

Table 1 Urinalysis of rats treated orally with 4,4'-biphenyldiol in combined repeated dose and reproductive/developmental toxicity

Dose(mg/kg)	On day 31 of administration				On day 11 of recovery		
	0	8	40	200	0	200	
Male							
Number of animals	10	5	5	10	5	5	
Specific gravity ^{a)}	1.030 ± 0.010	1.038 ± 0.008	1.031 ± 0.011	1.031 ± 0.004	1.033 ± 0.004	1.029 ± 0.009	
Quality							
Color	light yellow	10	5	5	10	5	5
Turbidity	negative	10	5	4	0	5	5
	slight	0	0	0	3	0	0
	moderate	0	0	1	4	0	0
	marked	0	0	0	3	0	0
pH	7.0	2	2	0	7	1	1
	7.5	5	2	1	2	4	1
	8.0	2	0	4	1	0	3
	8.5	1	1	0	0	0	0
Protein	negative	2	0	2	7	0	0
	trace	4	2	0	2	0	1
	30 ≤ and <100 mg/dL	3	3	3	1	4	4
	100 ≤ and <300 mg/dL	1	0	0	0	1	0
Glucose	negative	10	5	5	10	5	5
Ketone	negative	7	1	3	7	1	3
	trace	2	4	1	3	3	2
	slight	1	0	1	0	1	0
Bilirubin	negative	10	5	5	10	5	5
Occult blood	negative	10	5	5	10	5	5
Urobilinogen	0.1 ≤ and <1.0 EU/dL	10	5	5	10	4	4
	1.0 ≤ and <2.0 EU/dL	0	0	0	0	1	1
Microscopic examination of urinary sediment							
Crystal							
Grade	a few	10	4	3	0	5	5
	abundant	0	1	2	10	0	0
Shape	phosphate-like	10	5	5	8	5	5
	calcium oxalate-like	0	0	0	8	0	0
Epithelial cells	a few	0	0	0	0	3	3

a) values represent mean ± S.D.

Table 1 (Continued)

Dose (mg/kg)	On day 32 of administration						On day 11 of recovery	
	0	8	40	200	0 ^{a)}	200 ^{a)}	0 ^{a)}	200 ^{a)}
Female								
Number of animals	7	7	7	7	5	5	5	5
Specific gravity ^{b)}	1.038 ± 0.008	1.039 ± 0.006	1.028 ± 0.008*	1.026 ± 0.005**	1.034 ± 0.014	1.028 ± 0.004	1.029 ± 0.013	1.033 ± 0.012
Quality								
Color	light yellow	7	7	7	7	5	5	5
Turbidity	negative	7	7	5	1	5	1	5
	slight	0	0	2	5	0	2	0
	moderate	0	0	0	1	0	2	0
pH	6.0	0	1	0	0	0	0	0
	6.5	1	1	0	0	0	0	0
	7.0	2	1	2	4	2	2	0
	7.5	2	2	5	3	1	2	1
	8.0	1	1	0	0	2	1	3
	8.5	1	1	0	0	0	0	1
Protein	negative	3	4	7	7	3	5	3
	trace	3	1	0	0	0	0	0
	30 ≤ and <100 mg/dL	1	2	0	0	2	0	2
	100 ≤ and <300 mg/dL	0	0	0	0	0	0	0
Glucose	negative	7	7	7	7	5	5	5
Ketone	negative	5	5	7	7	5	5	5
	trace	2	2	0	0	0	0	0
Bilirubin	negative	7	7	7	7	5	5	5
Occult blood	negative	7	7	7	7	5	5	5
Urobilinogen	0.1 ≤ and <1.0 EU/dL	5	5	7	7	3	5	3
	1.0 ≤ and <2.0 EU/dL	2	2	0	0	2	0	2
Microscopic examination of urinary sediment								
Crystal								
Grade	a few	5	3	6	0	5	1	4
	abundant	0	2	1	7	0	4	0
Shape	phosphate-like	5	5	7	5	5	5	4
	calcium oxalate-like	0	0	1	6	0	4	0
Epithelial cells	a few	0	1	0	0	0	0	0

a) satellite group

b) values represent mean ± S.D.

