

Table 10 Necropsy findings
Male, Female, 13w

Organs and findings	Sex	Male				Female			
	Group and dose	Control	4 mg/kg	20 mg/kg	100 mg/kg	Control	4 mg/kg	20 mg/kg	100 mg/kg
	Number of animals	10	9	10	9	10	10	10	10
Genital system									
Testis						NA	NA	NA	NA
Enlargement		0	1	0	0	NA	NA	NA	NA
Epididymis									
Nodule, light yellow		0	0	1	0				
Endocrine system									
Pituitary									
Enlargement		0	0	0	0	0	0	0	1
Special sense organs									
Eye									
Dyscoria		1	0	0	0	0	0	0	0

Not significantly different from control.

NA: not applicable.

No appreciable changes in all other organs and tissues.

One male in the 4 mg/kg group was imminently sacrificed when moribund and one male in the 100 mg/kg group died.

Table 11 Necropsy findings
Male, Female, 52w

Organs and findings	Sex	Male				Female			
	Group and dose	Control	4 mg/kg	20 mg/kg	100 mg/kg	Control	4 mg/kg	20 mg/kg	100 mg/kg
	Number of animals	10	8	8	10	10	10	9	10
Digestive system									
Liver									
Macule, dark red		0	0	0	1	1	1	0	0
Enlargement		0	0	1	4	0	0	0	3
Mass, light gray		1	0	0	0	0	0	0	0
Pancreas									
Mass, light gray		0	1	0	0	0	0	0	0
Hematopoietic system									
Thymus									
Small		10	8	8	10	10	10	9	10
Spleen									
Enlargement		0	0	0	1	0	1	0	0
Cyst		0	0	0	0	1	0	0	0
Urinary system									
Kidney									
Rough, surface		0	1	0	0	0	0	0	0
Dilatation, pelvic cavity		0	1	0	0	1	0	0	0
Genital system									
Testis									
Softening		1	0	1	0	NA	NA	NA	NA
Small		0	0	1	0				
Uterus									
Enlargement		NA	NA	NA	NA				
Cyst, endometrium						0	1	0	0
Mammary gland									
Retention, milk		0	1	0	0	7	1*	3	3
Endocrine system									
Pituitary									
Spot, dark red		0	0	1	1	1	1	1	0
Mass, dark red		0	0	1	1	0	1	0	0
Thyroid									
Nodule, light gray		0	0	1	0	0	0	0	0

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

NA: not applicable.

No appreciable changes in all other organs and tissues.

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 and one female in the 20 mg/kg group died.

Table 11 - continued

Necropsy findings
Male, Female, 52w

Organs and findings	Sex	Male				Female			
	Group and dose	Control	4 mg/kg	20 mg/kg	100 mg/kg	Control	4 mg/kg	20 mg/kg	100 mg/kg
	Number of animals	10	8	8	10	10	10	9	10
Endocrine system									
Adrenal									
Spot, brown		0	0	0	0	4	1	2	1
Enlargement		0	0	0	0	0	1	0	0
Nodule, brown		0	0	0	0	2	0	0	0
Integumentary system									
Integument									
Mass, subcutis, light gray		1	0	0	0	2	2	2	3
Others									
Extremity									
Swelling, hindlimb		0	0	1	0	0	0	0	1
Corn, hindlimb		4	2	2	4	2	2	1	2

Not significantly different from control.

No appreciable changes in all other organs and tissues.

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 and one female in the 20 mg/kg group died.

