Table 84

Two generation reproductive toxicity study of NP by oral administration in rats

Macroscopic findings of F1 males

Group	0 mg/kg		2 mg/kg		10 mg/kg		50 mg/kg	
Grade	-	+	-	+	-	+	-	+
(Seminal vessicle)	[30]		[21]		[25]		[23]	
Small, left side	30	0	20	1	25	0	23	0
(Brain)	[30]		[21]		[25]		[23]	
Recessed area	30	0	21	0	24	1	23	0
(Kidney)	[30]		[21]		[25]		[23]	
Dilatation, renal pelvis, bilateral	29	1	21	0	25	0	23	0
Dilatation, renal pelvis, right side	28	2	21	0	22	3	21	2
Cyst, left side	29	1	21	0	25	0	23	0
(Liver)	[30]		[21]		[25]		[23]	
Yellowish/pale	30	0	19	2	25	0	23	0
Pale, cauda lobe	30	0	21	0	25	0	22	1
Small, cauda lobe	29	1	21	0	25	0	22	1
(Lung)	[30]		[21]		[25]		[23]	
Yellowish	30	0	21	0	24	1	23	0
Insufficiency, retraction	30	0	21	0	24	1	23	0
(Spleen)	[30]		[21]		[25]		[23]	
Spot, white, multiple	30	0	21	0	25	0	22	1
(Thymus)	[30]		[21]		[25]		[23]	
Small	30	0	20	1	25	0	23	0

-, Negative; +, Positive

[ ], Number of animals examined

Table 85

Two generation reproductive toxicity study of NP by oral administration in rats

Summary of histopathological findings in F1 males

Group	0 mg/kg						2 mg/kg						10 mg/kg						50 mg/kg					
Grade	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.
(Testis)	[10]						[0]						[0]						[10]					
Multinucleated giant cell, seminiferous tubule	9	1	0	0	0	1													10	0	0	0	0	0
(Epididymis)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Prostate: ventral lobe)	[10]						[0]						[0]						[10]					
Cellular infiltration, lymphocyte, interstitium	3	5	1	1	0	7													4	3	1	2	0	6
Cellular infiltration, lymphocyte /neutrophil, epithelium	8	2	0	0	0	2													8	2	0	0	0	2
(Seminal vesicle & coagulating gland)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Liver)	[10]						[10]						[10]						[10]					
Hypertrophy, hepatocyte, centrilobular	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	5	5	0	0	0	5 #
Fatty change, periportal	10	0	0	0	0	0	9	0	1	0	0	1	6	0	1	3	0	4 #	10	0	0	0	0	0
Necrosis, with hemorrhage & fibrosis, caudate lobe	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	9	0	0	0	1	1
(Spleen)	[10]						[0]						[0]						[10]					
Hematopoiesis, extramedullary	0	2	8	0	0	10													0	1	8	1	0	10
Deposit, pigment, brown	0	4	6	0	0	10													0	4	6	0	0	10
Necrosis, focal	10	0	0	0	0	0													9	0	1	0	0	1
(Thymus)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Kidney)	[10]						[0]						[0]						[10]					
Basophilic tubule, cortex	6	3	1	0	0	4													3	7	0	0	0	7
Eosinophilic body	4	2	2	2	0	6													5	1	2	2	0	5
Cast, cortex	9	1	0	0	0	1													9	1	0	0	0	1
Cyst, subcapsule	9	0	1	0	0	1													10	0	0	0	0	0
Fibrosis, subcapsule, focal	10	0	0	0	0	0													9	1	0	0	0	1
Hyperplasia, transitional epithelium, focal, renal pelvis	10	0	0	0	0	0													7	3	0	0	0	3
Dilatation, renal pelvis, unilateral	10	0	0	0	0	0													7	1	2	0	0	3
Mineralization	8	2	0	0	0	2													8	2	0	0	0	2
(Mammary gland)	[10]						[0]						[0]						[10]					
Atrophy	9	0	0	1	0	1													9	0	1	0	0	1
(Thyroid gland)	[10]						[0]						[0]						[10]					
Ectopic thymus	9	0	1	0	0	1													10	0	0	0	0	0
(Parathyroid gland)	[8]						[0]						[0]						[8]					
No remarkable change																								
(Pituitary gland)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Adrenal gland)	[10]						[0]						[0]						[10]					
Hemorrhage, focal, fascicular zone	9	0	0	1	0	1													10	0	0	0	0	0

-, Negative; +/-, Very slight; +, Slight; ++, Moderate; +++, Severe; Pos., Total of positive grade

[ ], Number of animals examined

#, Significantly different from control $p<0.05$ (One-tailed Fisher exact test)