p*<0.05, *p*<0.01

Table 2 Hematological examination in rats treated orally with 4,4'-biphenyldiol in combined repeated dose and reproductive/developmental toxicity screening test

Dose (mg/kg)	At the end of administration period				At the end of recovery period	
	0	8	40	200	0	200
Male						
Number of animals	5	5	5	5	5	5
RBC ($\times 10^6/\mu\text{L}$)	841 \pm 19	852 \pm 32	873 \pm 20	843 \pm 27	859 \pm 31	889 \pm 32
Hemoglobin (g/dL)	15.2 \pm 0.5	15.4 \pm 0.5	14.9 \pm 0.4	14.9 \pm 0.6	15.1 \pm 0.1	15.6 \pm 0.5
Hematocrit (%)	46.0 \pm 1.6	46.4 \pm 1.8	45.0 \pm 1.1	45.1 \pm 1.7	45.6 \pm 0.7	46.8 \pm 1.7
MCV (fL)	54.6 \pm 2.0	54.5 \pm 1.4	51.5 \pm 1.3*	53.5 \pm 1.5	53.1 \pm 2.0	52.7 \pm 0.9
MCH (pg)	18.1 \pm 0.7	18.1 \pm 0.5	17.1 \pm 0.4*	17.7 \pm 0.7	17.5 \pm 0.6	17.6 \pm 0.3
MCHC (g/dL)	33.0 \pm 0.3	33.2 \pm 0.3	33.1 \pm 0.3	33.0 \pm 0.5	33.0 \pm 0.3	33.4 \pm 0.2
Platelet ($\times 10^6/\mu\text{L}$)	103.1 \pm 6.8	105.5 \pm 16.9	115.2 \pm 7.4	111.1 \pm 9.3	113.2 \pm 13.2	110.0 \pm 9.4
PT (sec)	19.0 \pm 3.9	20.1 \pm 2.9	18.4 \pm 1.4	17.7 \pm 2.5	15.8 \pm 2.0	20.2 \pm 4.4
APTT (sec)	24.0 \pm 2.7	24.4 \pm 1.6	24.0 \pm 1.0	23.6 \pm 1.1	23.1 \pm 1.7	24.4 \pm 1.8
WBC ($\times 100/\mu\text{L}$)	91.3 \pm 43.3	78.5 \pm 31.0	92.5 \pm 41.8	87.3 \pm 27.7	116.8 \pm 21.6	80.9 \pm 14.8*
Differential leukocyte counts (%)						
Neutrophil	15 \pm 5	14 \pm 5	13 \pm 4	10 \pm 5	10 \pm 3	10 \pm 1
Eosinophil	2 \pm 0	2 \pm 1	2 \pm 1	2 \pm 1	1 \pm 0	2 \pm 0
Basophil	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0
Monocyte	4 \pm 1	5 \pm 1	6 \pm 3	3 \pm 1	4 \pm 0	5 \pm 1
Lymphocyte	79 \pm 7	78 \pm 5	80 \pm 7	85 \pm 6	85 \pm 3	83 \pm 2
Female						
Number of animals	5	5	5	5	5 ^{a)}	5 ^{a)}
RBC ($\times 10^6/\mu\text{L}$)	688 \pm 42	651 \pm 67	643 \pm 39	655 \pm 62	806 \pm 17	820 \pm 59
Hemoglobin (g/dL)	13.3 \pm 0.3	13.2 \pm 0.9	12.4 \pm 0.7	12.7 \pm 0.9	15.0 \pm 0.5	15.1 \pm 0.7
Hematocrit (%)	40.2 \pm 1.4	39.8 \pm 2.6	37.4 \pm 2.3	38.1 \pm 2.9	44.6 \pm 1.1	45.2 \pm 2.1
MCV (fL)	58.5 \pm 2.0	61.4 \pm 3.2	58.2 \pm 2.8	58.3 \pm 1.3	55.4 \pm 0.7	55.2 \pm 1.9
MCH (pg)	19.3 \pm 0.9	20.3 \pm 1.0	19.3 \pm 0.9	19.4 \pm 0.4	18.6 \pm 0.4	18.5 \pm 0.7
MCHC (g/dL)	33.1 \pm 0.5	33.1 \pm 0.5	33.2 \pm 0.4	33.3 \pm 0.1	33.5 \pm 0.3	33.5 \pm 0.3
Platelet ($\times 10^6/\mu\text{L}$)	107.7 \pm 9.4	108.1 \pm 11.8	114.2 \pm 11.1	110.4 \pm 14.5	108.2 \pm 13.8	106.7 \pm 11.3
PT (sec)	12.7 \pm 0.7	13.4 \pm 0.9	12.7 \pm 0.4	13.0 \pm 0.7	12.3 \pm 0.6	12.4 \pm 0.6
APTT (sec)	18.4 \pm 1.4	18.8 \pm 2.3	18.7 \pm 0.9	18.7 \pm 0.7	18.6 \pm 0.8	19.8 \pm 0.9
WBC ($\times 100/\mu\text{L}$)	80.1 \pm 14.5	80.6 \pm 18.9	99.1 \pm 30.7	93.7 \pm 22.8	52.6 \pm 23.5	59.2 \pm 22.2
Differential leukocyte counts (%)						
Neutrophil	32 \pm 21	24 \pm 11	27 \pm 9	22 \pm 9	10 \pm 4	12 \pm 10
Eosinophil	1 \pm 1	1 \pm 1	1 \pm 0	1 \pm 0	2 \pm 1	2 \pm 2
Basophil	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0
Monocyte	4 \pm 2	4 \pm 1	5 \pm 2	4 \pm 1	4 \pm 2	3 \pm 2
Lymphocyte	63 \pm 20	71 \pm 11	68 \pm 10	73 \pm 10	85 \pm 6	83 \pm 13

