

Table 1 Urinalysis in 28-day repeat dose oral toxicity test of 4-ethylbiphenyl in rats

Dose (mg/kg)	On day 3 of administration period				
	0	20	100	500	1000
Male					
Number of animals	5	5	5	5	5 ^{b)}
Volume (mL) ^{b)}	8.7 ± 3.6	12.9 ± 9.2	10.1 ± 5.7	16.3 ± 8.9	34.1 ± 10.4**
Specific gravity ^{b)}	1.055 ± 0.022	1.05 ± 0.013	1.047 ± 0.023	1.039 ± 0.011	1.032 ± 0.009
Color	light yellow	5	5	5	5
	yellow	0	0	0	0
Turbidity ^{c)}	+	0	0	0	1
Protein ^{d)}	±	1	4	0	0
	+	4	0	1	0
	++	0	0	0	2
Ketone ^{e)}	±	1	0	0	0
	+	0	0	0	0
Bilirubin ^{e)}	+	1	0	0	0
Occult blood ^{f)}	±	0	0	0	1
	+	0	0	0	1
Urobilinogen ^{g)}	±	4	5	5	5
	+	1	0	0	1
Sediment					
Crystal ^{h)}	±	4	5	5	1
	+	0	0	0	0
Cast ^{h)}	±	0	0	0	0
Epithelial cell ^{h)}	±	3	4	3	4
	+	3	4	3	3
Female					
Number of animals	5	5	5	5	5
Volume (mL) ^{b)}	9.8 ± 3.1	7.1 ± 3.4	6.5 ± 2.5	18.7 ± 7.4	21.9 ± 14.5
Specific gravity ^{b)}	1.047 ± 0.012	1.05 ± 0.018	1.055 ± 0.023	1.032 ± 0.013	1.033 ± 0.011
Color	light yellow	5	5	5	5
	yellow	0	0	0	0
Turbidity ^{c)}	+	0	0	0	1
Protein ^{d)}	±	3	0	2	0
	+	0	1	0	1
	++	0	0	0	2
Ketone ^{e)}	±	3	1	0	0
Bilirubin ^{e)}	+	1	0	0	0
Occult blood ^{f)}	±	0	2	0	0
	+	0	0	0	0
Urobilinogen ^{g)}	±	5	4	5	5
	+	0	1	0	1
Sediment					
Crystal ^{h)}	±	3	4	5	2
	+	0	0	0	2
Cast ^{h)}	±	0	0	0	0
Epithelial cell ^{h)}	±	2	4	0	1
	+	0	0	0	0

a) Urinary volume was measured in 3 of 5 animals b) parameter, mean ± S.D. c) ±: trace, +: slight
d) ±: trace, +: 30 mg/kg, ++: 100 mg/dL e) ±: 0.1 EU/dL, +: 1.0 EU/dL f) ±: a few, +: abundant
g) ±: 1-9 per 3 visual fields **: significantly different from 0 mg/kg, p < 0.01

Table 1 (Continued)

	Dose (mg/kg)	On day 24 of administration period					On day 10 of recovery period		
		0	20	100	500	1000	0	500	1000
Male									
Number of animals		5	5	5	5	5	5	5	0
Volume (mL) ^{b)}		20.2 ± 4.6	24.4 ± 6.7	21.5 ± 10.2	32.6 ± 8.6	54.0 ± 14.2**	27.4 ± 6.9	26.4 ± 10.5	
Specific gravity ^{b)}		1.031 ± 0.011	1.030 ± 0.013	1.034 ± 0.021	1.024 ± 0.010	1.015 ± 0.003	1.042 ± 0.010	1.037 ± 0.013	
Color	light yellow	5	5	4	3	4	5	4	
	yellow	0	0	1	2	1	0	0	
Turbidity ^{c)}	+	0	0	0	0	0	0	0	
Protein ^{d)}	±	2	1	0	0	0	0	0	
	+	3	3	4	3	1	5	4	
	++	0	0	1	2	1	0	0	
Ketone ^{e)}	±	2	2	1	2	0	2	1	
	+	0	0	1	0	0	1	0	
Bilirubin ^{e)}	+	0	0	1	1	0	0	0	
Occult blood ^{f)}	±	0	0	0	0	1	0	0	
	+	0	0	0	0	0	0	0	
Urobilinogen ^{g)}	±	5	5	4	3	5	5	5	
	+	0	0	1	2	0	0	0	
Sediment									
Crystal ^{h)}	±	5	5	5	4	3	5	3	
	+	0	0	0	1	0	0	0	
Cast ⁱ⁾	±	0	0	0	0	0	0	0	
	+	0	0	3	2	2	0	0	
Female									
Number of animals		5	5	5	5	5	5	5	3
Volume (mL) ^{b)}		20.1 ± 4.0	10.7 ± 5.8	10.8 ± 5.4	39.8 ± 7.9**	43.4 ± 13.9**	22.4 ± 4.1	24.0 ± 7.2	34.8 ± 11.5
Specific gravity ^{b)}		1.027 ± 0.008	1.037 ± 0.014	1.045 ± 0.017	1.010 ± 0.003	1.012 ± 0.005	1.032 ± 0.005	1.034 ± 0.008	1.033 ± 0.005
Color	light yellow	5	4	2	4	5	5	5	3
	yellow	0	1	3	1	0	0	0	0
Turbidity ^{c)}	+	0	0	0	1	1	0	0	0
Protein ^{d)}	±	0	0	2	1	1	0	0	0
	+	0	1	3	1	2	0	0	0
	++	0	0	0	1	0	0	1	0
Ketone ^{e)}	±	0	1	4	2	0	0	0	0
Bilirubin ^{e)}	+	0	0	0	0	0	0	0	0
Occult blood ^{f)}	±	0	0	0	1	1	0	0	0
	+	0	0	0	0	0	0	0	0
Urobilinogen ^{g)}	±	5	4	3	5	5	5	5	3
	+	0	1	2	0	0	0	0	0
Sediment									
Crystal ^{h)}	±	5	5	5	4	2	4	3	0
	+	0	0	0	0	0	0	0	0
Cast ⁱ⁾	±	0	0	0	1	0	0	0	0
	+	0	4	0	3	4	0	0	2
Epithelial cell ^{h)}	±	0	0	0	0	0	0	1	0
	+	0	0	0	0	0	0	0	0

