0	2		
Dilatation, distal tubule	10	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Dilatation, pelvic cavity	10	0	0	0	0	9	1	0	0	1	10	0	0	0	0		
Cyst, medulla	10	0	0	0	0	9	1	0	0	1	10	0	0	0	0		
Hemorrhage, pelvis	10	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Cellular infiltration, mononuclear cell, pelvis	10	0	0	0	0	9	1	0	0	1	10	0	0	0	0		
Cellular infiltration, mononuclear cell, cortex	10	0	0	0	0	10	0	0	0	0	10	0	0	0	0		
Cellular exudation, pelvic cavity, neutrophil	10	0	0	0	0	9	1	0	0	1	10	0	0	0	0		
Mineralization, pelvis	10	0	0	0	0	10	0	0	0	0	8	2	0	0	2		
Mineralization, cortex	8	2	0	0	2	10	0	0	0	0	10	0	0	0	0		
Mineralization, medulla	10	0	0	0	0	8	2	0	0	2	6	4	0	0	4		
Urinary bladder	NR(10)					NR(10)					(0)						
Genital system																	
Testis	(10)					NA					NA						
Atrophy, seminiferous tubule	10	0	0	0	0												
Edema, interstitium	10	0	0	0	0												
Epididymis	(10)					NA					NA						
Decrease, sperm, lumen	10	0	0	0	0												
Prostate	(10)					NA					NA						
Cellular infiltration, mononuclear cell	9	1	0	0	1												
Fibrosis, interstitium	9	1	0	0	1												
Seminal vesicle	NR(10)					NA					NA						
Ovary	NA					NR(10)					(0)						

Not significantly different from control.

Grade sign: -, none; +, mild (existence 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, 52w

Study No.P030098

Organs and findings	Sex Group and dose Number of animals	Male					Female									
		100 mg/kg					Control					4 mg/kg				
		10					10					10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Genital system																
Uterus																
	Metaplasia, epithelial cell, gland, squamous			NA				(10)						(0)		
	Cyst, endometrium					7	3	0	0	3						
	Vagina					10	0	0	0	0						
	Degeneration, epithelium, mucous			NA				(10)						(0)		
	Mammary gland			(10)		6	4	0	0	4				(0)		
	Ectasia, alveolus/duct	9	1	0	0	1	2	2	6	0	8					
	Adenoma	10	0	0	0	0	10	0	0	0	0					
Endocrine system																
Pituitary																
	Hyperplasia, anterior lobe, focal	9	1	0	0	1	8	2	(10)	0	2			(0)		
	Cyst, anterior lobe	9	1	0	0	1	10	0	0	0	0					
	Hemorrhage, Rathke's pouch	10	0	0	0	0	9	1	0	0	1					
	Gliosis, posterior lobe	10	0	0	0	0	10	0	0	0	0					
	Ectopic tissue, posterior lobe	10	0	0	0	0	10	0	0	0	0					
	Adenoma, anterior lobe	9	1	0	0	1	10	0	0	0	0					
Thyroid																
	Hyperplasia, C cell, focal			(10)					(10)					(0)		
	Remnant, ultimobranchial body	10	0	0	0	0	10	0	0	0	0					
Parathyroid																
Adrenal																
	Hypertrophy, cortical cell, focal	10	0	0	0	0	10	0	0	0	0			(0)		
	Hyperplasia, cortical cell, focal	9	1	0	0	1	4	6	0	0	6			(0)		
	Angiectasis	10	0	0	0	0	3	7	0	0	7					
Nervous system																
	Cerebrum			NR (10)					NR (10)					(0)		
	Cerebellum			NR (10)					NR (10)					(0)		
	Medulla oblongata			NR (10)					NR (10)					(0)		
	Spinal cord			NR (10)					NR (10)					(0)		
	Optic nerve			NR (10)					NR (10)					(0)		
	Sciatic nerve			NR (10)					NR (10)					(0)		

Not significantly different from control.

Grade sign: -, none; +, mild (existence 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, 52w

Study No. P030098

Organs and findings	Sex Group and dose Number of animals	Male					Female									
		100 mg/kg					Control					4 mg/kg				
		10					10					10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Special sense organs																
Eye																
Atrophy, retina, focal				(10)				(10)							(0)	
Dysplasia, retina	10	0	0	0	0	10	0	0	0	0						
Mineralization, cornea	10	0	0	0	0	10	0	0	0	0						
Harderian gland	9	1	0	0	1	10	0	0	0	0						
				NR(10)				NR(10)							(0)	
Musculoskeletal system																
M. biceps femoris																
Sternum				NR(10)				NR(10)							(0)	
Femur				NR(10)				NR(10)							(0)	
				NR(10)				NR(10)							(0)	
Integumentary system																
Integument																
Cellular infiltration, mononuclear cell, subcutis				(10)				(10)							(0)	
Keratoacanthoma	9	1	0	0	1	10	0	0	0	0						
	10	0	0	0	0	10	0	0	0	0						
Others																
Extremity																
Formation, callus, hindlimb				(4)				(2)							(0)	
Ulcer, hindlimb	4	0	0	0	0	2	0	0	0	0						
	0	4	0	0	4	0	2	0	0	2						

Not significantly different from control.