a) satellite group
 Values represent mean \pm S.D.
 * $p < 0.05$

Table 3 Blood chemical examination in rats treated orally with 4,4'-biphenyldiol in combined repeated dose and reproductive/developmental toxicity screening test

Dose(mg/kg)	At the end of administration period				At the end of recovery period	
	0	8	40	200	0	200
Male						
Number of animals	5	5	5	5	5	5
Total protein (g/dL)	5.9 ± 0.1	5.8 ± 0.2	5.8 ± 0.3	6.0 ± 0.1	6.1 ± 0.2	6.2 ± 0.2
Albumin (g/dL)	3.5 ± 0.1	3.5 ± 0.1	3.5 ± 0.3	3.6 ± 0.1	3.7 ± 0.2	3.8 ± 0.2
A/G	1.48 ± 0.16	1.50 ± 0.08	1.5 ± 0.1	1.49 ± 0.11	1.58 ± 0.14	1.62 ± 0.2
BUN(mg/dL)	16 ± 1	18 ± 2	18 ± 1	18 ± 1	14 ± 1	16 ± 2
Creatinine(mg/dL)	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.9 ± 0.2
Glucose(mg/dL)	169 ± 13	160 ± 10	172 ± 15	175 ± 17	195 ± 29	174 ± 14
Total cholesterol(mg/dL)	40 ± 13	39 ± 4	46 ± 4	31 ± 6	55 ± 10	49 ± 8
Triglyceride(mg/dL)	40 ± 25	33 ± 6	53 ± 31	53 ± 16	61 ± 32	49 ± 20
ALP(U/L)	222 ± 45	195 ± 38	190 ± 63	237 ± 48	148 ± 22	155 ± 18
ALT(GPT) (U/L)	32 ± 6	33 ± 4	32 ± 8	30 ± 6	44 ± 14	32 ± 5
AST(GOT) (U/L)	73 ± 9	66 ± 5	68 ± 15	61 ± 9	76 ± 23	63 ± 7
γ-GTP(U/L)	1 ± 1	1 ± 1	1 ± 1	1 ± 1	2 ± 1	1 ± 0
Total bilirubin(mg/dL)	0.05 ± 0.01	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.00	0.05 ± 0.03	0.04 ± 0.02
Inorg. phos. (mg/dL)	6.1 ± 0.3	6.6 ± 0.4	6.9 ± 0.5	6.6 ± 0.7	6.7 ± 0.7	6.8 ± 0.5
Ca (mg/dL)	9.0 ± 0.2	9.0 ± 0.2	8.9 ± 0.2	9.1 ± 0.3	9.6 ± 0.2	9.3 ± 0.2
Na (mEq/L)	144.7 ± 0.3	144.9 ± 0.7	144.7 ± 0.7	143.7 ± 0.7*	143.9 ± 0.5	144.0 ± 0.9
K (mEq/L)	4.17 ± 0.27	4.31 ± 0.29	4.19 ± 0.32	4.46 ± 0.32	4.36 ± 0.3	4.32 ± 0.21
Cl (mEq/L)	107.3 ± 1.6	108.2 ± 0.8	107.8 ± 1.3	106.8 ± 1.7	105.8 ± 1.0	105.0 ± 2.1
Female						
Number of animals	5	5	5	5	5 ^{a)}	5 ^{a)}
Total protein (g/dL)	6.1 ± 0.3	5.9 ± 0.4	5.9 ± 0.4	5.9 ± 0.3	6.7 ± 0.2	6.4 ± 0.2
Albumin (g/dL)	4.0 ± 0.3	3.8 ± 0.4	3.9 ± 0.3	3.9 ± 0.3	4.6 ± 0.2	4.3 ± 0.3
A/G	1.98 ± 0.24	1.81 ± 0.16	1.92 ± 0.28	2.01 ± 0.26	2.24 ± 0.15	1.97 ± 0.27
BUN(mg/dL)	17 ± 2.0	19 ± 2	16 ± 2	15 ± 2	22 ± 3	20 ± 2
Creatinine (mg/dL)	0.7 ± 0.0	0.7 ± 0.0	0.6 ± 0.1	0.7 ± 0.1	0.9 ± 0.2	0.8 ± 0.1
Glucose (mg/dL)	120 ± 3	117 ± 9	119 ± 3	117 ± 8	150 ± 17	163 ± 11
Total cholesterol (mg/dL)	53 ± 11	47 ± 10	49 ± 11	40 ± 13	65 ± 15	72 ± 9
Triglyceride (mg/dL)	39 ± 13	36 ± 36	27 ± 3	38 ± 11	29 ± 9	26 ± 10
ALP(U/L)	73 ± 27	85 ± 47	111 ± 29	121 ± 20	70 ± 17	86 ± 19
ALT(GPT) (U/L)	48 ± 10	40 ± 12	38 ± 7	42 ± 5	39 ± 20	25 ± 7
AST(GOT) (U/L)	73 ± 13	71 ± 5	59 ± 9	71 ± 6	87 ± 19	58 ± 13*
γ-GTP(U/L)	3 ± 1	2 ± 1	2 ± 1	3 ± 1	2 ± 1	2 ± 1
Total bilirubin(mg/dL)	0.05 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.07 ± 0.02	0.06 ± 0.01
Inorg. phos. (mg/dL)	5.3 ± 0.5	5.6 ± 0.2	5.4 ± 0.7	5.2 ± 0.5	4.5 ± 0.7	4.6 ± 0.5
Ca (mg/dL)	9.2 ± 0.3	9.2 ± 0.4	9.2 ± 0.3	9.1 ± 0.1	9.5 ± 0.3	9.3 ± 0.4
Na (mEq/L)	142.9 ± 1.0	142.0 ± 1.0	142.0 ± 0.6	142.2 ± 1.0	142.1 ± 0.8	141.9 ± 0.7
K (mEq/L)	3.90 ± 0.18	3.82 ± 0.20	3.67 ± 0.10	3.69 ± 0.25	4.36 ± 0.23	4.24 ± 0.21
Cl (mEq/L)	108.8 ± 1.0	108.3 ± 2.3	108.3 ± 1.2	108.6 ± 0.9	106.5 ± 2.4	106.3 ± 1.0

a) satellite group

Values represent mean ± S.D.