Table 12 Absolute and relative organ weights
Male, Female, 13w

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	609.0	2.37	0.39	15.5	2.6	24.6	4.0	1.69	0.28
		S.D.	±49.7	±0.08	±0.03	±2.1	±0.3	±3.4	±0.6	±0.17	±0.02
	4 mg/kg	N	9	9	9	9	9	9	9	9	9
		Mean	582.8	2.36	0.41	14.8	2.6	20.9	3.6	1.66	0.29
		S.D.	±62.6	±0.07	±0.05	±1.8	±0.3	±5.1	±0.9	±0.17	±0.02
	20 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	593.6	2.29	0.39	14.9	2.5	26.3	4.4	1.61	0.27
		S.D.	±42.4	±0.12	±0.03	±2.7	±0.3	±4.3	±0.7	±0.15	±0.02
	100 mg/kg	N	9	9	9	9	9	9	9	9	9
		Mean	628.5	2.33	0.37	15.0	2.4	26.4	4.2	1.67	0.27
		S.D.	±37.9	±0.07	±0.02	±2.0	±0.3	±4.5	±0.8	±0.16	±0.02
Female	Control	N	10	10	10	10	10	10	10	10	10
		Mean	316.4	2.05	0.65	17.3	5.6	16.9	5.4	1.02	0.32
		S.D.	±25.1	±0.06	±0.05	±2.7	±1.2	±2.2	±0.8	±0.10	±0.03
	4 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	306.7	2.06	0.67	18.2	5.9	16.0	5.3	0.96	0.31
		S.D.	±17.6	±0.07	±0.03	±3.1	±0.9	±2.8	±1.0	±0.07	±0.02
	20 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	314.6	2.10	0.67	19.2	6.1	16.8	5.4	1.03	0.33
		S.D.	±34.6	±0.07	±0.06	±3.0	±0.8	±2.5	±0.6	±0.11	±0.02
	100 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	307.4	2.13	0.70	19.3	6.3	19.7	6.4*	0.99	0.33
		S.D.	±29.4	±0.06	±0.07	±4.0	±1.0	±3.9	±1.1	±0.09	±0.03

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

One male in the 4 mg/kg group was imminently sacrificed when moribund and one male in the 100 mg/kg group died.

Table 12 - continued Absolute and relative organ weights
Male, Female, 13w

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	1.71	0.28	0.31	0.05	16.72	2.75	0.91	0.15
		S.D.	±0.10	±0.02	±0.10	±0.02	±1.53	±0.13	±0.13	±0.01
	4 mg/kg	N	9	9	9	9	9	9	9	9
		Mean	1.64	0.28	0.33	0.06	16.25	2.79	0.87	0.15
		S.D.	±0.15	±0.02	±0.09	±0.02	±2.42	±0.23	±0.10	±0.02
	20 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.63	0.28	0.30	0.05	16.94	2.85	0.81	0.14
		S.D.	±0.14	±0.03	±0.10	±0.02	±1.83	±0.21	±0.12	±0.01
	100 mg/kg	N	9	9	9	9	9	9	9	9
		Mean	1.72	0.28	0.28	0.05	20.20**	3.21**	0.88	0.14
		S.D.	±0.10	±0.02	±0.07	±0.01	±1.76	±0.20	±0.14	±0.02
Female	Control	N	10	10	10	10	10	10	10	10
		Mean	1.14	0.36	0.27	0.09	8.24	2.61	0.51	0.16
		S.D.	±0.07	±0.02	±0.06	±0.02	±0.81	±0.20	±0.05	±0.02
	4 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.19	0.39	0.27	0.09	8.42	2.75	0.50	0.16
		S.D.	±0.07	±0.03	±0.06	±0.02	±0.65	±0.19	±0.07	±0.02
	20 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.22	0.39	0.27	0.08	9.24	2.93**	0.55	0.18
		S.D.	±0.10	±0.04	±0.06	±0.02	±1.40	±0.21	±0.07	±0.02
	100 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.22	0.40*	0.28	0.09	10.51**	3.42**	0.51	0.17
		S.D.	±0.09	±0.03	±0.08	±0.03	±1.18	±0.23	±0.06	±0.02

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

One male in the 4 mg/kg group was imminently sacrificed when moribund and one male in the 100 mg/kg group died.

Table 12 - continued Absolute and relative organ weights
Male, Female, 13w

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	3.63	0.60	61.5	10.1	1.36	0.23	3.59	0.59
		S.D.	±0.19	±0.05	±5.9	±1.1	±0.06	±0.03	±0.32	±0.06
	4 mg/kg	N	9	9	9	9	9	9	9	9
		Mean	3.70	0.64	60.4	10.4	1.40	0.24	3.78	0.66
		S.D.	±0.45	±0.05	±10.8	±1.7	±0.09	±0.03	±0.62	±0.13
	20 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	3.69	0.62	58.3	9.8	1.35	0.23	3.45	0.58
		S.D.	±0.52	±0.07	±8.6	±1.2	±0.18	±0.02	±0.31	±0.05
	100 mg/kg	N	9	9	9	9	9	9	9	9
		Mean	4.01	0.64	59.6	9.5	1.34	0.21	3.59	0.57
		S.D.	±0.55	±0.06	±4.9	±0.8	±0.13	±0.03	±0.34	±0.05
Female	Control	N	10	10	10	10				
		Mean	1.88	0.60	67.0	21.3				
		S.D.	±0.15	±0.05	±7.5	±2.6				
	4 mg/kg	N	10	10	10	10				
		Mean	1.87	0.61	64.9	21.1				
		S.D.	±0.14	±0.04	±9.4	±2.6				
	20 mg/kg	N	10	10	10	10				
		Mean	2.01	0.64	66.4	21.1				
		S.D.	±0.21	±0.04	±11.2	±2.0				
	100 mg/kg	N	10	10	10	10				
		Mean	2.01	0.65*	68.7	22.4				
		S.D.	±0.19	±0.05	±9.5	±2.5				

