

Table 13 - continued

Organ weights
Male, Female, 13w

Study No. P030097

Sex	Group and dose		Kidneys		Adrenals		Epididymides		Testes	
			(g)	(g/100 gB.W.)	(mg)	(mg/100 gB.W.)	(g)	(g/100 gB.W.)	(g)	(g/100 gB.W.)
Male	Control	N	10	10	10	10	10	10	10	10
		Mean	3.30	0.62	57.1	10.8	1.39	0.26	3.46	0.65
		S.D.	±0.28	±0.04	±7.0	±1.5	±0.14	±0.02	±0.28	±0.07
	0.1 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	3.49	0.62	61.0	10.8	1.39	0.25	3.47	0.62
		S.D.	±0.29	±0.02	±6.1	±1.0	±0.15	±0.02	±0.23	±0.07
	0.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	3.64	0.67	58.0	10.7	1.24*	0.23*	3.31	0.61
		S.D.	±0.29	±0.06	±3.9	±0.8	±0.08	±0.02	±0.39	±0.06
	2.5 mg/kg	N	9	9	9	9	9	9	9	9
		Mean	3.16	0.70*	50.5*	11.2	1.27	0.28	3.65	0.81**
		S.D.	±0.45	±0.07	±5.3	±1.1	±0.11	±0.03	±0.15	±0.07
Female	Control	N	10	10	10	10				
		Mean	2.12	0.70	66.0	21.8				
		S.D.	±0.72	±0.25	±7.8	±2.6				
	0.5 mg/kg	N	10	10	10	10				
		Mean	1.93	0.64	66.5	22.1				
		S.D.	±0.29	±0.07	±6.4	±2.4				
	2.5 mg/kg	N	10	10	10	10				
		Mean	1.89	0.64	64.7	21.8				
		S.D.	±0.11	±0.05	±6.1	±2.5				
	12.5 mg/kg	N	10	10	10	10				
		Mean	1.96	0.66	61.8	20.6				
		S.D.	±0.15	±0.06	±6.7	±1.6				

*: P<0.05, **: P<0.01 (significantly different from control).
One male in the 2.5 mg/kg group died.

Table 13 - continued

Organ weights
Male, Female, 13w

Study No. P030097

Sex	Group and dose		Ovaries		Uterus	
			(mg)	(mg/100 gB.W.)	(g)	(g/100 gB.W.)
Male	Control	N Mean S.D.				
	0.1 mg/kg	N Mean S.D.				
	0.5 mg/kg	N Mean S.D.				
	2.5 mg/kg	N Mean S.D.				
Female	Control	N Mean S.D.	10 78.5 ±7.8	10 26.1 ±4.0	10 0.58 ±0.09	10 0.19 ±0.03
	0.5 mg/kg	N Mean S.D.	10 79.8 ±8.9	10 26.5 ±3.2	10 0.65 ±0.08	10 0.22 ±0.04
	2.5 mg/kg	N Mean S.D.	10 79.3 ±11.9	10 26.9 ±4.6	10 0.56 ±0.06	10 0.19 ±0.03
	12.5 mg/kg	N Mean S.D.	10 80.4 ±10.9	10 27.0 ±4.0	10 0.63 ±0.08	10 0.21 ±0.03

Not significantly different from control.