* p < 0.05

Table 4 Absolute and relative organ weights in rats treated orally with 4,4'-biphenyldiol in combined repeated dose and reproductive/developmental toxicity screening test

Dose(mg/kg)	At the end of administration period				At the end of recovery period	
	0	8	40	200	0	200
Male						
Number of animals	5	5	5	5	5	5
Terminal body weight (g)	536.2 ± 29.1	517.2 ± 8.5	541.0 ± 31.4	509.5 ± 44.4	540.5 ± 40.2	534.7 ± 51.4
Brain (g)	2.05 ± 0.08	1.99 ± 0.05	2.10 ± 0.07	2.01 ± 0.07	2.00 ± 0.07	2.05 ± 0.09
	(g%) 0.38 ± 0.02	0.38 ± 0.01	0.39 ± 0.02	0.40 ± 0.05	0.37 ± 0.03	0.39 ± 0.04
Thymus (mg)	315.1 ± 35.2	367.1 ± 107.2	322.7 ± 46.2	379.0 ± 52.0	309.3 ± 57.1	291.2 ± 59.5
	(mg%) 59.0 ± 7.9	71.1 ± 21.1	59.5 ± 5.7	75.0 ± 13.1	57.6 ± 12.5	54.1 ± 7.2
Heart (g)	1.44 ± 0.08	1.41 ± 0.12	1.49 ± 0.15	1.35 ± 0.12	1.49 ± 0.20	1.52 ± 0.10
	(g%) 0.27 ± 0.02	0.27 ± 0.02	0.27 ± 0.02	0.27 ± 0.02	0.28 ± 0.03	0.28 ± 0.02
Liver (g)	15.13 ± 1.72	14.92 ± 1.24	16.67 ± 1.84	16.49 ± 1.86	15.14 ± 2.79	15.62 ± 2.24
	(g%) 2.82 ± 0.22	2.88 ± 0.23	3.08 ± 0.21	3.23 ± 0.24*	2.79 ± 0.32	2.91 ± 0.21
Kidneys (g)	3.40 ± 0.19	3.38 ± 0.38	3.61 ± 0.18	3.50 ± 0.24	3.58 ± 0.22	3.50 ± 0.28
	(g%) 0.64 ± 0.05	0.66 ± 0.08	0.67 ± 0.05	0.69 ± 0.06	0.67 ± 0.05	0.66 ± 0.03
Spleen (g)	0.88 ± 0.04	0.88 ± 0.02	0.90 ± 0.13	0.89 ± 0.13	0.81 ± 0.13	0.81 ± 0.09
	(g%) 0.17 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	0.17 ± 0.03	0.15 ± 0.01	0.15 ± 0.02
Testes (g)	3.40 ± 0.15	3.29 ± 0.21	3.47 ± 0.46	3.41 ± 0.14	3.56 ± 0.13	3.40 ± 0.16
	(g%) 0.64 ± 0.03	0.64 ± 0.04	0.65 ± 0.11	0.68 ± 0.09	0.66 ± 0.04	0.64 ± 0.06