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

One male in the 4 mg/kg group was imminently sacrificed when moribund and one male in the 100 mg/kg group died.

Table 12 - continued
Absolute and relative organ weights
Male, Female, 13w

Sex	Group and dose		Ovaries		Uterus	
			(mg)	(mg/100 gB.W.)	(g)	(g/100 gB.W.)
Male	Control	N				
		Mean				
		S. D.				
	4 mg/kg	N				
		Mean				
		S. D.				
	20 mg/kg	N				
		Mean				
		S. D.				
	100 mg/kg	N				
		Mean				
		S. D.				
Female	Control	N	10	10	10	10
		Mean	77.7	24.6	0.65	0.21
		S. D.	±10.4	±3.4	±0.15	±0.06
	4 mg/kg	N	10	10	10	10
		Mean	77.7	25.4	0.72	0.24
		S. D.	±9.1	±3.0	±0.17	±0.06
	20 mg/kg	N	10	10	10	10
		Mean	82.4	26.4	0.64	0.21
		S. D.	±10.2	±4.1	±0.11	±0.03
	100 mg/kg	N	10	10	10	10
		Mean	81.3	26.5	0.61	0.20
		S. D.	±8.8	±2.5	±0.13	±0.06

Not significantly different from control.

Table 13 Absolute and relative organ weights
Male, Female, 52w

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	853.9	2.52	0.30	17.3	2.0	33.1	3.9	2.05	0.24
		S.D.	±106.6	±0.13	±0.04	±3.8	±0.4	±5.2	±0.7	±0.23	±0.02
	4 mg/kg	N	8	8	8	8	8	8	8	8	8
		Mean	801.5	2.44	0.31	16.0	2.0	37.3	4.7	1.89	0.24
		S.D.	±79.6	±0.08	±0.03	±1.9	±0.2	±7.2	±1.0	±0.15	±0.01
	20 mg/kg	N	8	8	8	8	8	8	8	8	8
		Mean	846.9	2.42	0.29	25.9	3.2	34.1	4.0	1.93	0.23
		S.D.	±138.4	±0.08	±0.04	±18.1	±2.8	±10.1	±0.7	±0.24	±0.01
	100 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	884.2	2.48	0.29	32.6	3.6	42.1*	4.8*	1.99	0.23
		S.D.	±135.7	±0.08	±0.04	±48.0	±4.9	±7.5	±0.5	±0.28	±0.02
Female	Control	N	10	10	10	10	10	10	10	10	10
		Mean	432.9	2.11	0.50	27.3	6.4	23.8	5.6	1.21	0.28
		S.D.	±77.3	±0.11	±0.08	±6.1	±1.6	±5.2	±1.2	±0.10	±0.03
	4 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	408.3	2.10	0.52	46.8	12.2	22.2	5.4	1.18	0.29
		S.D.	±53.6	±0.10	±0.07	±47.8	±14.4	±6.2	±1.3	±0.12	±0.04
	20 mg/kg	N	9	9	9	9	9	9	9	9	9
		Mean	435.3	2.12	0.49	36.3	8.3	23.8	5.5	1.22	0.28
		S.D.	±38.5	±0.06	±0.05	±15.3	±3.4	±1.6	±0.5	±0.11	±0.02
	100 mg/kg	N	10	10	10	10	10	10	10	10	10
		Mean	452.8	2.18	0.50	32.4	7.4	26.9	6.1	1.29	0.29
		S.D.	±93.4	±0.08	±0.11	±7.8	±2.4	±3.7	±0.9	±0.18	±0.03

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

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 and one female in the 20 mg/kg group died.