Table 14 Organ weights
Male, Female, 52w

Study No. P030097

Sex	Group and dose		Final body weight	Brain		Pituitary		Thyroids		Heart	
			(g)	(g)	(g/100 gB.W.)	(mg)	(mg/100 gB.W.)	(mg)	(mg/100 gB.W.)	(g)	(g/100 gB.W.)
Male	Control	N	10	10	10	10	10	10	10	10	10
		Mean	819.9	2.41	0.30	15.8	2.0	31.5	3.8	1.89	0.23
		S.D.	±145.4	±0.12	±0.04	±1.8	±0.2	±11.3	±0.9	±0.25	±0.02
	0.1 mg/kg	N	8	8	8	8	8	8	8	8	8
		Mean	792.5	2.41	0.31	15.7	2.0	31.4	3.9	1.93	0.25
		S.D.	±140.4	±0.08	±0.07	±1.7	±0.5	±11.9	±1.0	±0.19	±0.04
	0.5 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	842.4	2.41	0.29	16.2	1.9	34.0	4.1	2.05	0.25
		S.D.	±136.1	±0.07	±0.04	±1.3	±0.3	±6.0	±0.8	±0.17	±0.03
	2.5 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	614.2**	2.36	0.39**	16.8	2.8**	29.7	4.9*	1.87	0.31**
		S.D.	±97.3	±0.10	±0.05	±3.1	±0.3	±5.7	±0.9	±0.27	±0.03
Female	Control	N	10	10	10	10	10	10	10	10	10
		Mean	423.2	2.17	0.54	27.9	6.6	24.0	5.7	1.15	0.28
		S.D.	±87.2	±0.08	±0.12	±11.9	±2.3	±5.8	±1.1	±0.16	±0.04
	0.5 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	441.8	2.20	0.51	30.9	7.0	24.6	5.5	1.23	0.28
		S.D.	±71.4	±0.09	±0.07	±16.5	±3.8	±8.7	±1.3	±0.16	±0.04
	2.5 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	481.0	2.16	0.47	32.8	7.1	27.6	5.9	1.23	0.26
		S.D.	±104.7	±0.06	±0.10	±13.6	±3.2	±4.7	±1.1	±0.17	±0.04
	12.5 mg/kg	N	9	9	9	9	9	9	9	9	9
		Mean	425.8	2.17	0.52	30.5	7.4	26.5	6.4	1.24	0.29
		S.D.	±71.4	±0.07	±0.08	±9.9	±2.4	±4.1	±1.4	±0.09	±0.03

*: P<0.05, **: P<0.01 (significantly different from control).
Two males in the 0.1 mg/kg group and one female in the 12.5 mg/kg group died.

Table 14 - continued

Organ weights
Male, Female, 52w

Study No. P030097

Sex	Group and dose		Lungs		Thymus		Liver		Spleen	
			(g)	(g/100 gB.W.)	(g)	(g/100 gB.W.)	(g)	(g/100 gB.W.)	(g)	(g/100 gB.W.)
Male	Control	N	10	10	10	10	10	10	10	10
		Mean	1.88	0.23	0.08	0.01	18.35	2.22	0.99	0.12
		S.D.	±0.16	±0.02	±0.02	±0.00	±4.61	±0.25	±0.24	±0.02
	0.1 mg/kg	N	8	8	8	8	8	8	8	8
		Mean	1.86	0.24	0.08	0.01	17.79	2.26	0.96	0.13
		S.D.	±0.05	±0.05	±0.03	±0.00	±2.65	±0.20	±0.07	±0.03
	0.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.88	0.23	0.07	0.01	24.85**	2.95**	1.06	0.13
		S.D.	±0.22	±0.02	±0.02	±0.00	±5.23	±0.47	±0.15	±0.03
	2.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.79	0.29**	0.09	0.01	25.09**	4.13**	0.89	0.15
		S.D.	±0.16	±0.03	±0.02	±0.00	±3.69	±0.62	±0.19	±0.02
Female	Control	N	10	10	10	10	10	10	10	10
		Mean	1.34	0.33	0.09	0.02	10.55	2.48	0.62	0.15
		S.D.	±0.17	±0.07	±0.03	±0.01	±3.14	±0.39	±0.15	±0.02
	0.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.29	0.30	0.10	0.02	10.70	2.42	0.60	0.14
		S.D.	±0.12	±0.05	±0.03	±0.01	±2.03	±0.14	±0.09	±0.02
	2.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.35	0.29	0.10	0.02	11.66	2.45	0.62	0.13
		S.D.	±0.12	±0.07	±0.02	±0.00	±2.41	±0.32	±0.10	±0.03
	12.5 mg/kg	N	9	9	9	9	9	9	9	9
		Mean	1.33	0.32	0.09	0.02	15.04**	3.54**	0.60	0.14
		S.D.	±0.08	±0.05	±0.02	±0.01	±2.96	±0.41	±0.06	±0.02

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

Two males in the 0.1 mg/kg group and one female in the 12.5 mg/kg group died.