Epididymides (g)	1.29 ± 0.06	1.21 ± 0.12	1.22 ± 0.12	1.23 ± 0.05	1.31 ± 0.07	1.31 ± 0.08
	(g%) 0.24 ± 0.02	0.24 ± 0.02	0.23 ± 0.03	0.24 ± 0.03	0.24 ± 0.02	0.25 ± 0.03
Adrenal glands (mg)	67.6 ± 7.4	61.1 ± 9.1	57.1 ± 3.7	53.3 ± 5.8*	61.8 ± 13.5	62.0 ± 11.7
	(mg%) 12.6 ± 1.1	11.8 ± 1.7	10.6 ± 1.0	10.5 ± 1.3	11.3 ± 1.8	11.6 ± 1.7
Female						
Number of animals	5	5	5	5	5 ^{a)}	5 ^{a)}
Terminal body weight (g)	317.4 ± 15.9	303.5 ± 23.1	297.0 ± 2.8	298.5 ± 5.4	283.7 ± 27.8	276.6 ± 17.6
Brain (g)	1.91 ± 0.04	1.88 ± 0.07	1.89 ± 0.07	1.84 ± 0.06	1.81 ± 0.11	1.87 ± 0.10
	(g%) 0.60 ± 0.03	0.62 ± 0.03	0.64 ± 0.03	0.61 ± 0.02	0.64 ± 0.08	0.68 ± 0.06
Thymus (mg)	256.4 ± 74.0	227.5 ± 26.1	192.2 ± 30.8	298.1 ± 80.9	291.0 ± 47.3	259.8 ± 41.8
	(mg%) 80.7 ± 21.8	74.9 ± 5.7	64.7 ± 10.3	99.6 ± 25.8	102.2 ± 9.3	93.8 ± 13.0
Heart (g)	1.00 ± 0.12	0.98 ± 0.07	0.89 ± 0.04	0.91 ± 0.07	0.89 ± 0.04	0.92 ± 0.09
	(g%) 0.32 ± 0.04	0.32 ± 0.01	0.30 ± 0.01	0.30 ± 0.02	0.32 ± 0.02	0.33 ± 0.02
Liver (g)	10.56 ± 0.64	9.64 ± 1.61	9.94 ± 0.30	10.36 ± 0.34	7.82 ± 0.75	7.90 ± 1.06
	(g%) 3.33 ± 0.14	3.16 ± 0.34	3.35 ± 0.11	3.47 ± 0.11	2.77 ± 0.19	2.85 ± 0.22
Kidneys (g)	1.94 ± 0.12	1.88 ± 0.15	1.98 ± 0.07	1.86 ± 0.10	1.94 ± 0.19	2.02 ± 0.21
	(g%) 0.61 ± 0.06	0.62 ± 0.05	0.66 ± 0.03	0.62 ± 0.04	0.69 ± 0.10	0.73 ± 0.06
Spleen (g)	0.75 ± 0.05	0.78 ± 0.19	0.67 ± 0.07	0.65 ± 0.09	0.51 ± 0.11	0.50 ± 0.09
	(g%) 0.24 ± 0.02	0.26 ± 0.05	0.22 ± 0.03	0.22 ± 0.03	0.18 ± 0.03	0.18 ± 0.02
Adrenal glands (mg)	79.5 ± 10.9	76.3 ± 4.6	74.8 ± 11.6	67.6 ± 6.9	60.8 ± 11.0	65.5 ± 4.8
	(mg%) 25.1 ± 3.6	25.3 ± 3.3	25.2 ± 4.0	22.7 ± 2.7	21.4 ± 2.4	23.7 ± 0.7