Table 13 - continued Absolute and relative organ weights
Male, Female, 52w

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	1.93	0.23	0.11	0.01	20.37	2.40	1.01	0.12
		S.D.	±0.19	±0.03	±0.03	±0.00	±1.92	±0.15	±0.16	±0.02
	4 mg/kg	N	8	8	8	8	8	8	8	8
		Mean	1.88	0.24	0.09	0.01	19.58	2.42	1.05	0.13
		S.D.	±0.13	±0.02	±0.03	±0.00	±4.28	±0.33	±0.35	±0.03
	20 mg/kg	N	8	8	8	8	8	8	8	8
		Mean	1.94	0.23	0.09	0.01	20.56	2.42	0.97	0.11
		S.D.	±0.20	±0.02	±0.02	±0.00	±5.01	±0.34	±0.19	±0.02
	100 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.97	0.23	0.10	0.01	25.21*	2.86**	1.32	0.15
		S.D.	±0.18	±0.02	±0.03	±0.00	±4.20	±0.27	±0.42	±0.06
Female	Control	N	10	10	10	10	10	10	10	10
		Mean	1.30	0.31	0.10	0.02	10.00	2.34	0.60	0.14
		S.D.	±0.08	±0.04	±0.03	±0.01	±1.17	±0.27	±0.09	±0.02
	4 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.32	0.33	0.08	0.02	11.09	2.73*	0.72	0.18
		S.D.	±0.09	±0.03	±0.02	±0.01	±1.61	±0.36	±0.30	±0.10
	20 mg/kg	N	9	9	9	9	9	9	9	9
		Mean	1.36	0.31	0.10	0.02	11.77*	2.71*	0.64	0.15
		S.D.	±0.08	±0.03	±0.03	±0.00	±1.20	±0.19	±0.15	±0.03
	100 mg/kg	N	10	10	10	10	10	10	10	10
		Mean	1.37	0.32	0.08	0.02	15.66**	3.48**	0.74	0.17
		S.D.	±0.08	±0.07	±0.02	±0.01	±3.19	±0.41	±0.21	±0.05

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

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 and one female in the 20 mg/kg group died.

Table 13 - continued Absolute and relative organ weights
Male, Female, 52w

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	4.20	0.50	63.4	7.5	1.43	0.17	3.87	0.46	
		S.D.	±0.38	±0.05	±7.3	±0.7	±0.18	±0.03	±0.39	±0.06	
	4 mg/kg	N	8	8	8	8	8	8	8	8	
		Mean	4.10	0.51	65.7	8.2	1.43	0.18	3.87	0.49	
		S.D.	±0.46	±0.03	±12.1	±0.8	±0.15	±0.02	±0.33	±0.06	
	20 mg/kg	N	8	8	8	8	8	8	8	8	
		Mean	4.23	0.50	64.1	7.7	1.27	0.15	3.56	0.42	
		S.D.	±0.73	±0.05	±6.1	±1.5	±0.25	±0.03	±0.77	±0.08	
	100 mg/kg	N	10	10	10	10	10	10	10	10	
		Mean	4.61	0.53	68.0	7.8	1.31	0.15	3.83	0.44	
		S.D.	±0.68	±0.08	±13.5	±1.4	±0.15	±0.03	±0.54	±0.05	
	Female	Control	N	10	10	10	10				
			Mean	2.29	0.54	83.8	19.7				
			S.D.	±0.26	±0.10	±18.3	±4.5				
		4 mg/kg	N	10	10	10	10				
Mean			2.31	0.57	80.4	19.9					
S.D.			±0.30	±0.07	±12.6	±3.3					
20 mg/kg		N	9	9	9	9					
		Mean	2.45	0.56	77.1	17.9					
		S.D.	±0.30	±0.06	±13.3	±3.8					
100 mg/kg		N	10	10	10	10					
		Mean	2.75**	0.63	81.3	18.6					
		S.D.	±0.33	±0.12	±17.3	±5.5					

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

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 and one female in the 20 mg/kg group died.

Table 13 - continued
Absolute and relative organ weights
Male, Female, 52w

Sex	Group and dose		Ovaries		Uterus	
			(mg)	(mg/100 gB. W.)	(g)	(g/100 gB. W.)
Male	Control	N				
		Mean				
		S.D.				
	4 mg/kg	N				
Mean						
S.D.						
20 mg/kg	N					
	Mean					
	S.D.					
100 mg/kg	N					
	Mean					
	S.D.					
Female	Control	N	10	10	10	10
		Mean	51.4	12.2	0.95	0.23
		S.D.	±10.3	±3.1	±0.19	±0.07
	4 mg/kg	N	10	10	10	10
		Mean	48.7	11.9	1.22	0.30
		S.D.	±12.1	±2.3	±0.43	±0.11
	20 mg/kg	N	9	9	9	9
		Mean	52.1	12.0	1.03	0.24
		S.D.	±15.8	±4.0	±0.25	±0.06
	100 mg/kg	N	10	10	10	10
		Mean	56.8	13.1	1.03	0.24
		S.D.	±19.5	±5.2	±0.18	±0.06

Not significantly different from control.
One female in the 20 mg/kg group died.