Table 14 - continued

Organ weights
Male, Female, 52w

Study No. P030097

Sex	Group and dose		Kidneys		Adrenals		Epididymides		Testes	
			(g)	(g/100 gB.W.)	(mg)	(mg/100 gB.W.)	(g)	(g/100 gB.W.)	(g)	(g/100 gB.W.)
Male	Control	N	10	10	10	10	10	10	10	10
		Mean	3.78	0.47	63.7	7.9	1.30	0.16	3.60	0.45
		S.D.	±0.50	±0.05	±8.7	±1.2	±0.10	±0.03	±0.33	±0.06
	0.1 mg/kg	N	8	8	8	8	8	8	8	8
		Mean	3.76	0.48	61.6	8.0	1.35	0.18	3.61	0.47
		S.D.	±0.46	±0.08	±8.3	±1.9	±0.08	±0.04	±0.36	±0.10
	0.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	4.29	0.51	60.9	7.3	1.37	0.17	3.78	0.46
		S.D.	±0.63	±0.06	±10.9	±1.1	±0.13	±0.02	±0.31	±0.07
	2.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	4.12	0.68**	55.6	9.1	1.28	0.22*	3.65	0.61**
		S.D.	±0.40	±0.09	±8.8	±0.9	±0.26	±0.06	±0.73	±0.15
Female	Control	N	10	10	10	10	10	10	10	10
		Mean	2.29	0.55	76.3	18.4				
		S.D.	±0.43	±0.08	±16.8	±4.0				
	0.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	2.35	0.54	79.6	18.0				
		S.D.	±0.33	±0.06	±25.3	±4.7				
	2.5 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	2.39	0.52	81.2	17.6				
		S.D.	±0.29	±0.13	±32.9	±8.1				
	12.5 mg/kg	N	9	9	9	9	9	9	9	9
		Mean	2.63	0.63	73.9	17.7				
		S.D.	±0.26	±0.09	±10.2	±3.4				

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

Two males in the 0.1 mg/kg group and one female in the 12.5 mg/kg group died.

Table 14 - continued

Organ weights
Male, Female, 52w

Study No. P030097

Sex	Group and dose		Ovaries		Uterus		
			(mg)	(mg/100 gB.W.)	(g)	(g/100 gB.W.)	
Male	Control	N					
		Mean					
		S.D.					
	0.1 mg/kg	N					
		Mean					
		S.D.					
	0.5 mg/kg	N					
		Mean					
		S.D.					
	2.5 mg/kg	N					
		Mean					
		S.D.					
Female	Control	N	10	10	10	10	
		Mean	67.0	16.0	0.97	0.24	
		S.D.	±17.0	±3.3	±0.25	±0.08	
		0.5 mg/kg	N	10	10	10	10
			Mean	62.2	14.3	0.96	0.22
			S.D.	±17.5	±4.4	±0.24	±0.06
		2.5 mg/kg	N	10	10	10	10
			Mean	64.5	13.5	0.97	0.22
			S.D.	±32.6	±5.5	±0.26	±0.09
		12.5 mg/kg	N	8	8	9	9
			Mean	60.9	14.3	1.03	0.25
		S.D.	±18.2	±2.5	±0.22	±0.08	

Not significantly different from control.

One female in the 12.5 mg/kg group died.

The ovaries in one female in the 12.5 mg/kg group were not weighed due to the dilatation of paraovarian bursa, prevents obtaining the actual ovary weights.

Table 15 - continued

Histopathological findings
Male, Female, 13w

Study No. P030097

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
Hematopoietic system																				
Spleen																				
Bone marrow (sternum)																				
Bone marrow (femur)																				
Cardiovascular system																				
Heart																				
Cellular infiltration, mononuclear cell																				
Aorta																				
Urinary system																				
Kidney																				
Tubule, basophilic																				
Cast, proteinaceous																				
Cellular infiltration, pelvis, neutrophil																				
Mineralization, corticomedullary																				
Nephroblastoma																				
Urinary bladder																				
Genital system																				
Testis																				
Epididymis																				
Prostate																				
Cellular infiltration, mononuclear cell																				
Seminal vesicle																				
Ovary																				
Uterus																				
Vagina																				
Mammary gland																				
Endocrine system																				
Pituitary																				
Thyroid																				
Remnant, ultimobranchial body																				

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

Study No. P030097

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				10				10				9						
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++
Endocrine system																				
Parathyroid																				
Adrenal																				
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.