a) satellite group
 Values represent mean ± S.D.
 * p<0.05

Table 5 Histopathological examination in rats treated orally with 4,4'-biphenyldiol in combined repeated dose and reproductive/developmental toxicity screening test

Sex	Dose (mg/kg)	Male						Female					
		At the end of administration period				At the end of recovery period		At the end of administration period				At the end of recovery period	
		0	8	40	200	0	200	0	8	40	200	0 ^a	200 ^a
(Testis)		[7]	[12]	[12]	[7]	[5]	[5]						
Atrophy, focal, seminiferous tubule	±	1	1	1	1	0	1						
	Total	1	1	1	1	0	1						
(Epididymis)		[7]	[12]	[12]	[7]	[5]	[5]						
Spermatic granuloma, cauda, unilateral	++	0	0	1	0	0	0						
	Total	0	0	1	0	0	0						
(Prostate: ventral lobe)		[5]	[0]	[0]	[5]	[0]	[0]						
Cellular infiltration, lymphocyte & neutrophil, epithelium/interstitium	±	1			1								
	+	0			1								
	++	1			0								
	Total	2			2								
(Liver)		[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]
Hypertrophy, hepatocyte, centrilobular	±	0	0	0	2	0	0	0	0	0	0	0	0
	Total	0	0	0	2	0	0	0	0	0	0	0	0
Fatty change, periportal	±	0	2	2	5	2	4	4	5	3	4	1	3
	+	4	2	3	0	2	1	0	0	0	0	0	0
	++	1	1	0	0	1	0	0	0	0	0	0	0
	Total	5	5	5	5	5	5	4	5	3	4	1	3
Microgranuloma	±	3	3	4	3	1	1	2	1	1	0	2	1
	Total	3	3	4	3	1	1	2	1	1	0	2	1
Hematopoiesis, extramedullary	±	0	0	0	0	0	0	0	1	0	1	0	0
	Total	0	0	0	0	0	0	0	1	0	1	0	0
(Kidney)		[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]	[5]
Eosinophilic body	±	1	0	2	2	1	3	0	0	0	0	0	0
	+	1	2	0	1	1	1	0	0	0	0	0	0
	++	0	0	3	2	0	1	0	0	0	0	0	0
	Total	2	2	5	5	2	5	0	0	0	0	0	0
Basophilic tubule, cortex	±	4	5	4	3	4	4	3	2	3	3	1	0
	Total	4	5	4	3	4	4	3	2	3	3	1	0
Mineralization	±	1	0	2	0	0	0	1	1	1	1	0	1
	Total	1	0	2	0	0	0	1	1	1	1	0	1
Cyst, focal, cortico-medullary junction	±	0	1	0	0	0	0	0	0	0	0	0	0
	Total	0	1	0	0	0	0	0	0	0	0	0	0
Cellular infiltration, lymphocyte, interstitium	±	2	0	1	1	2	1	0	0	1	0	0	0
	Total	2	0	1	1	2	1	0	0	1	0	0	0
Dilatation, lumen, diffuse, distal tubule	+	0	0	0	0	0	0	0	1	0	0	0	0
	Total	0	0	0	0	0	0	0	1	0	0	0	0