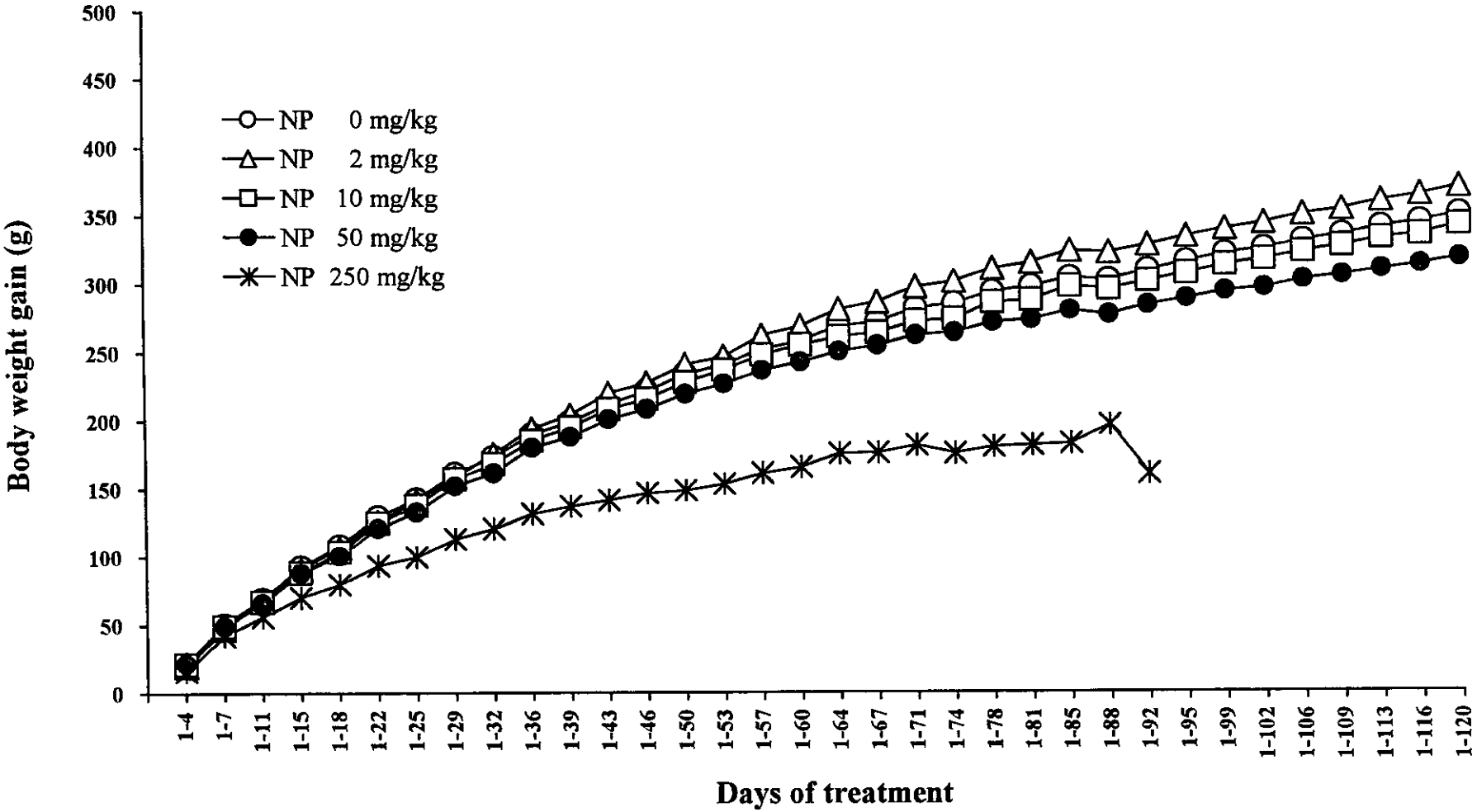


Fig. 1 Body weight gain of F_0 males during treatment period

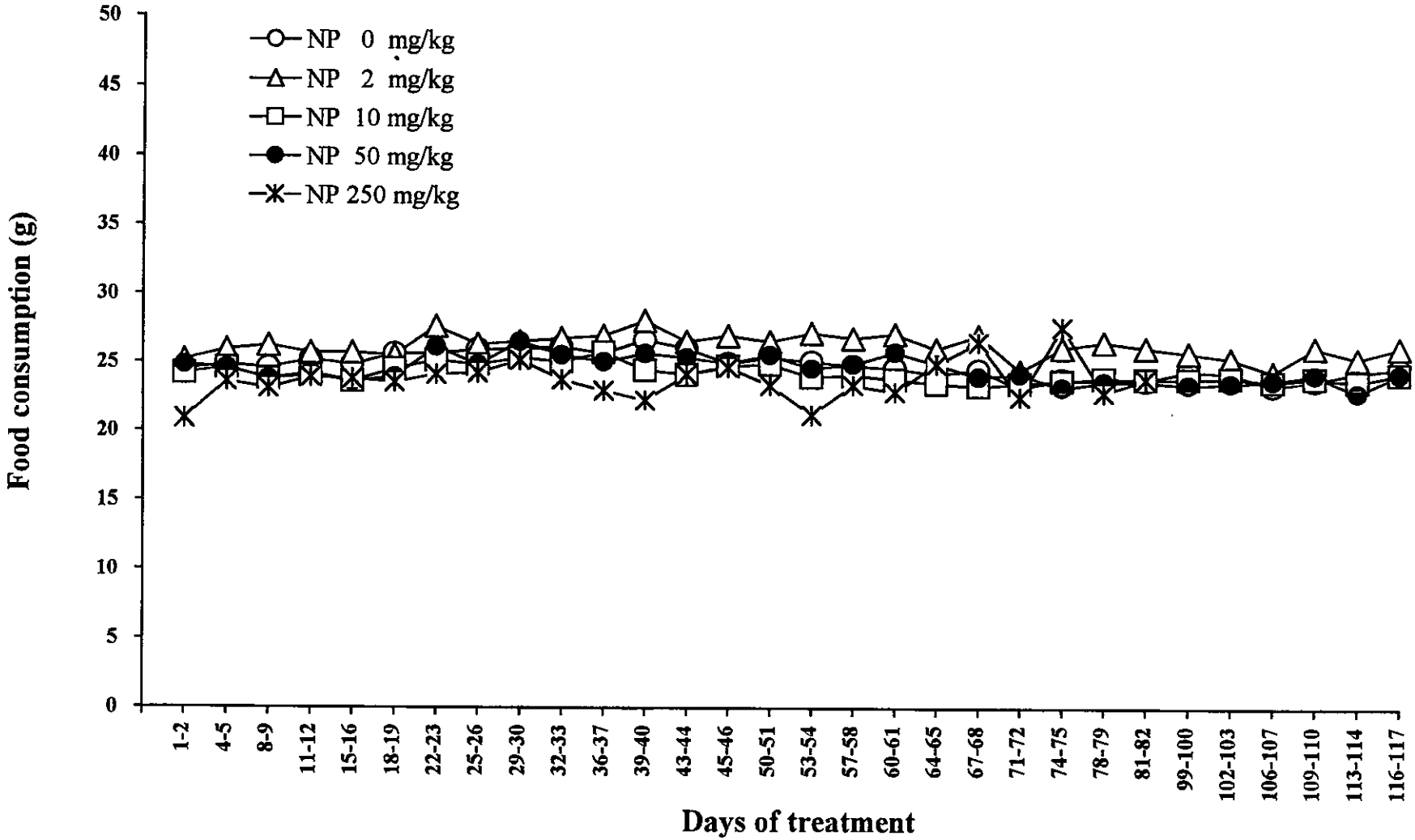
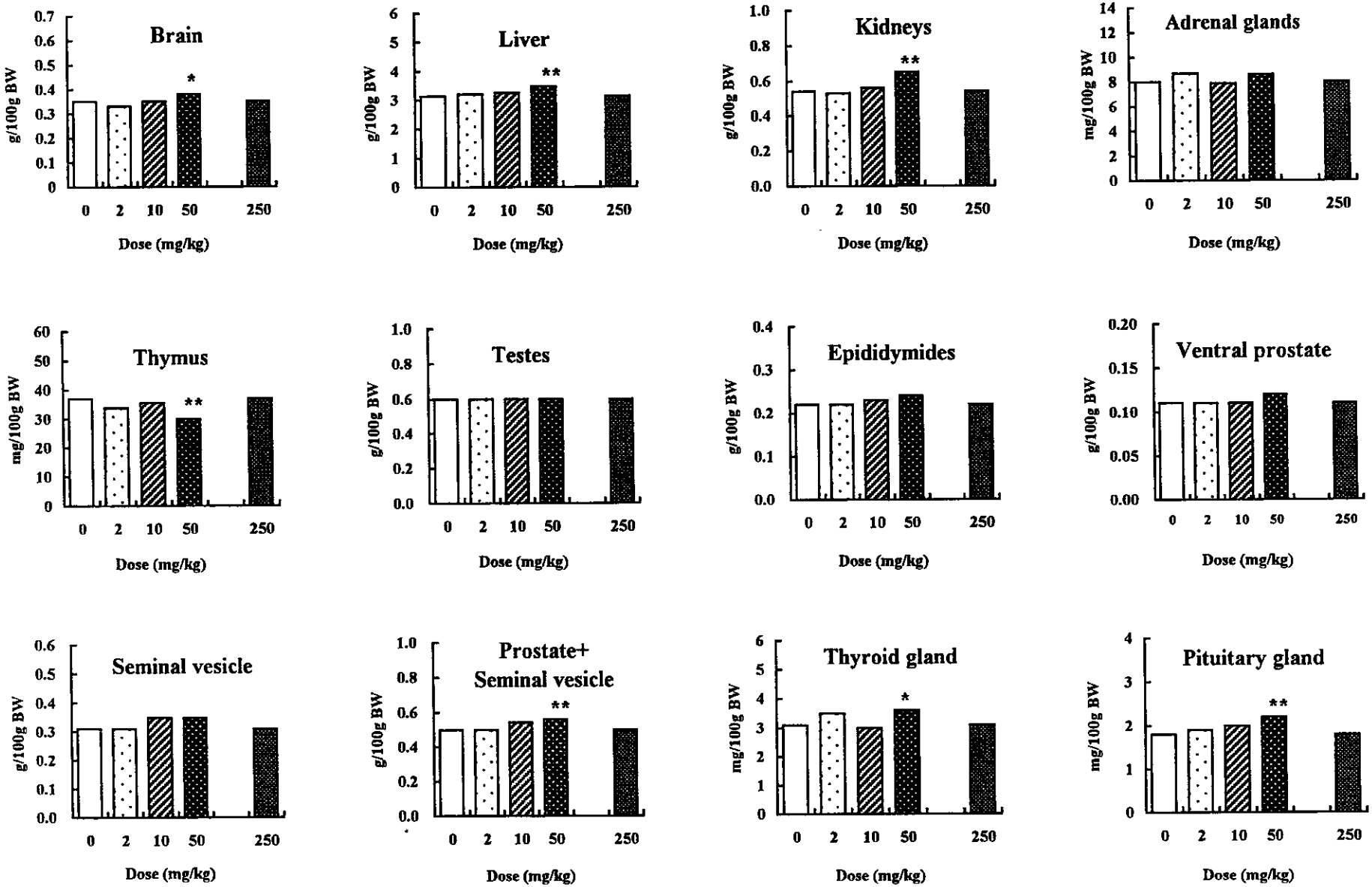