One male in the 2.5 mg/kg group died.

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
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	10	0	0	0	0
Degeneration, hepatocyte, fatty, periportal																				
	9	1	0	0	1						10	0	0	0	0	10	0	0	0	0
Necrosis, hepatocyte, focal																				
	10	0	0	0	0						9	1	0	0	1	10	0	0	0	0
Hypertrophy, hepatocyte ¹⁾ , centrilobular																				
	10	0	0	0	0						10	0	0	0	0	10	0	0	0	0
Cellular infiltration, mononuclear cell																				
	7	3	0	0	3						10	0	0	0	0	4	6	0	0	6**
Pancreas																				
Atrophy, acinus, focal																				
	9	1	0	0	1										8	2	0	0	2	9
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											10	0	0	0	0
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.

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Table 15 - continued

Histopathological findings
Male, Female, 13w

Study No. P030097

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																				
Bone marrow (sternum)																				
Bone marrow (femur)																				
Cardiovascular system																				
Heart																				
Cellular infiltration, mononuclear cell																				
Aorta																				
Urinary system																				
Kidney																				
Tubule, basophilic																				
Cast, proteinaceous																				
Cellular infiltration, pelvis, neutrophil																				
Mineralization, corticomedullary																				
Nephroblastoma																				
Urinary bladder																				
Genital system																				
Testis																				
Epididymis																				
Prostate																				
Cellular infiltration, mononuclear cell																				
Seminal vesicle																				
Ovary																				
Uterus																				
Vagina																				
Mammary gland																				
Endocrine system																				
Pituitary																				
Thyroid																				
Remnant, ultimobranchial body																				

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

Study No. P030097

Organs and findings	Sex Group and dose Number of animals	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																					
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

Study No. PG30097.

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
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.

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Table 16 - continued

Histopathological findings
Male, Female, 52w

Study No. P030097

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						
Digestive system																													
Pancreas																													
				(10)					(0)										(10)										
Atrophy, acinus, focal	10	0	0	0	0													9	1	0	0	1							
Hyperplasia, acinar cell, focal	8	2	0	0	2													7	3	0	0	3							
Cellular infiltration, lymphocyte	10	0	0	0	0													10	0	0	0	0							
Fibrosis, islet	9	1	0	0	1													10	0	0	0	0							
Respiratory system																													
Trachea																													
				(10)					(0)											(10)									
Cellular infiltration, lamina propria, neutrophil	10	0	0	0	0													10	0	0	0	0							
Lung																													
				(10)					(0)											(10)									
Accumulation, foam cell, alveolus	7	3	0	0	3													4	5	1	0	6							
Pneumonia, aspiration	10	0	0	0	0													9	1	0	0	1							
Mineralization, artery	6	4	0	0	4													5	5	0	0	5							
Hematopoietic system																													
Thymus																													
				(10)					(0)											(10)									
Atrophy	1	8	1	0	9													1	9	0	0	9							
Submaxillary lymph node				NR(10)					(0)											NR(10)									
Popliteal lymph node				(1)					(0)											(1)									
Proliferation, plasma cell	0	1	0	0	1													0	1	0	0	1							
Mesenteric lymph node				NR(10)					(0)											NR(10)									
Spleen																													
				(10)					(0)											(10)									
Thickening, capsule	9	1	0	0	1													10	0	0	0	0							
Hematopoiesis, extramedullary	10	0	0	0	0													10	0	0	0	0							
Deposit, pigment, red pulp, brown	10	0	0	0	0													10	0	0	0	0							
Bone marrow (sternum)				(10)					(0)											(10)									
Atrophy, focal	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

Study No. P030097

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
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.