Table 14 Histopathological findings
Male, Female, 13w

Organs and findings	Sex		Male														
	Group and dose		Control					4 mg/kg					20 mg/kg				
	Number of animals		10					9					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	10	0	0	0	0	9	0	0	0	0	8	2	0	0	2		
Degeneration, hepatocyte, fatty, periportal	7	3	0	0	3	6	3	0	0	3	5	5	0	0	5		
Necrosis, hepatocyte, focal	10	0	0	0	0	9	0	0	0	0	10	0	0	0	0		
Hypertrophy, hepatocyte, centrilobular	10	0	0	0	0	9	0	0	0	0	10	0	0	0	0		
Cellular infiltration, mononuclear cell	10	0	0	0	0	9	0	0	0	0	10	0	0	0	0		
Fibrosis	9	1	0	0	1	9	0	0	0	0	10	0	0	0	0		
Pancreas																	
Atrophy, acinus, focal	8	2	0	0	2												
Cellular infiltration, mixed	9	1	0	0	1												
Respiratory system																	
Trachea																	
Lung																	
Metaplasia, osseous	7	3	0	0	3												
Accumulation, foam cell, alveolus	9	1	0	0	1												
Mineralization, artery	9	1	0	0	1												
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 4 mg/kg group was imminently sacrificed when moribund.

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

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																		
Accumulation, foam cell			(10)					(0)					(10)					
Spleen			NR(10)					(0)					(0)					
Bone marrow (sternum)			NR(10)					(0)					(0)					
Bone marrow (femur)			NR(10)					(0)					(0)					
Cardiovascular system																		
Heart			(10)					(0)					(0)					
Cellular infiltration, mononuclear cell			8	2	0	0	2											
Fibrosis, myocardium			9	1	0	0	1											
Aorta			NR(10)					(0)					(0)					
Urinary system																		
Kidney			(10)					(9)					(10)					
Tubule, basophilic			6	4	0	0	4	6	3	0	0	3	8	2	0	0	2	
Droplet, epithelial cell, proximal tubule, hyaline			10	0	0	0	0	9	0	0	0	0	7	3	0	0	3	
Cast, proteinaceous			10	0	0	0	0	9	0	0	0	0	10	0	0	0	0	
Cyst, medulla			10	0	0	0	0	8	1	0	0	1	10	0	0	0	0	
Cellular infiltration, mononuclear cell, pelvis			10	0	0	0	0	9	0	0	0	0	10	0	0	0	0	
Fibrosis, medulla			10	0	0	0	0	9	0	0	0	0	9	1	0	0	1	
Mineralization, cortex			9	1	0	0	1	9	0	0	0	0	10	0	0	0	0	
Mineralization, medulla			9	1	0	0	1	8	1	0	0	1	9	1	0	0	1	
Urinary bladder			(10)					(0)					(0)					
Granuloma, adventitia			10	0	0	0	0											
Genital system																		
Testis			NR(10)					(0)					(0)					
Epididymis			NR(10)					(0)					(0)					
Prostate			(10)					(0)					(0)					
Cellular infiltration, mononuclear cell			7	3	0	0	3											
Seminal vesicle			NR(10)					(0)					(0)					
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

Organs and findings	Sex Group and dose Number of animals	Male														
		Control					4 mg/kg					20 mg/kg				
		10					9					10				
		-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Genital system																
Vagina																
Degeneration, epithelium, mucous																
Mammary gland																
Endocrine system																
Pituitary																
Cyst, anterior lobe		10	0	0	0	0										
Thyroid																
Remnant, ultimobranchial body		9	1	0	0	1										
Parathyroid																
Adrenal																
Hypertrophy, cortical cell, focal		9	1	0	0	1										
Nervous system																
Cerebrum																
Cerebellum																
Medulla oblongata																
Spinal cord																
Optic nerve																
Sciatic nerve																
Special sense organs																
Eye																
Dysplasia, retina		9	1	0	0	1										
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.