Fig. 2 Food consumption of Fo males



*:p<0.05, **:p<0.01

Fig. 3 Relative organ weight of F0 males

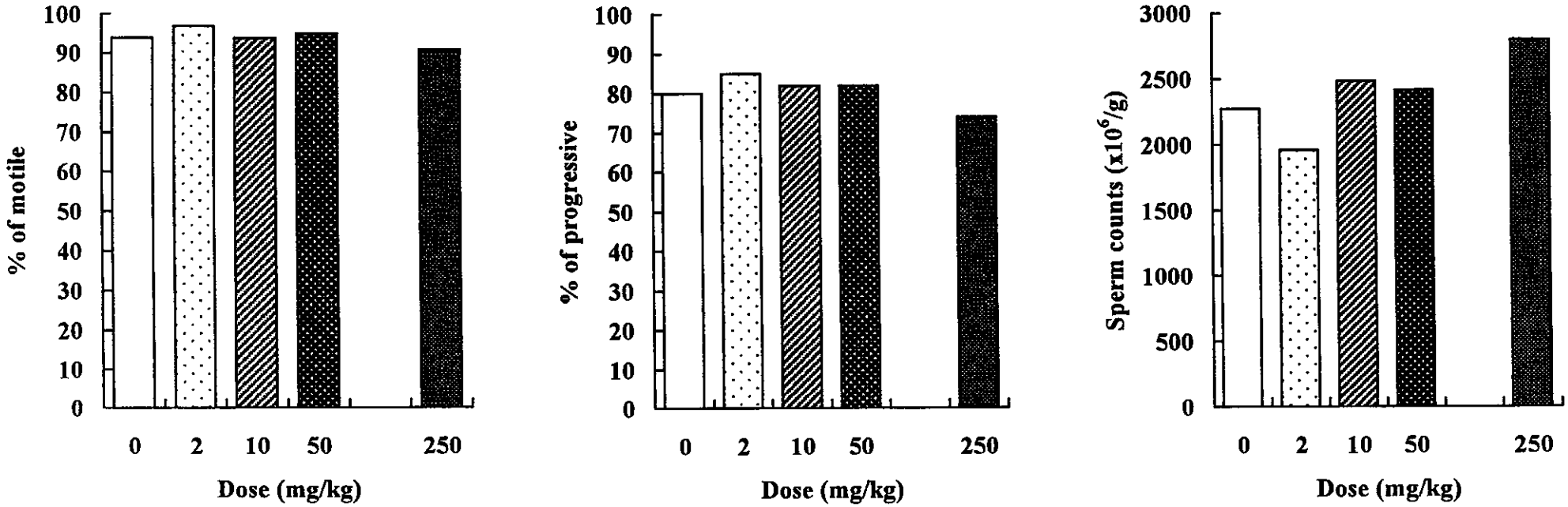
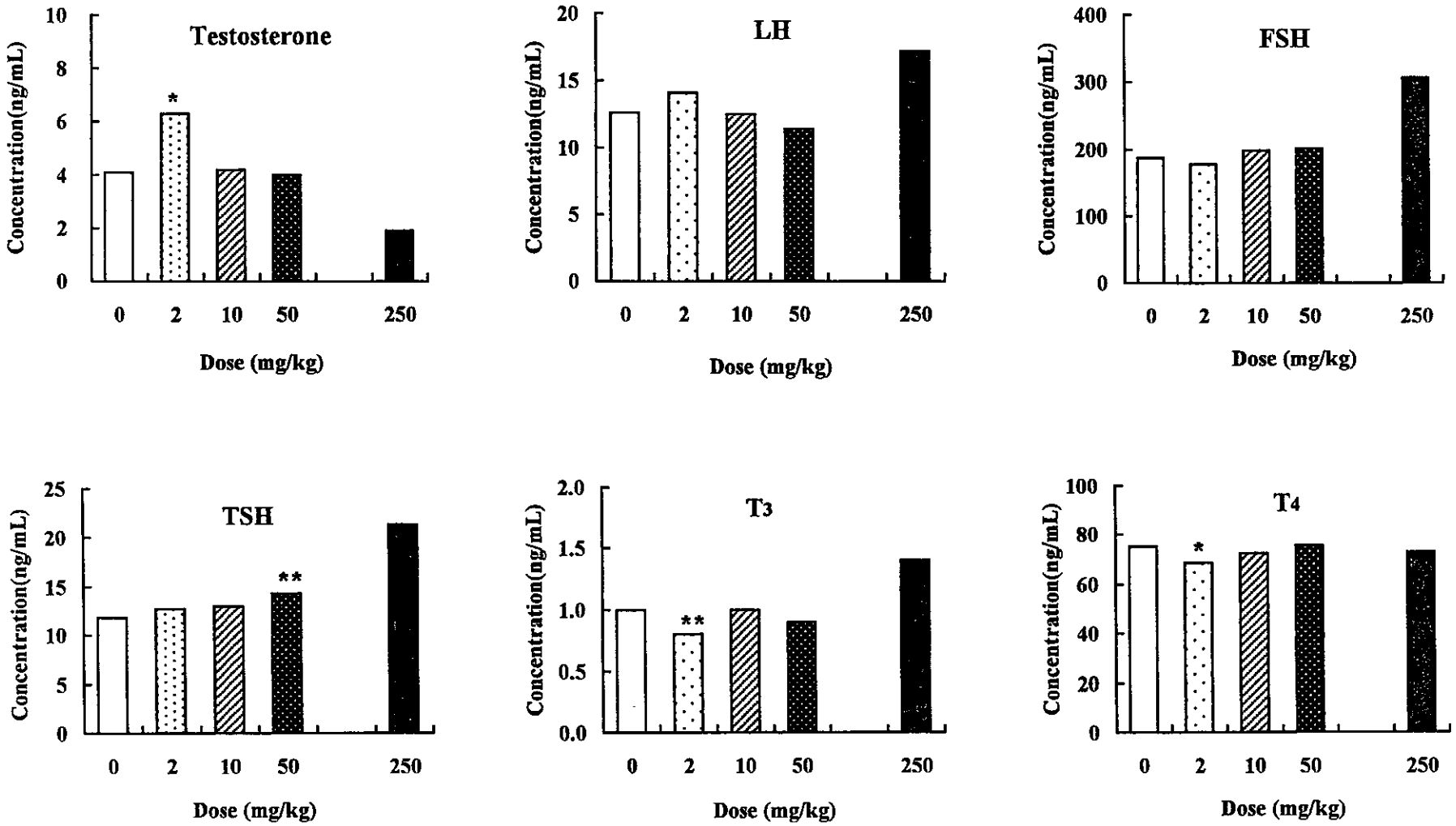


Fig. 4 Epididymal sperm findings in F0 males



*: p<0.05, **: p<0.01

Fig. 5 Serum concentrations of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), triiodthyronine (T_3), thyroxine (T_4) in F_0 males

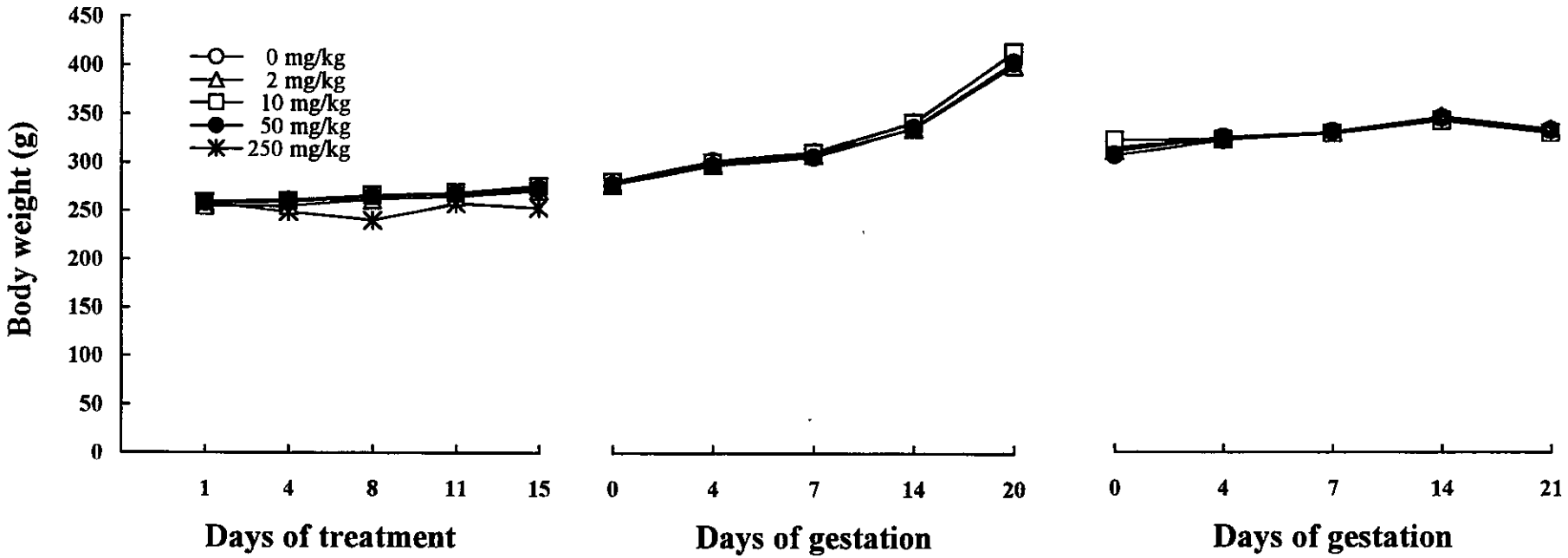


Fig. 6 Body weight of F_0 females during pre-mating, gestation and lactation period