a) satellite group

Grade of histopathological finding; ±: very slight, +: slight, ++: moderate.

Total: total number of animals with positive grade.

** p<0.01

Table 5 (Continued)

Sex	Dose(mg/kg)	Male						Female					
		At the end of administration period				At the end of recovery period		At the end of administration period				At the end of recovery period	
		0	8	40	200	0	200 ^{a)}	0	8	40	200	0 ^{a)}	200 ^{a)}
(Lung & Bronchus)		[5]	[0]	[0]	[5]	[0]	[0]	[5]	[0]	[0]	[5]	[0]	[0]
Accumulation, foam cell, focal, alveolus	±	3			3			1			3		
	Total	3			3			1			3		
Mineralization, artery wall, lung	±	0			1			0			1		
	Total	0			1			0			1		
Metaplasia, osseous, focal, alveolus	±	0			1			1			1		
	Total	0			1			1			1		
(Thyroid gland)		[5]	[0]	[0]	[5]	[0]	[0]	[5]	[0]	[0]	[5]	[0]	[0]
Ectopic thymus	±	0			1			0			0		
	Total	0			1			0			0		
(Spleen)		[5]	[0]	[0]	[5]	[0]	[0]	[5]	[0]	[0]	[5]	[0]	[0]
Hematopoiesis, extramedullary	±	1			2			0			0		
	+	2			3			1			2		
	++	2			0			4			3		
	Total	5			5			5			5		
Deposit, pigment, brown	+	2			1			4			3		
	++	3			4			1			2		
	Total	5			5			5			5		

a) satellite group

Grade of histopathological finding; ±: very slight, +: slight, ++: moderate.

Total: total number of animals with positive grade.

Table 6 Estrous cycle and reproductive performance in rats treated orally with 4,4'-biphenyldiol in combined repeated dose and reproductive/developmental toxicity screening test

Dose(mg/kg)	0		8		40		200	
Estrous cycle								
Type of cycle during pre-treatment period								
4-day cycle	12		12		12		12	
Length of estrous cycle in days	4.0±0.0	(12)	4.0±0.0	(12)	4.0±0.0	(12)	4.0±0.0	(12)
Type of cycle during treatment period								
4-day cycle	12		11		12		12	
4-day and 5-day cycle	0		1		0		0	
Length of estrous cycle in days	4.0±0.0	(12)	4.0±0.1	(12)	4.0±0.0	(12)	4.0±0.0	(12)
Frequency of animals of which type of cycle was changed after the treatment	0/12		1/12		0/12		0/12	
Reproductive performance								
Number of mated pairs	12		12		12		12	
Number of copulated pairs	11		11		12		12	
Copulation index ^{a)}	91.7		91.7		100		100	
Number of pregnant animals	11		11		10		12	
Fertility index ^{b)}	100		100		83.3		100	
Pairing days until copulation	2.5±1.1	(11)	2.6±1.2	(11)	2.7±0.8	(12)	2.7±1.2	(12)
Frequency of vaginal estrus	1.0±0.0	(11)	1.0±0.0	(11)	1.0±0.0	(12)	1.0±0.0	(12)

Values represent mean ± S.D., and parentheses indicate the number of females evaluated.

a) Copulation index = (Number of copulated pairs/Number of mated pairs) × 100, %

b) Fertility index = (Number of pregnant females/Number of copulated pairs) × 100, %