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

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		NR (9)					NR (10)					(0)				
Esophagus		NR (9)					NR (10)					(0)				
Stomach		NR (9)					NR (10)					(0)				
Duodenum		NR (9)					NR (10)					(0)				
Jejunum		NR (9)					NR (10)					(0)				
Ileum		NR (9)					NR (10)					(0)				
Cecum		NR (9)					NR (10)					(0)				
Colon		NR (9)					NR (10)					(0)				
Rectum		NR (9)					NR (10)					(0)				
Submaxillary gland		NR (9)					NR (10)					(0)				
Sublingual gland		NR (9)					NR (10)					(0)				
Parotid gland		NR (9)					NR (10)					(0)				
Liver		(9)					(10)					(10)				
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
Hyper trophy, 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		(9)					(10)					(0)				
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		NR (9)					NR (10)					(0)				
Lung		(9)					(10)					(0)				
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		NR (9)					NR (10)					(0)				
Submaxillary lymph node		NR (9)					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 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		
Hematopoietic system																	
Mesenteric lymph node			(9)					(10)						(0)			
Accumulation, foam cell	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																	
Cellular infiltration, mononuclear cell	5	4	0	0	4	10	0	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																	
Tubule, basophilic	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	9	1	0	0	1		
Urinary bladder			(9)					(10)						(0)			
Granuloma, adventitia	9	0	0	0	0	9	1	0	0	1							
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

Organs and findings	Sex		Female							
	Group and dose		20 mg/kg		100 mg/kg					
	Number of animals		10		10					
	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system										
Tongue			(0)							NR (10)
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			(10)							(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

Organs and findings	Sex		Female							
	Group and dose		20 mg/kg			100 mg/kg				
	Number of animals		10			10				
	-	+	++	+++	Total	-	+	++	+++	Total
Hematopoietic system										
Mesenteric lymph node			(10)					(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	0	0	0	0	8	2	0	0	2
Droplet, epithelial cell, proximal tubule, hyaline	10	0	0	0	0	10	0	0	0	0
Cast, proteinaceous	10	0	0	0	0	9	1	0	0	1
Cyst, medulla	10	0	0	0	0	10	0	0	0	0
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	8	2	0	0	2	10	0	0	0	0
Urinary bladder			(0)					(10)		
Granuloma, adventitia						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

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

Organs and findings	Sex		Male												
	Group and dose		Control				4 mg/kg				20 mg/kg				
	Number of animals		10				8				8				
	-	+	++	+++	Total	-	+	++	+++	Total	-	+	++	+++	Total
Digestive system															
Tongue					NR (10)					(0)					(0)
Esophagus					NR (10)					(0)					(0)
Stomach					(10)					(0)					(0)
Dilatation, glandular space, glandular stomach	5	5	0	0	5										
Duodenum					(10)					(0)					(8)
Accumulation, foam cell, lamina propria	10	0	0	0	0						8	0	0	0	0
Jejunum					(10)					(0)					(8)
Accumulation, foam cell, lamina propria	10	0	0	0	0						8	0	0	0	0
Ileum					(10)					(0)					(8)
Accumulation, foam cell, lamina propria	10	0	0	0	0						8	0	0	0	0
Accumulation, foam cell, peyer's patch	10	0	0	0	0						8	0	0	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					(10)					(8)					(8)
Degeneration, hepatocyte, fatty, centrilobular	9	1	0	0	1	7	1	0	0	1	8	0	0	0	0
Degeneration, hepatocyte, fatty, periportal	4	5	1	0	6	7	1	0	0	1*	4	3	1	0	4
Necrosis, hepatocyte, focal	10	0	0	0	0	5	2	1	0	3*	8	0	0	0	0
Hypertrophy, hepatocyte, centrilobular	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Hyperplasia, bile duct	9	1	0	0	1	8	0	0	0	0	6	2	0	0	2
Hematopoiesis, extramedullary	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Focus, altered cell, basophilic	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Focus, altered cell, clear	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Angiectasis	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Hemorrhage	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Cellular infiltration, mononuclear cell	8	2	0	0	2	8	0	0	0	0	5	3	0	0	3
Accumulation, foam cell, sinusoid ⁶⁰	10	0	0	0	0	8	0	0	0	0	6	2	0	0	2
Cholangioma	9	1	0	0	1	8	0	0	0	0	8	0	0	0	0