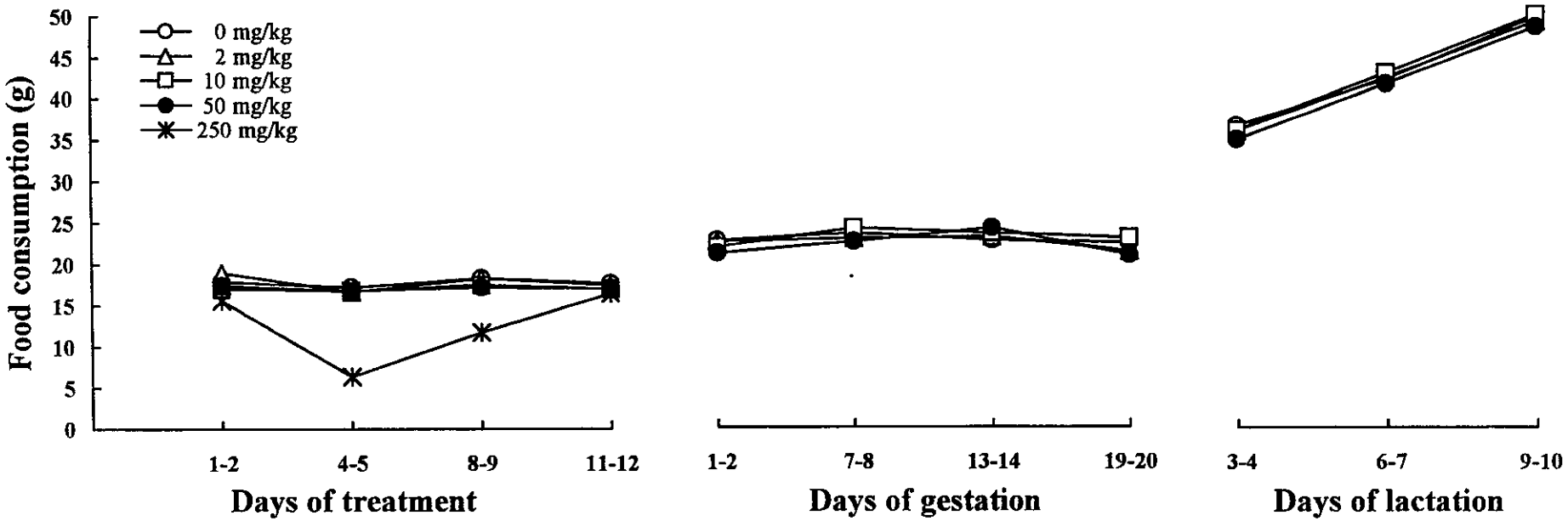


Fig. 7 Food consumption of F0 females during pre-mating, gestation and lactation period