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

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

Table 15 - continued Histopathological findings
Male, Female, 52w

Organs and findings	Sex		Female							
	Group and dose		20 mg/kg				100 mg/kg			
	Number of animals		9				10			
	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system										
Tongue			(0)					NR(10)		
Esophagus			(0)					NR(10)		
Stomach			(0)					(10)		
Dilatation, glandular space, glandular stomach						7	3	0	0	3
Duodenum			(9)					(10)		
Accumulation, foam cell, lamina propria	9	0	0	0	0	9	1	0	0	1
Jejunum			(9)					(10)		
Accumulation, foam cell, lamina propria	9	0	0	0	0	4	6	0	0	6**
Ileum			(9)					(10)		
Accumulation, foam cell, lamina propria	9	0	0	0	0	9	1	0	0	1
Accumulation, foam cell, peyer's patch	9	0	0	0	0	9	1	0	0	1
Cecum			(0)					NR(10)		
Colon			(0)					NR(10)		
Rectum			(0)					NR(10)		
Submaxillary gland			(0)					NR(10)		
Sublingual gland			(0)					NR(10)		
Parotid gland			(0)					NR(10)		
Liver			(9)					(10)		
Degeneration, hepatocyte, fatty, centrilobular	9	0	0	0	0	10	0	0	0	0
Degeneration, hepatocyte, fatty, periportal	7	2	0	0	2	3	3	4	0	7*
Necrosis, hepatocyte, focal	9	0	0	0	0	10	0	0	0	0
Hypertrophy, hepatocyte, centrilobular	5	4	0	0	4*	0	0	10	0	10**
Hyperplasia, bile duct	7	2	0	0	2	9	1	0	0	1
Hematopoiesis, extramedullary	9	0	0	0	0	10	0	0	0	0
Focus, altered cell, basophilic	9	0	0	0	0	10	0	0	0	0
Focus, altered cell, clear	9	0	0	0	0	10	0	0	0	0
Angiectasis	9	0	0	0	0	10	0	0	0	0
Hemorrhage	9	0	0	0	0	10	0	0	0	0
Cellular infiltration, mononuclear cell	9	0	0	0	0	10	0	0	0	0
Accumulation, foam cell, sinusoid ^{a)}	8	1	0	0	1	1	7	2	0	9**
Cholangioma	9	0	0	0	0	10	0	0	0	0

*: P<0.05, **: P<0.01 (significantly different from control).
 Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.
 NR: no remarkable changes.
 a) with lymphocyte infiltration.
 Figures in parentheses are number of animals with tissues examined histopathologically.
 One female in the 20 mg/kg group died.

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Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex		Female							
	Group and dose		20 mg/kg				100 mg/kg			
	Number of animals		9				10			
	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system										
Pancreas										
			(0)				(10)			
	Atrophy, acinus, focal					10	0	0	0	0
	Hyperplasia, acinar cell, focal					10	0	0	0	0
	Focus, acinar cell, basophilic					10	0	0	0	0
	Metaplasia, hepatocyte					10	0	0	0	0
	Hemorrhage					10	0	0	0	0
	Polyarteritis					10	0	0	0	0
Respiratory system										
Trachea										
			(0)							
Lung										
	Metaplasia, osseous		(0)					NR (10)		
	Accumulation, foam cell, alveolus					10	0	0	0	0
	Mineralization, artery					10	0	0	0	0
						9	1	0	0	1
Hematopoietic system										
Thymus										
	Atrophy		(0)					(10)		
	Submaxillary lymph node		(0)			0	8	2	0	10
Mesenteric lymph node										
	Accumulation, foam cell		(9)					NR (10)		
		6	3	0	0	3	0	4	6	0
Spleen										
	Hematopoiesis, extramedullary		(9)					(10)		10**
	Cyst, capsule	8	1	0	0	1	10	0	0	0
	Accumulation, foam cell, white pulp	9	0	0	0	0	10	0	0	0
	Accumulation, foam cell, red pulp	9	0	0	0	0	6	4	0	4*
Bone marrow (sternum)										
		9	0	0	0	0	6	4	0	4*
Bone marrow (femur)										
			(0)					NR (10)		
			(0)					NR (10)		
Cardiovascular system										
Heart										
	Cellular infiltration, mononuclear cell		(0)					(10)		
	Fibrosis, myocardium					9	1	0	0	1
						10	0	0	0	0

*: P<0.05, **: P<0.01 (significantly different from control).

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

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

One female in the 20 mg/kg group died.