*: 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

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)				
Atrophy, acinus, focal			10	0	0	0	0										
Hyperplasia, acinar cell, focal			8	2	0	0	2										
Focus, acinar cell, basophilic			8	2	0	0	2										
Metaplasia, hepatocyte			10	0	0	0	0										
Hemorrhage			9	1	0	0	1										
Polyarteritis			10	0	0	0	0										
Respiratory system																	
Trachea																	
			NR(10)					(0)					(0)				
Lung																	
			(10)					(0)					(0)				
Metaplasia, osseous			8	2	0	0	2										
Accumulation, foam cell, alveolus			9	1	0	0	1										
Mineralization, artery			6	4	0	0	4										
Hematopoietic system																	
Thymus																	
			(10)					(0)					(0)				
Atrophy			0	7	3	0	10										
Submaxillary lymph node																	
			NR(10)					(0)					(0)				
Mesenteric lymph node																	
			(10)					(8)					(8)				
Accumulation, foam cell			10	0	0	0	0	8	0	0	0	0	3	5	0	0	5**
Spleen																	
			(10)					(8)					(8)				
Hematopoiesis, extramedullary			10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Cyst, capsule			10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Accumulation, foam cell, white pulp			10	0	0	0	0	8	0	0	0	0	7	1	0	0	1
Accumulation, foam cell, red pulp			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)				
Cellular infiltration, mononuclear cell			4	6	0	0	6										
Fibrosis, myocardium			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

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
Tubule, basophilic	5	4	1	0	5	3	4	1	0	5	3	5	0	0	5
Karyomegaly, epithelial cell, proximal tubule	10	0	0	0	0	8	0	0	0	0	8	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
Cast, proteinaceous	8	2	0	0	2	6	2	0	0	2	4	4	0	0	4
Dilatation, distal tubule	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Dilatation, pelvic cavity	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Cyst, medulla	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Hemorrhage, pelvis	10	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Cellular infiltration, mononuclear cell, pelvis	9	1	0	0	1	5	3	0	0	3	5	3	0	0	3
Cellular infiltration, mononuclear cell, cortex	9	1	0	0	1	6	2	0	0	2	7	1	0	0	1
Cellular exudation, pelvic cavity, neutrophil	9	1	0	0	1	6	2	0	0	2	5	3	0	0	3
Mineralization, pelvis	9	1	0	0	1	8	0	0	0	0	8	0	0	0	0
Mineralization, cortex	10	0	0	0	0	7	1	0	0	1	4	4	0	0	4*
Mineralization, medulla	10	0	0	0	0	8	0	0	0	0	7	1	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

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		NA					NA					NA				
Metaplasia, epithelial cell, gland, squamous																
Cyst, endometrium																
Vagina		NA					NA					NA				
Degeneration, epithelium, mucous																
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

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

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

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																	
Esophagus																	
Stomach																	
Dilatation, glandular space, glandular stomach	7	3	0	0	3	8	2	0	0	2							
Duodenum																	
Accumulation, foam cell, lamina propria	9	1	0	0	1	10	0	0	0	0							
Jejunum																	
Accumulation, foam cell, lamina propria	2	8	0	0	8**	10	0	0	0	0							
Ileum																	
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																	
Colon																	
Rectum																	
Submaxillary gland																	
Sublingual gland																	
Parotid gland																	
Liver																	
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

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																	
Pancreas			(10)					(10)					(0)				
Atrophy, acinus, focal	9	1	0	0	1	7	3	0	0	3							
Hyperplasia, acinar cell, focal	9	1	0	0	1	10	0	0	0	0							
Focus, acinar cell, basophilic	10	0	0	0	0	10	0	0	0	0							
Metaplasia, hepatocyte	9	1	0	0	1	10	0	0	0	0							
Hemorrhage	10	0	0	0	0	10	0	0	0	0							
Polyarteritis	10	0	0	0	0	9	1	0	0	1							
Respiratory system																	
Trachea			NR (10)					NR (10)					(0)				
Lung			(10)					(10)					(0)				
Metaplasia, osseous	10	0	0	0	0	10	0	0	0	0							
Accumulation, foam cell, alveolus	8	2	0	0	2	9	1	0	0	1							
Mineralization, artery	8	2	0	0	2	10	0	0	0	0							
Hematopoietic system																	
Thymus			(10)					(10)					(0)				
Atrophy	0	6	4	0	10	1	8	1	0	9							
Submaxillary lymph node			NR (10)					NR (10)					(0)				
Mesenteric lymph node			(10)					(10)					(10)				
Accumulation, foam cell	0	3	6	1	10**	10	0	0	0	0	10	0	0	0	0		
Spleen			(10)					(10)					(10)				
Hematopoiesis, extramedullary	10	0	0	0	0	10	0	0	0	0	8	1	1	0	2		
Cyst, capsule	10	0	0	0	0	9	1	0	0	1	10	0	0	0	0		
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			(10)					(10)					(0)				
Cellular infiltration, mononuclear cell	5	5	0	0	5	9	1	0	0	1							
Fibrosis, myocardium	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