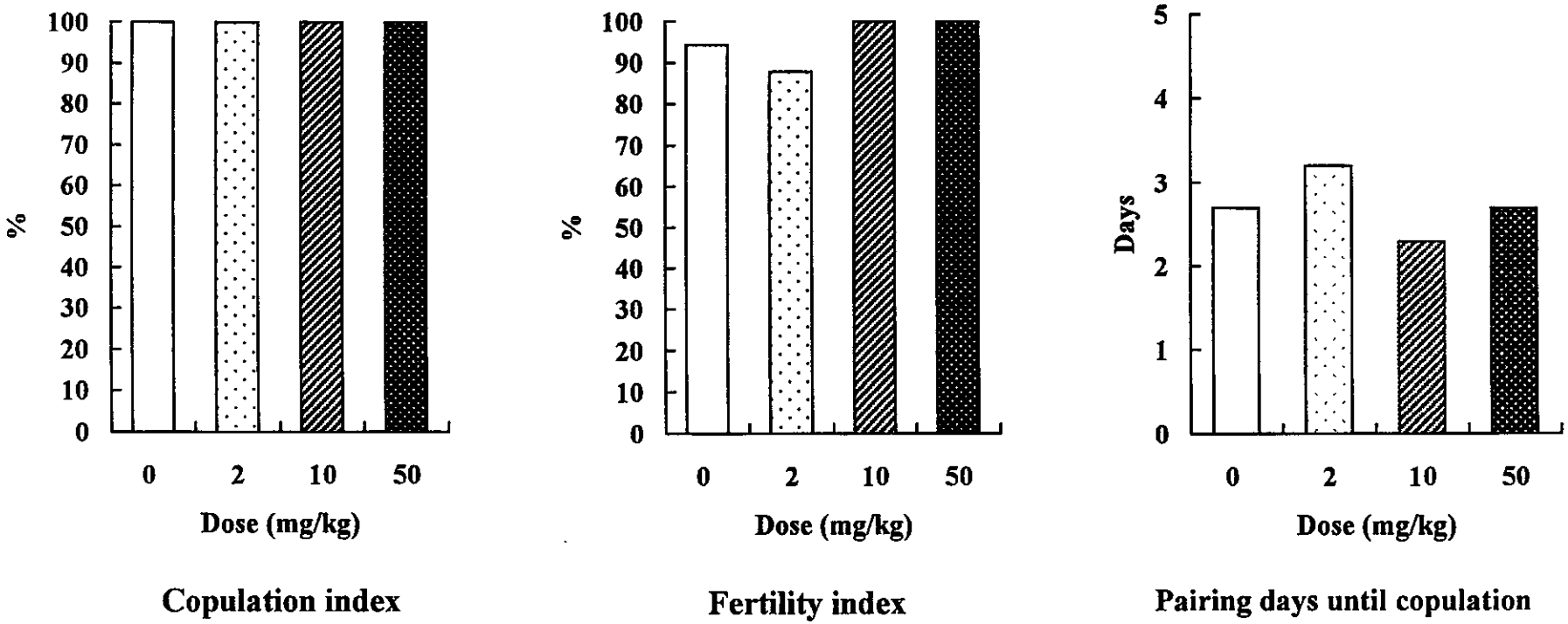


Fig. 8 Reproductive performance of F0 animals

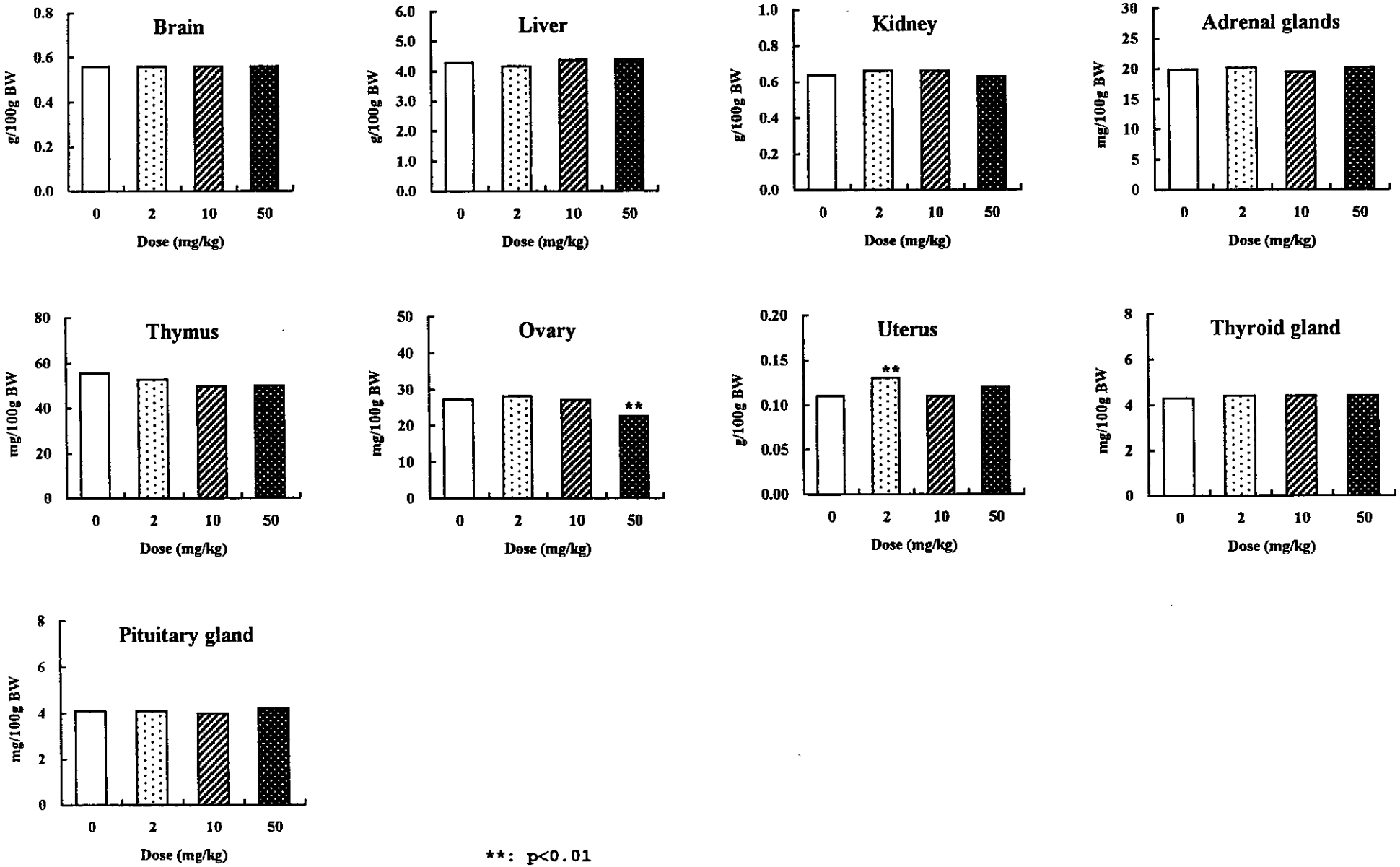


Fig. 9 Relative organ weight of Fo females

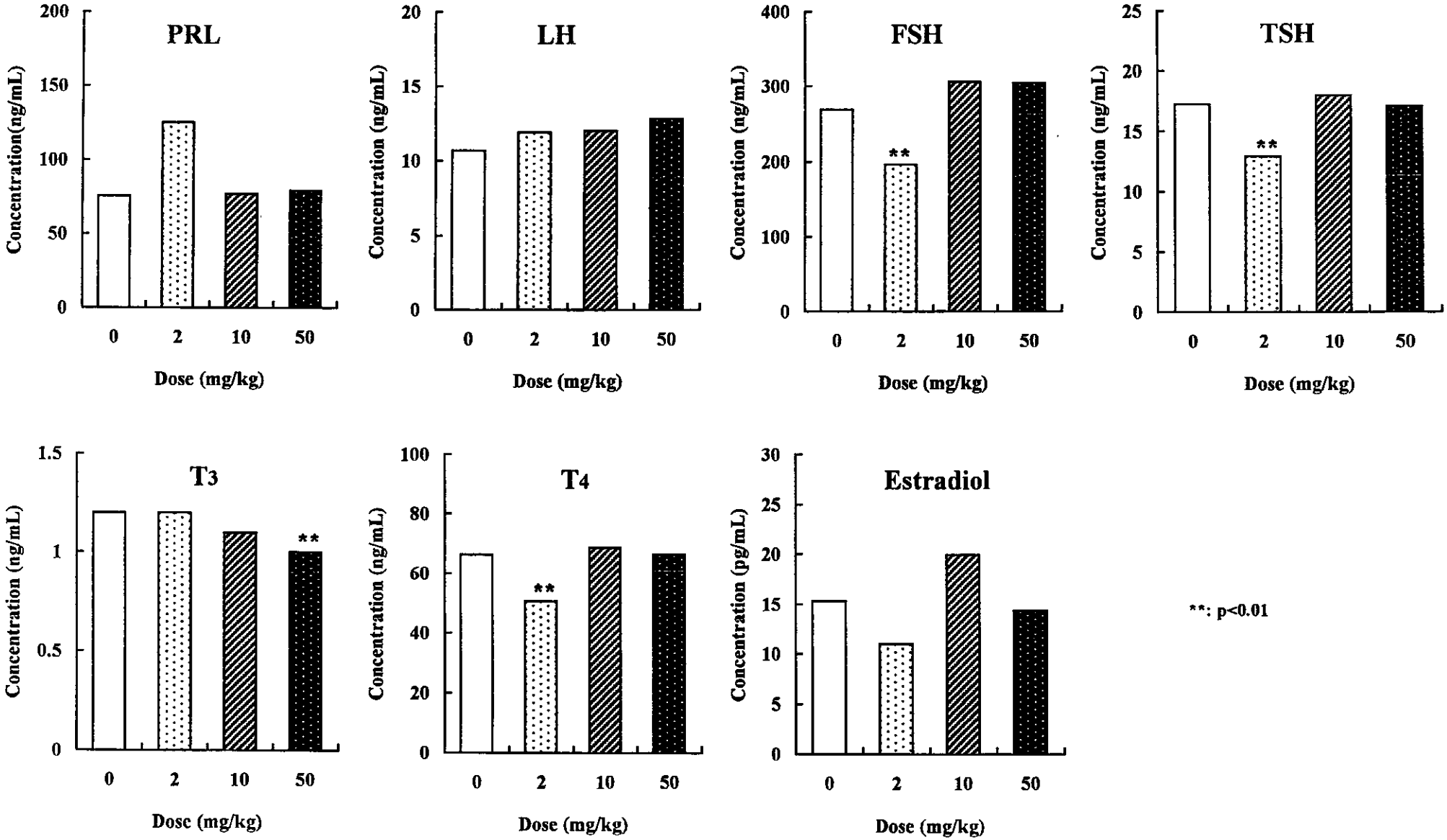


Fig. 10 Serum concentrations of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), triiodthyronine (T_3), thyroxine (T_4), estradiol in F_0 females