a) Urinary volume was measured in 3 of 5 animals b) parameter, mean ± S.D. c) ±: trace, +: slight d) ±: trace, +: 30 mg/kg, ++: 100 mg/dL e) ±: 0.1 EU/dL, +: 1.0 EU/dL f) ±: a few, +: abundant g) ±: 1-9 per 3 visual fields **: significantly different from 0 mg/kg, p < 0.01

Table 2 Hematological examination in 28-day repeat dose oral toxicity test of 4-ethylbiphenyl in rats

Dose (mg/kg)	End of administration period					End of recovery period		
	0	20	100	500	1000	0	500	1000
Male								
Number of animals	5	5	5	5	5	5	4	0
RBC($\times 10000/\text{mm}^3$)	685 \pm 30	674 \pm 49	658 \pm 17	679 \pm 26	712 \pm 43	744 \pm 30	744 \pm 35	
Hemoglobin (g/dL)	14.8 \pm 0.4	14.8 \pm 1.1	14.3 \pm 0.3	14.1 \pm 0.5	14.6 \pm 0.7	15.0 \pm 0.2	14.7 \pm 0.5	
Hematocrit (%)	44.2 \pm 1.4	43.1 \pm 3.3	40.9 \pm 0.8	41.1 \pm 0.9	42.7 \pm 2.2	45.0 \pm 1.5	43.1 \pm 1.5	
MCV (μm^3)	64.6 \pm 1.2	64.0 \pm 2.6	62.1 \pm 1.4	60.5 \pm 1.3**	60.0 \pm 2.2**	60.5 \pm 1.2	57.9 \pm 1.5*	
MCH (pg)	21.6 \pm 0.6	21.9 \pm 0.7	21.8 \pm 0.5	20.8 \pm 0.4	20.5 \pm 0.7*	20.2 \pm 0.6	19.8 \pm 0.4	
MCHC (%)	33.4 \pm 0.5	34.3 \pm 0.4	35.0 \pm 0.3**	34.4 \pm 0.6	34.2 \pm 0.8	33.4 \pm 0.7	34.2 \pm 0.2	
Reticulocyte (%)	4.8 \pm 1.4	5.3 \pm 1.2	4.3 \pm 0.7	4.6 \pm 0.9	3.8 \pm 0.8	3.6 \pm 0.7	4.6 \pm 1.5	
Platelet ($\times 10000/\text{mm}^3$)	111.8 \pm 4.2	107.7 \pm 12.1	103.0 \pm 9.0	112.5 \pm 8.9	108.9 \pm 10.4	99.9 \pm 12.7	104.5 \pm 5.3	
PT (sec)	20.6 \pm 7.5	26.3 \pm 5.7	23.0 \pm 4.3	18.5 \pm 0.6	18.6 \pm 0.6	25.0 \pm 2.4	19.6 \pm 0.7**	
APTT (sec)	22.0 \pm 3.6	26.6 \pm 2.3*	25.0 \pm 2.0	22.2 \pm 2.6	21.5 \pm 2.0	25.2 \pm 1.4	22.7 \pm 0.6*	
WBC ($\times 100/\text{mm}^3$)	101 \pm 43	94 \pm 17	70 \pm 14	81 \pm 18	85 \pm 30	111 \pm 29	112 \pm 38	
Differential leukocyte counts (%)								
Band neutrophil	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	
Segmented neutrophil	7 \pm 4	6 \pm 6	9 \pm 5	15 \pm 9	14 \pm 8	7 \pm 4	5 \pm 5	
Eosinophil	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 1	0 \pm 0	0 \pm 0	
Basophil	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	