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

Study No. P030097

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

Study No. P030097

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																			
		Cyst, anterior lobe	7	3	0	0	3														
		Thyroid	10	0	0	0	0														
		Hyperplasia, C cell				(10)															
		Deposit, material, interstitium, eosinophilic	10	0	0	0	0														
		Remnant, ultimobranchial body	10	0	0	0	0														
		Parathyroid	9	1	0	0	1														
		Adrenal				NR (10)															
		Hypertrophy, cortical cell, focal				(10)															
		Hyperplasia, cortical cell, focal	8	2	0	0	2														
		Angiectasis	9	1	0	0	1														
			10	0	0	0	0														
Nervous system																					
Cerebrum																					
						NR (10)															
Cerebellum																					
						NR (10)															
Medulla oblongata																					
						NR (10)															
Spinal cord																					
						NR (10)															
Optic nerve																					
						NR (10)															
Sciatic nerve																					
						NR (10)															
Special sense organs																					
Eye																					
		Harderian gland				NR (10)															
		Cellular infiltration, lymphocyte				(10)															
			10	0	0	0	0														
Musculoskeletal system																					
M. biceps femoris																					
						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

Study No. P030097

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
Musculoskeletal system																					
Sternum																					
Femur																					
Integumentary system																					
Integument																					
Others																					
Extremity																					
Ulcer, hindlimb																					

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

Study No. P030097

Organs and findings	Sex		Female																		
	Group and dose		Control				0.5 mg/kg				2.5 mg/kg				12.5 mg/kg						
	Number of animals		10				10				10				9						
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	
Digestive system																					
Tongue		NR (10)				(0)				(0)				NR (9)							
Esophagus		NR (10)				(0)				(0)				NR (9)							
Stomach		(10)				(0)				(0)				(9)							
Dilatation, glandular space, glandular stomach		10	0	0	0	0									9	0	0	0	0		
Cellular infiltration, mucosa, glandular stomach, neutrophil		10	0	0	0	0									8	1	0	0	0		
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		
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		
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	9	0	0	0	0	
Hematopoiesis, extramedullary		8	2	0	0	2					10	0	0	0	0	5	4	0	0	0	4*
Focus, altered cell, basophilic		6	4	0	0	4					8	2	0	0	2	7	2	0	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	0	
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	0	
Adenoma, hepatocellular		10	0	0	0	0					10	0	0	0	0	8	1	0	0	0	

*: 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		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	-	+	++	+++
Digestive system																					
Pancreas																					
		(10)				(0)				(0)				(9)							
Atrophy, acinus, focal		9	1	0	0	1									9	0	0	0	0		
Hyperplasia, acinar cell, focal		10	0	0	0	0									9	0	0	0	0		
Cellular infiltration, lymphocyte		10	0	0	0	0									8	1	0	0	1		
Fibrosis, islet		10	0	0	0	0									9	0	0	0	0		
Respiratory system																					
Trachea																					
		(10)				(0)				(0)				(9)							
Cellular infiltration, lamina propria, neutrophil		10	0	0	0	0									8	1	0	0	1		
Lung																					
		(10)				(0)				(0)				(9)							
Accumulation, foam cell, alveolus		6	4	0	0	4									5	4	0	0	4		
Pneumonia, aspiration		10	0	0	0	0									9	0	0	0	0		
Mineralization, artery		9	1	0	0	1									7	2	0	0	2		
Hematopoietic system																					
Thymus																					
		(10)				(0)				(0)				(9)							
Atrophy		1	8	1	0	9									0	7	2	0	9		
Submaxillary lymph node		NR (10)				(0)				(0)				NR (9)							
Popliteal lymph node		(0)				(0)				(0)				(0)							
Proliferation, plasma cell																					
Mesenteric lymph node		NR (10)				(0)				(0)				NR (9)							
Spleen																					
		(10)				(0)				(0)				(9)							
Thickening, capsule		10	0	0	0	0									9	0	0	0	0		
Hematopoiesis, extramedullary		8	2	0	0	2									8	1	0	0	1		
Deposit, pigment, red pulp, brown		9	1	0	0	1									7	2	0	0	2		
Bone marrow (sternum)																					
		(10)				(0)				(0)				(9)							
Atrophy, focal		10	0	0	0	0									8	1	0	0	1		

Not significantly different from control.