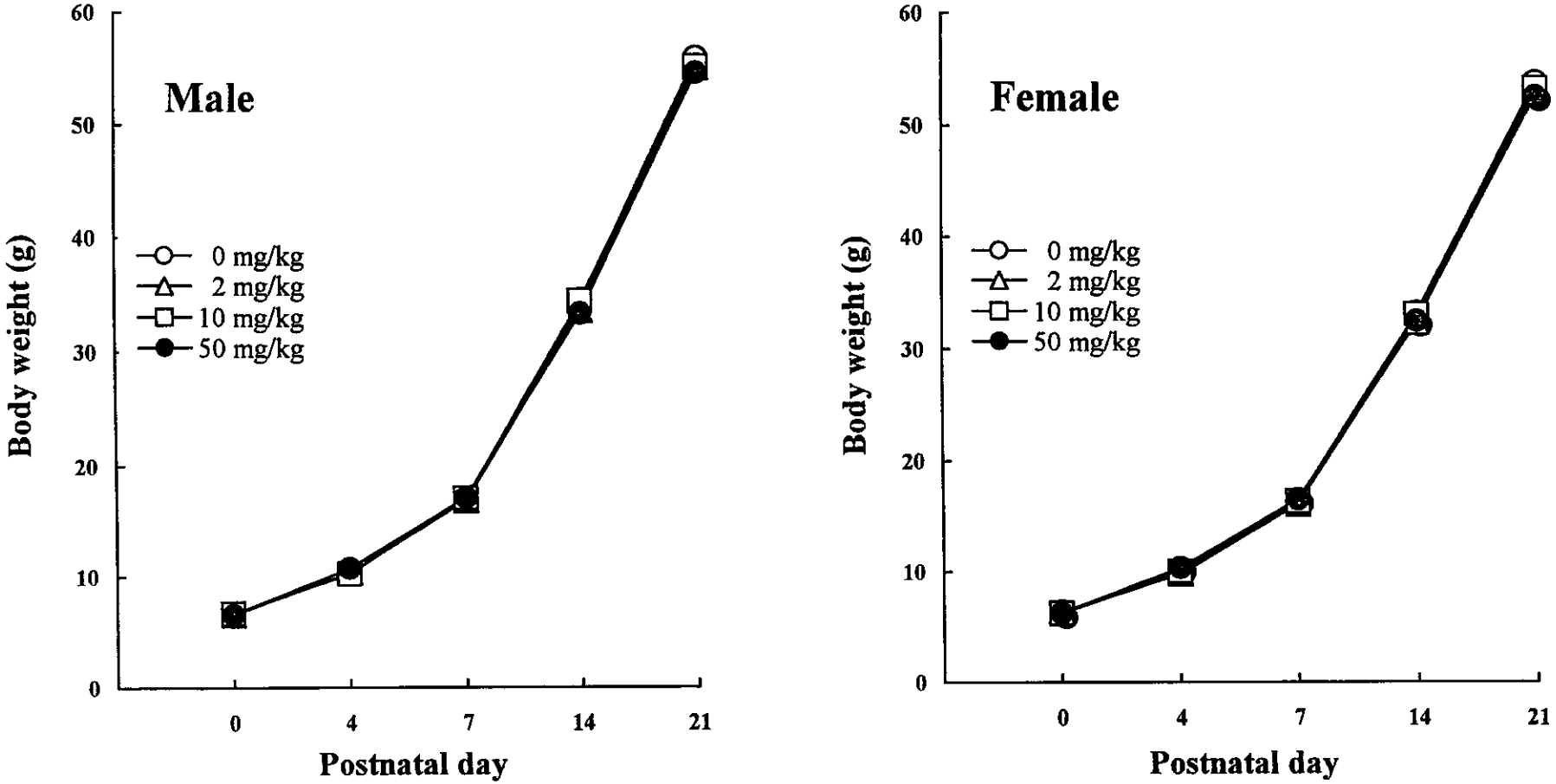


Fig. 11 Body weight of F_1 offspring up to weaning