Table 15 - continued
 Histopathological findings
 Male, Female, 52w

Study No. P030098

Organs and findings	Sex		Female							
	Group and dose		20 mg/kg				100 mg/kg			
	Number of animals		9				10			
	-	+	++	+++	Total	-	+	++	+++	Total
Cardiovascular system										
Aorta			(0)					NR(10)		
Urinary system										
Kidney			(9)					(10)		
Hyperplasia, transitional epithelium, pelvis	8	1	0	0	1	10	0	0	0	0
Tubule, basophilic	6	3	0	0	3	5	5	0	0	5*
Karyomegaly, epithelial cell, proximal tubule	9	0	0	0	0	10	0	0	0	0
Droplet, epithelial cell, proximal tubule, hyaline	9	0	0	0	0	10	0	0	0	0
Cast, proteinaceous	6	3	0	0	3	6	4	0	0	4
Dilatation, distal tubule	8	1	0	0	1	10	0	0	0	0
Dilatation, pelvic cavity	9	0	0	0	0	10	0	0	0	0
Cyst, medulla	9	0	0	0	0	10	0	0	0	0
Hemorrhage, pelvis	8	1	0	0	1	10	0	0	0	0
Cellular infiltration, mononuclear cell, pelvis	9	0	0	0	0	10	0	0	0	0
Cellular infiltration, mononuclear cell, cortex	9	0	0	0	0	10	0	0	0	0
Cellular exudation, pelvic cavity, neutrophil	9	0	0	0	0	10	0	0	0	0
Mineralization, pelvis	7	2	0	0	2	10	0	0	0	0
Mineralization, cortex	9	0	0	0	0	10	0	0	0	0
Mineralization, medulla	2	7	0	0	7*	6	4	0	0	4
Urinary bladder			(0)					NR(10)		
Genital system										
Testis										
Atrophy, seminiferous tubule										NA
Edema, interstitium										NA
Epididymis										NA
Decrease, sperm, lumen										NA
Prostate										NA
Cellular infiltration, mononuclear cell										NA
Fibrosis, interstitium										NA
Seminal vesicle										NA
Ovary					(0)					NR(10)

*: P<0.05 (significantly different from control).
 Grade sign: -, none; +, mild (existence 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 20 mg/kg group died.

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex Group and dose Number of animals	Female									
		20 mg/kg					100 mg/kg				
		9					10				
		-	+	++	+++	Total	-	+	++	+++	Total
Genital system											
Uterus					(0)						(10)
Metaplasia, epithelial cell, gland, squamous						8	2	0	0		2
Cyst, endometrium						9	1	0	0		1
Vagina					(0)						(10)
Degeneration, epithelium, mucous						9	1	0	0		1
Mammary gland					(0)						(10)
Ectasia, alveolus/duct						4	3	3	0		6
Adenoma						9	1	0	0		1
Endocrine system											
Pituitary					(0)						(10)
Hyperplasia, anterior lobe, focal						10	0	0	0		0
Cyst, anterior lobe						10	0	0	0		0
Hemorrhage, Rathke's pouch						10	0	0	0		0
Gliosis, posterior lobe						10	0	0	0		0
Ectopic tissue, posterior lobe						9	1	0	0		1
Adenoma, anterior lobe						10	0	0	0		0
Thyroid					(0)						(10)
Hyperplasia, C cell, focal						9	1	0	0		1
Remnant, ultimobranchial body						7	3	0	0		3
Parathyroid					(0)						NR (10)
Adrenal					(0)						(10)
Hypertrophy, cortical cell, focal						10	0	0	0		0
Hyperplasia, cortical cell, focal						7	3	0	0		3
Angiectasis						2	8	0	0		8
Nervous system											
Cerebrum					(0)						NR (10)
Cerebellum					(0)						NR (10)
Medulla oblongata					(0)						NR (10)
Spinal cord					(0)						NR (10)
Optic nerve					(0)						NR (10)
Sciatic nerve					(0)						NR (10)

Not significantly different from control.

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

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

One female in the 20 mg/kg group died.

Table 15 - continued

Histopathological findings
Male, Female, 52w

Study No. P030098

Organs and findings	Sex Group and dose Number of animals	Female									
		20 mg/kg					100 mg/kg				
		9					10				
		-	+	++	+++	Total	-	+	++	+++	Total
Special sense organs											
Eye											
				(0)				(10)			
	Atrophy, retina, focal					9	1	0	0		1
	Dysplasia, retina					9	1	0	0		1
	Mineralization, cornea					10	0	0	0		0
	Harderian gland			(0)				NR(10)			
Musculoskeletal system											
	M. biceps femoris			(0)				NR(10)			
	Sternum			(0)				NR(10)			
	Femur			(0)				NR(10)			
Integumentary system											
	Integument			(0)				(10)			
	Cellular infiltration, mononuclear cell, subcutis					10	0	0	0		0
	Keratoacanthoma					10	0	0	0		0
Others											
	Extremity			(0)				(3)			
	Formation, callus, hindlimb					2	1	0	0		1
	Ulcer, hindlimb					1	2	0	0		2

Not significantly different from control.

Grade sign: -, none; +, mild (existence of tumor); ++, moderate; +++, marked.

NR: no remarkable changes.

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

One female in the 20 mg/kg group died.