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

NR: no remarkable changes.

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

One female in the 12.5 mg/kg group died.

Table 16 - continued

Histopathological findings
Male, Female, 52w

Study No. P030097

Organs and findings	Sex Group and dose Number of animals	Female																						
		Control					0.5 mg/kg					2.5 mg/kg					12.5 mg/kg							
		10					10					10					9							
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total			
Hematopoietic system																								
Bone marrow (femur)																								
Atrophy, focal																								
Hematopoiesis, increased																								
				(10)					(0)					(0)					(9)					
	10	0	0	0	0															8	1	0	0	1
	9	1	0	0	1															9	0	0	0	0
Cardiovascular system																								
Heart																								
Cellular infiltration, mononuclear cell																								
Fibrosis, myocardium																								
Aorta																								
				(10)					(0)					(0)					(9)					
	9	1	0	0	1															7	2	0	0	2
	10	0	0	0	0															8	1	0	0	1
				NR(10)					(0)					(0)										
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																								
				(10)					(0)					(0)					(9)					
	10	0	0	0	0															8	1	0	0	1
	10	0	0	0	0															8	1	0	0	1
	10	0	0	0	0															7	2	0	0	2
	10	0	0	0	0															8	1	0	0	1
	10	0	0	0	0															8	1	0	0	1
	9	1	0	0	1															9	0	0	0	0
	10	0	0	0	0															9	0	0	0	0
	10	0	0	0	0															9	0	0	0	0
	10	0	0	0	0															8	1	0	0	1
	9	1	0	0	1															8	1	0	0	1
	9	1	0	0	1															8	1	0	0	1
	9	1	0	0	1															8	1	0	0	1
	7	3	0	0	3															8	1	0	0	1
	7	3	0	0	3															8	1	0	0	1
	7	3	0	0	3															8	1	0	0	1
	7	3	0	0	3															8	1	0	0	1
	10	0	0	0	0															9	0	0	0	0

Not significantly different from control.

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

NR: no remarkable changes.

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

One female in the 12.5 mg/kg group died.

Table 16 - continued

Histopathological findings
Male, Female, 52w

Study No. P030097

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

Not significantly different from control.

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

NR: no remarkable changes.

NA: not applicable.

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

One female in the 12.5 mg/kg group died.

Table 16 - continued

Histopathological findings
Male, Female, 52w

Study No. P030097

Organs and findings	Sex Group and dose Number of animals	Female																			
		Control					0.5 mg/kg					2.5 mg/kg					12.5 mg/kg				
		10					10					10					9				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Endocrine system																					
Pituitary																					
				(10)					(0)					(0)					(9)		
	7	3	0	0	3										6	3	0	0	3		
	10	0	0	0	0										9	0	0	0	0		
Thyroid																					
				(10)					(0)					(0)					(9)		
	10	0	0	0	0										8	1	0	0	1		
	10	0	0	0	0										9	0	0	0	0		
	8	2	0	0	2										9	0	0	0	0		
Parathyroid																					
				NR (10)					(0)					(0)					NR (9)		
Adrenal																					
				(10)					(0)					(0)					(9)		
	8	2	0	0	2										7	2	0	0	2		
	6	4	0	0	4										8	1	0	0	1		
	6	4	0	0	4										8	1	0	0	1		
Nervous system																					
				NR (10)					(0)					(0)					NR (9)		
				NR (10)					(0)					(0)					NR (9)		
				NR (10)					(0)					(0)					NR (9)		
				NR (10)					(0)					(0)					NR (9)		
				NR (10)					(0)					(0)					NR (9)		
				NR (10)					(0)					(0)					NR (9)		
Special sense organs																					
Eye																					
				NR (10)					(0)					(0)					NR (9)		
				(10)					(0)					(0)					(9)		
	10	0	0	0	0										8	1	0	0	1		
Musculoskeletal system																					
M. biceps femoris																					
				NR (10)					(0)					(0)					NR (9)		

Not significantly different from control.

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

NR: no remarkable changes.

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

One female in the 12.5 mg/kg group died.

Table 16 - continued

Histopathological findings
Male, Female, 52w

Study No. P030097

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