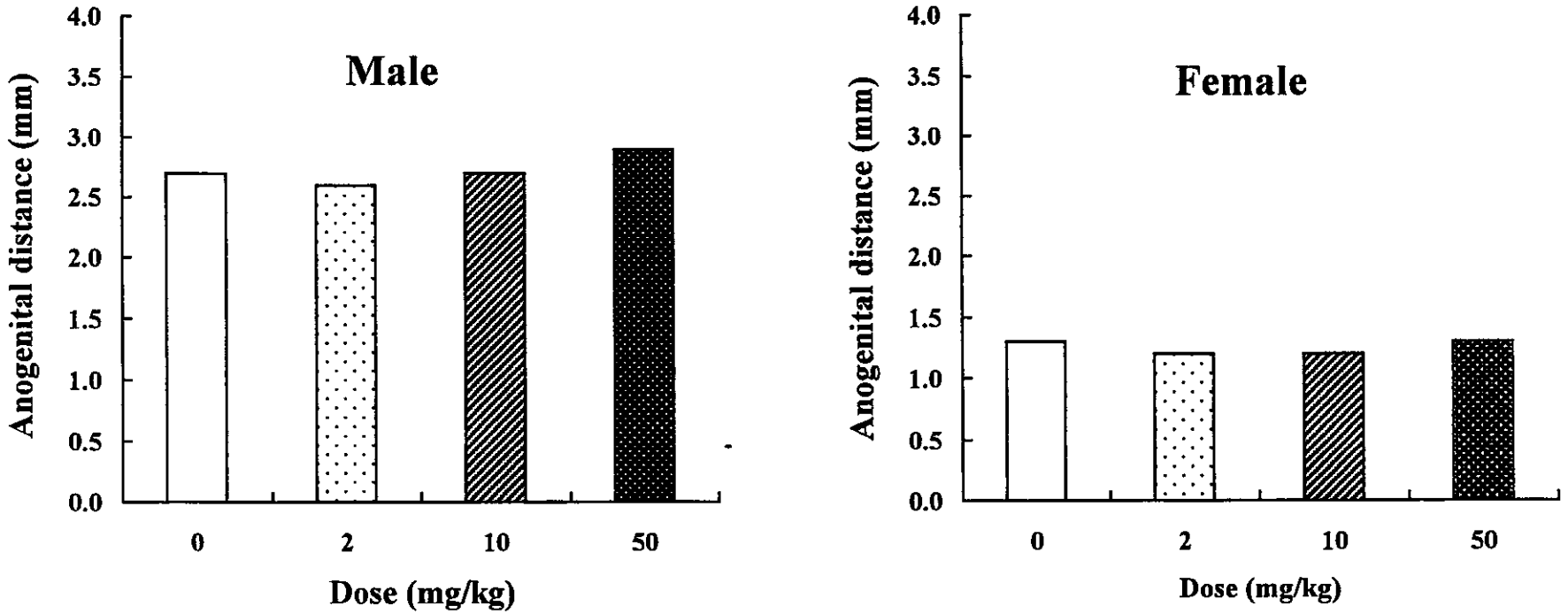
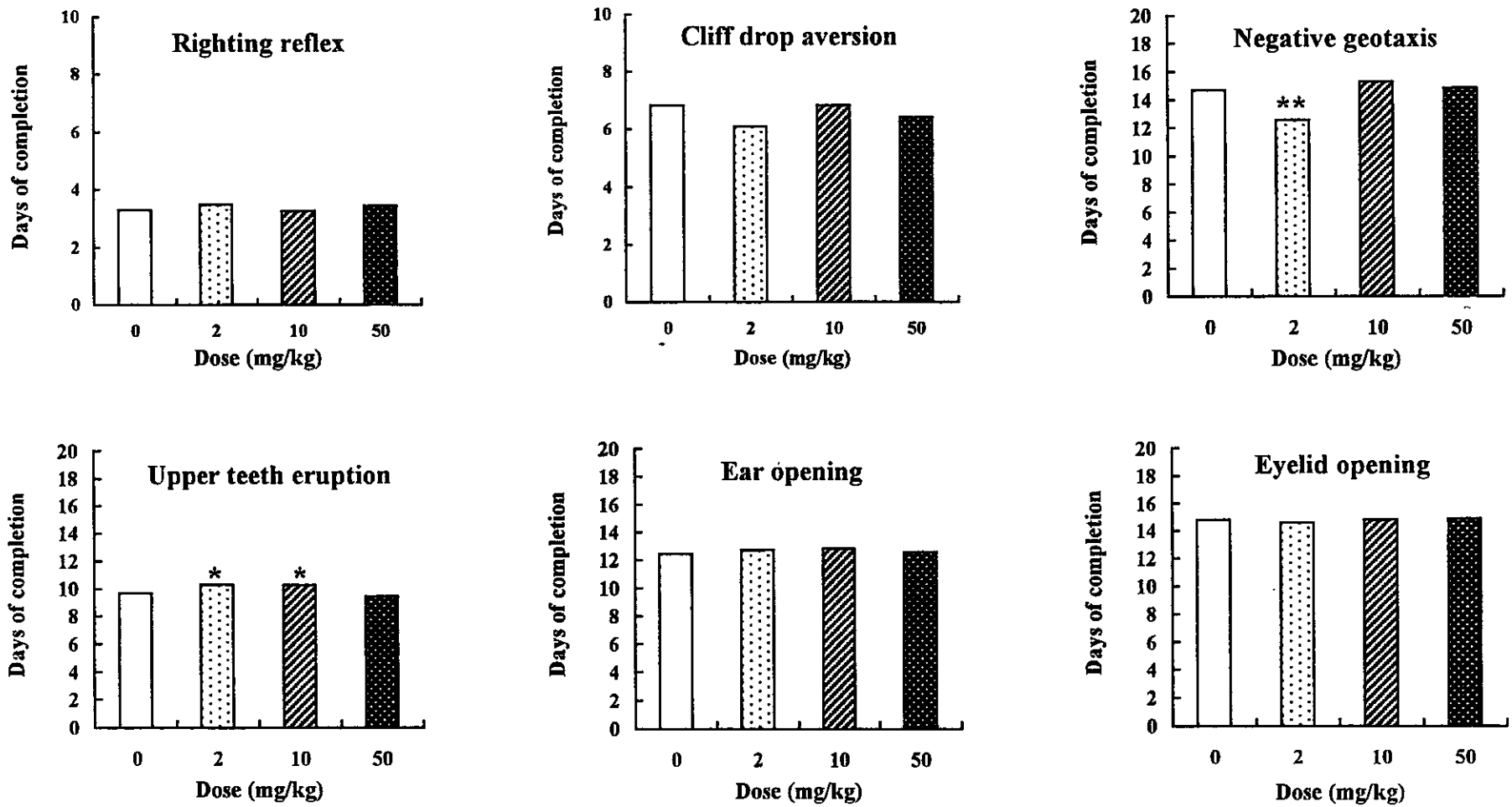
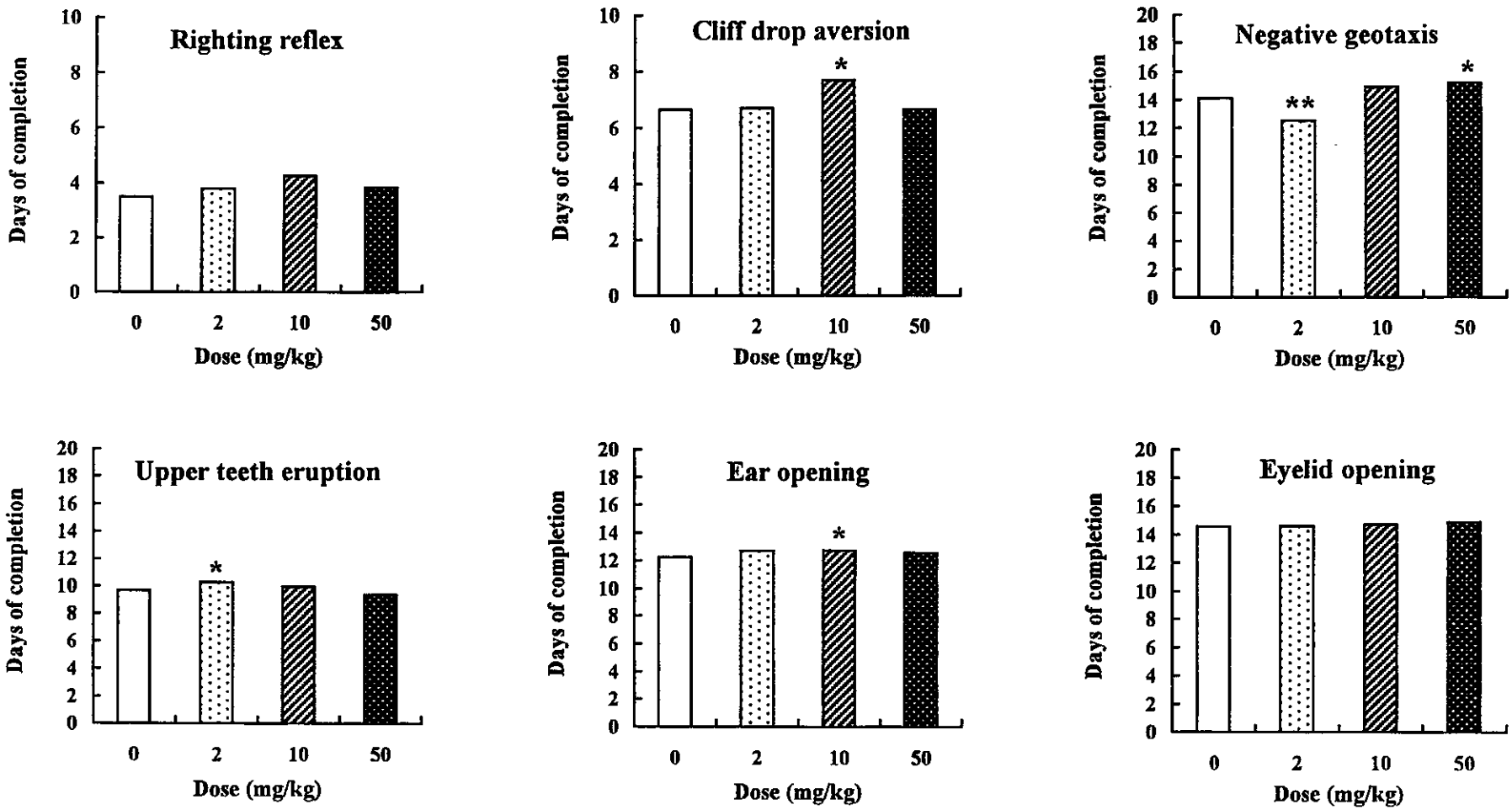