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

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		
Genital system																	
Uterus			NA					(10)					(0)				
Metaplasia, epithelial cell, gland, squamous						7	3	0	0	3							
Cyst, endometrium						10	0	0	0	0							
Vagina			NA					(10)					(0)				
Degeneration, epithelium, mucous						6	4	0	0	4							
Mammary gland			(10)					(10)					(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			(10)					(10)					(0)				
Hyperplasia, anterior lobe, focal	9	1	0	0	1	8	2	0	0	2							
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			(10)					(10)					(0)				
Hyperplasia, C cell, focal	10	0	0	0	0	10	0	0	0	0							
Remnant, ultimobranchial body	10	0	0	0	0	8	2	0	0	2							
Parathyroid			NR (10)					NR (9)					(0)				
Adrenal			(10)					(10)					(0)				
Hypertrophy, cortical cell, focal	10	0	0	0	0	10	0	0	0	0							
Hyperplasia, cortical cell, focal	9	1	0	0	1	4	6	0	0	6							
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

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	
Special sense organs																	
Eye																	
Atrophy, retina, focal	10	0	0	0	0	10	0	0	0	0	0	0	0	0	0	0	(0)
Dysplasia, retina	10	0	0	0	0	10	0	0	0	0	0	0	0	0	0	0	(0)
Mineralization, cornea	9	1	0	0	1	10	0	0	0	0	0	0	0	0	0	0	(0)
Harderian gland					NR(10)					NR(10)							(0)
Musculoskeletal system																	
M. biceps femoris																	
					NR(10)					NR(10)							(0)
Sternum																	
					NR(10)					NR(10)							(0)
Femur																	
					NR(10)					NR(10)							(0)
Integumentary system																	
Integument																	
Cellular infiltration, mononuclear cell, subcutis	9	1	0	0	1	10	0	0	0	0	0	0	0	0	0	0	(0)
Keratoacanthoma	10	0	0	0	0	10	0	0	0	0	0	0	0	0	0	0	(0)
Others																	
Extremity																	
Formation, callus, hindlimb	4	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	(0)
Ulcer, hindlimb	0	4	0	0	4	0	2	0	0	0	0	0	0	0	2	0	(0)

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.

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										
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)					NR (10)		
Lung			(0)					(10)		
Metaplasia, osseous						10	0	0	0	0
Accumulation, foam cell, alveolus						10	0	0	0	0
Mineralization, artery						9	1	0	0	1
Hematopoietic system										
Thymus			(0)					(10)		
Atrophy						0	8	2	0	10
Submaxillary lymph node			(0)					NR (10)		
Mesenteric lymph node			(9)					(10)		
Accumulation, foam cell	6	3	0	0	3	0	4	6	0	10**
Spleen			(9)					(10)		
Hematopoiesis, extramedullary	8	1	0	0	1	10	0	0	0	0
Cyst, capsule	9	0	0	0	0	10	0	0	0	0
Accumulation, foam cell, white pulp	9	0	0	0	0	6	4	0	0	4*
Accumulation, foam cell, red pulp	9	0	0	0	0	6	4	0	0	4*
Bone marrow (sternum)			(0)					NR (10)		
Bone marrow (femur)			(0)					NR (10)		
Cardiovascular system										
Heart			(0)					(10)		
Cellular infiltration, mononuclear cell						9	1	0	0	1
Fibrosis, myocardium						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

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			NA						NA	
Atrophy, seminiferous tubule										
Edema, interstitium										
Epididymis			NA						NA	
Decrease, sperm, lumen										
Prostate			NA						NA	
Cellular infiltration, mononuclear cell										
Fibrosis, interstitium										
Seminal vesicle			NA						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

Organs and findings	Sex	Female									
	Group and dose	20 mg/kg					100 mg/kg				
	Number of animals	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

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.