Table 7 Summary of development of pups from dams treated orally with 4,4'-biphenyldiol in combined repeated dose and reproductive/developmental toxicity screening test

Dose(mg/kg)	0		8		40		200	
Number of pregnant females	11		11		10		12	
Number of pregnant females with pups alive	11		11		10		12	
Gestation index ^{a)}	100		100		100		100	
Gestation length in days	22.4 ± 0.5	(11)	22.4 ± 0.5	(11)	22.0 ± 0.0	(10)	22.4 ± 0.5	(12)
Number of corpora lutea	15.9 ± 1.6	(11)	16.5 ± 1.1	(11)	16.2 ± 1.2	(10)	15.2 ± 1.5	(12)
Number of implantation sites	15.5 ± 1.7	(11)	14.3 ± 3.6	(11)	16.0 ± 1.6	(10)	14.7 ± 1.7	(12)
Implantation index ^{b)}	97.1 ± 4.3	(11)	86.9 ± 21.6	(11)	98.7 ± 4.2	(10)	96.7 ± 5.3	(12)
Day 0 of lactation								
Number of pups born	14.5 ± 2.3	(11)	13.8 ± 4.0	(11)	15.1 ± 1.7	(10)	14.0 ± 1.8	(12)
Delivery index ^{c)}	93.2 ± 6.9	(11)	94.6 ± 12.2	(11)	94.4 ± 4.8	(10)	95.5 ± 5.2	(12)
Number of pups alive	14.3 ± 2.3	(11)	13.8 ± 4.0	(11)	14.6 ± 1.6	(10)	12.8 ± 2.9	(12)
Birth index ^{d)}	92.0 ± 7.6	(11)	94.6 ± 12.2	(11)	91.5 ± 8.1	(10)	88.8 ± 20.1	(12)
Live birth index ^{e)}	98.7 ± 3.0	(11)	100.0 ± 0.0	(11)	97.0 ± 7.5	(10)	93.3 ± 20.8	(12)
Pups weight in grams								
Male	6.8 ± 0.8	(11)	6.9 ± 0.8	(11)	6.5 ± 0.5	(10)	6.6 ± 0.8	(12)
Female	6.6 ± 0.6	(11)	6.6 ± 0.7	(11)	6.0 ± 0.4	(10)	6.2 ± 0.8	(12)
Sex ratio on day 0 ^{f)}	1.4 ± 0.7	(11)	1.4 ± 1.5	(11)	1.3 ± 0.7	(10)	1.3 ± 0.8	(12)
Day 4 of lactation								
Number of pups alive	13.9 ± 2.1	(11)	13.6 ± 4.0	(11)	14.5 ± 1.5	(10)	12.4 ± 4.2	(12)
Viability index ^{g)}	97.7 ± 4.0	(11)	98.8 ± 2.6	(11)	99.4 ± 2.0	(10)	91.7 ± 28.9	(12)
Pups weight in grams								
Male	10.6 ± 1.7	(11)	10.7 ± 1.1	(11)	10.2 ± 1.1	(10)	10.8 ± 1.0	(11)
Female	10.3 ± 1.4	(11)	10.4 ± 1.4	(11)	9.8 ± 1.0	(10)	10.0 ± 0.9	(11)
Sex ratio on day 4 ^{h)}	1.4 ± 0.7	(11)	1.4 ± 1.5	(11)	1.3 ± 0.7	(10)	1.2 ± 0.8	(11)

Values represent mean ± S.D., and parentheses indicate the number of litters evaluated.

a) Gestation index = (Number of females with alive pups / Number of pregnant females) × 100, %

b) Implantation index = (Number of implantation sites / Number of corpora lutea) × 100, %

c) Delivery index = (Number of pups born / Number of implantation sites) × 100, %

d) Birth index = (Number of live pups on day 0 / Number of implantation sites) × 100, %

e) Live birth index = (Number of live pups on day 0 / Number of pups born) × 100, %

f) Sex ratio on day 0 = Number of male live pups on day 0 / Number of female live pups on day 0

g) Viability index = (Number of live pups on day 4 / Number of live pups on day 0) × 100, %

h) Sex ratio on day 4 = Number of male live pups on day 4 / Number of female live pups on day 4