Fig. 12 Anogenital distance of F_1 pups at birth



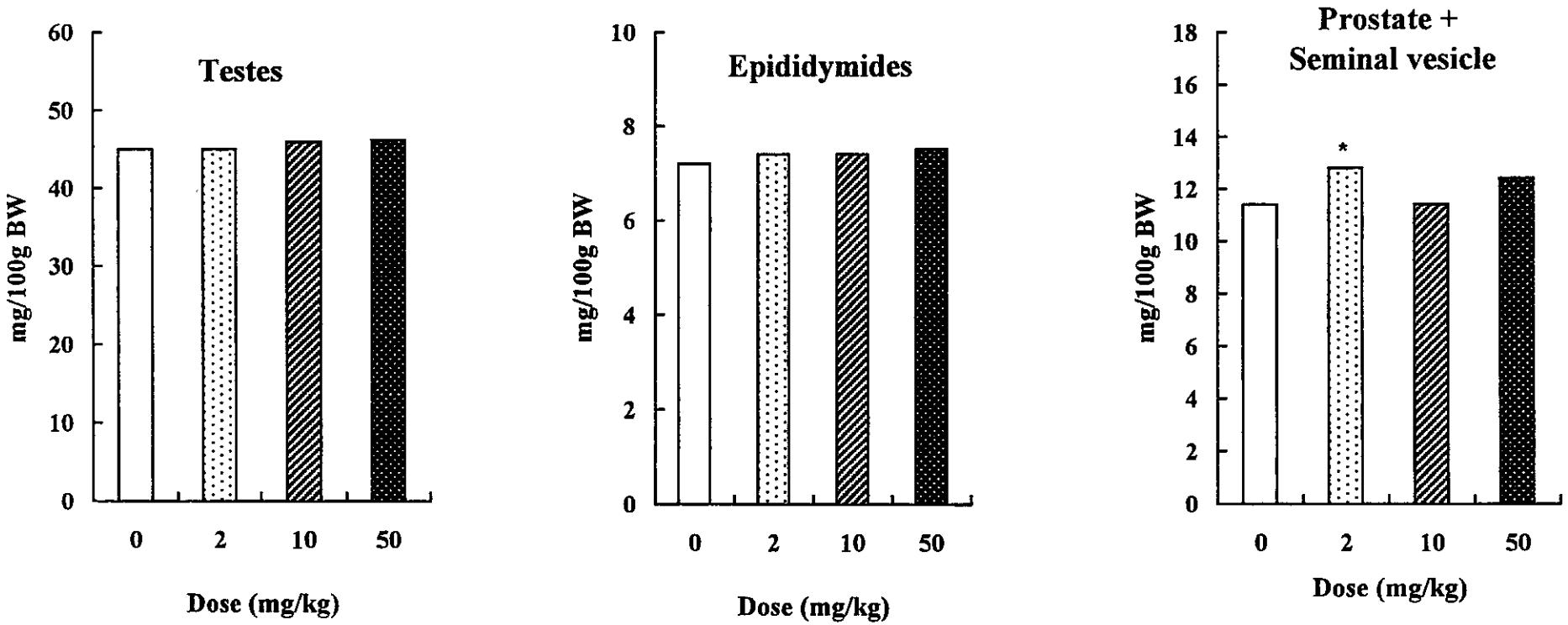
* : p<0.05
**: p<0.01

Fig. 13 Behavioral and physical development of F1 male offspring



* : p<0.05
**: p<0.01

Fig. 14 Behavioral and physical development of F1 female offspring



*: p<0.05

Fig. 15 Relative organ weight of F1 male weanlings

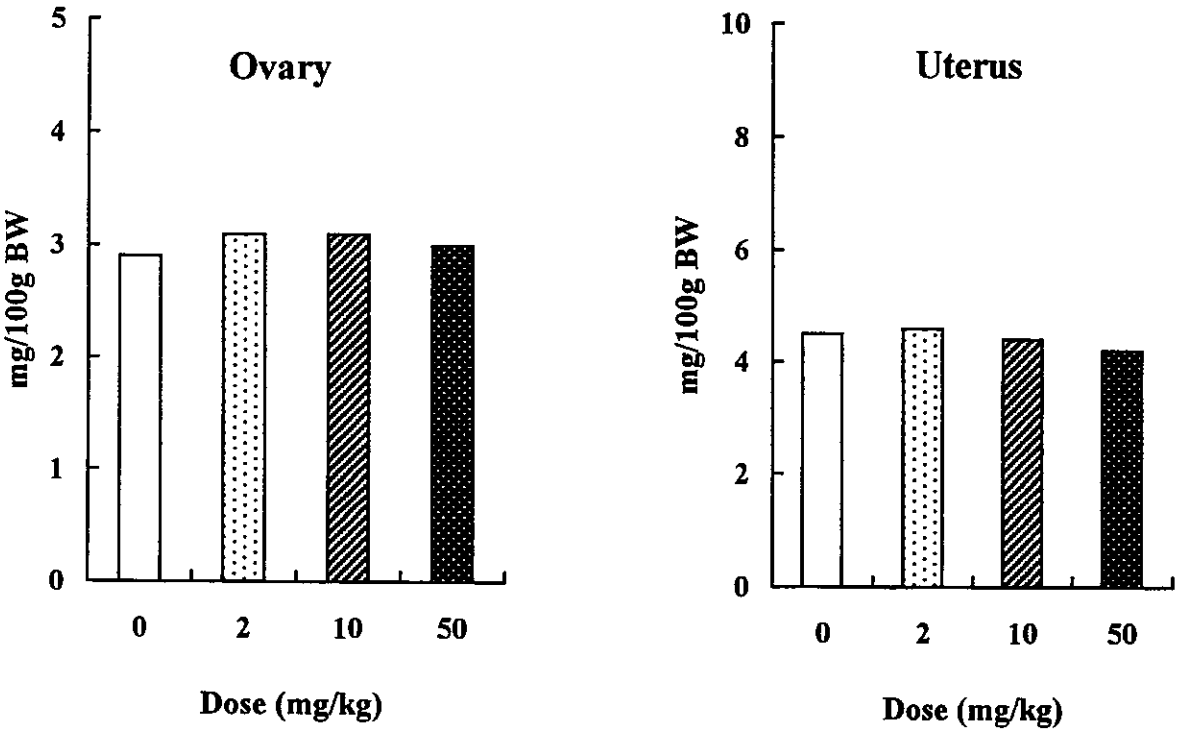
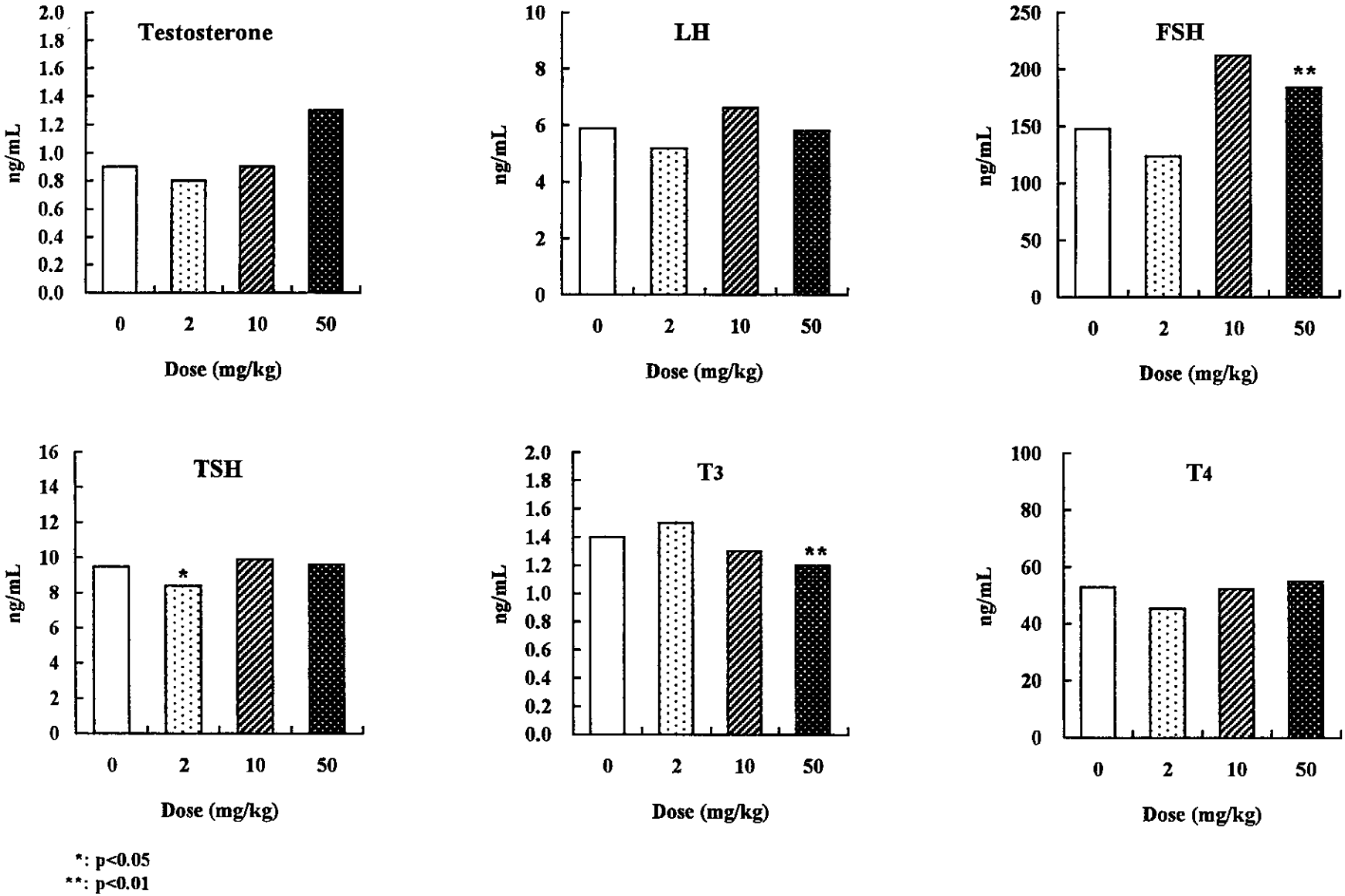


Fig. 16 Relative organ weight of F_1 female weanlings



*: $p<0.05$
**: $p<0.01$

Fig. 17 Serum concentrations of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), triiodthyronine (T3), thyroxine (T4) in F1 male weanlings

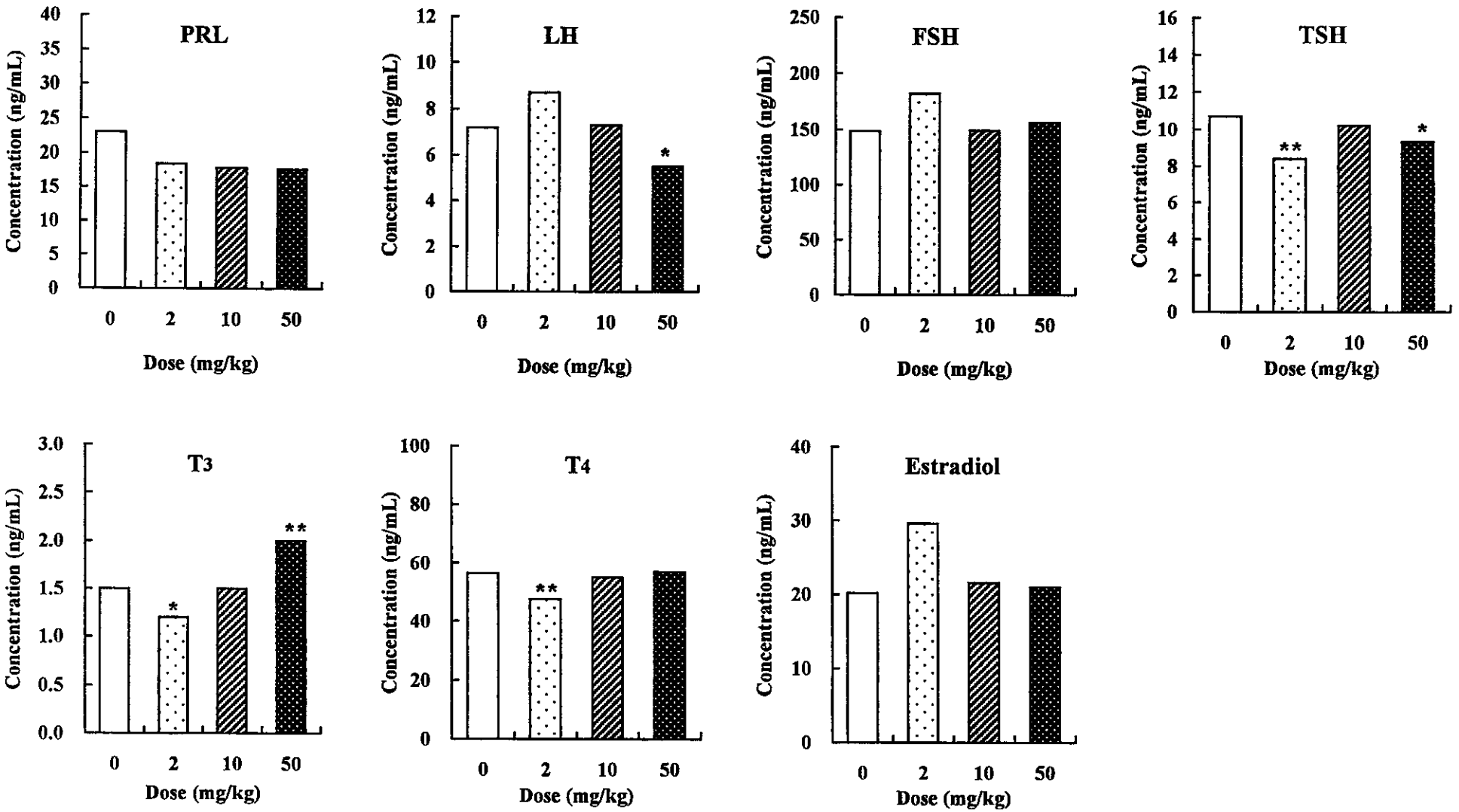


Fig. 18 Serum concentrations of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), triiodthyronine (T3), thyroxine (T4), estradiol in F1 female weanlings