Monocyte	3 \pm 1	1 \pm 1	2 \pm 0	2 \pm 1	2 \pm 2	4 \pm 2	2 \pm 2	
Lymphocyte	90 \pm 4	92 \pm 6	89 \pm 5	83 \pm 10	83 \pm 7	89 \pm 6	93 \pm 5	
Female								
Number of animals	5	5	5	5	3	5	5	3
RBC ($\times 10000/\text{mm}^3$)	664 \pm 54	684 \pm 12	669 \pm 30	654 \pm 23	683 \pm 62	734 \pm 39	706 \pm 34	640 \pm 43*
Hemoglobin (g/dL)	14.4 \pm 1.0	14.5 \pm 0.4	14.5 \pm 0.5	13.7 \pm 0.6	14.0 \pm 1.2	15.1 \pm 0.5	14.1 \pm 0.7*	13.5 \pm 0.4**
Hematocrit (%)	42.0 \pm 3.0	41.7 \pm 1.2	41.3 \pm 1.1	39.8 \pm 2.5	40.9 \pm 2.4	43.6 \pm 2.2	41.4 \pm 2.2	38.8 \pm 1.2*
MCV (μm^3)	63.3 \pm 1.2	60.9 \pm 1.5	61.8 \pm 1.8	60.8 \pm 2.3	60.0 \pm 1.9	59.4 \pm 1.0	58.7 \pm 1.8	60.7 \pm 2.3
MCH (pg)	21.7 \pm 0.5	21.2 \pm 0.5	21.7 \pm 0.8	21.0 \pm 0.6	20.6 \pm 0.2	20.5 \pm 0.4	20.0 \pm 0.8	21.1 \pm 1.0
MCHC (%)	34.4 \pm 0.6	34.8 \pm 0.5	35.1 \pm 0.7	34.5 \pm 1.0	34.3 \pm 0.9	34.6 \pm 0.6	34.0 \pm 0.5	34.7 \pm 0.9
Reticulocyte (%)	3.3 \pm 1.5	2.6 \pm 0.6	2.8 \pm 0.6	3.5 \pm 0.9	3.4 \pm 1.3	4.0 \pm 1.7	2.9 \pm 0.4	4.8 \pm 2.1
Platelet ($\times 10000/\text{mm}^3$)	102.7 \pm 11.6	99.9 \pm 3.9	94.9 \pm 7.4	105.0 \pm 21.6	111.2 \pm 17.3	97.2 \pm 2.6	96.2 \pm 6.5	93.4 \pm 4.4
PT (sec)	18.0 \pm 0.9	18.0 \pm 1.4	16.8 \pm 0.8	18.6 \pm 0.9	18.1 \pm 0.2	16.8 \pm 1.0	16.8 \pm 1.1	16.5 \pm 0.7
APTT (sec)	23.6 \pm 2.2	23.4 \pm 2.1	22.1 \pm 2.2	24.5 \pm 2.6	23.5 \pm 0.6	23.3 \pm 1.2	23.4 \pm 3.4	20.0 \pm 1.6
WBC ($\times 100/\text{mm}^3$)	52 \pm 18	44 \pm 7	52 \pm 11	78 \pm 44	70 \pm 31	56 \pm 20	47 \pm 11	43 \pm 11
Differential leukocyte counts (%)								
Band neutrophil	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0
Segmented neutrophil	17 \pm 15	14 \pm 9	11 \pm 5	14 \pm 14	16 \pm 6	11 \pm 10	8 \pm 5	10 \pm 5
Eosinophil	0 \pm 0	1 \pm 1	1 \pm 1	1 \pm 1	0 \pm 1	0 \pm 0	0 \pm 0	0 \pm 1
Basophil	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 1
Monocyte	3 \pm 3	3 \pm 2	1 \pm 0	2 \pm 2	4 \pm 3	2 \pm 3	3 \pm 3	4 \pm 3
Lymphocyte	80 \pm 18	82 \pm 10	88 \pm 6	83 \pm 17	80 \pm 10	86 \pm 10	89 \pm 7	86 \pm 7

Parameter, mean \pm S.D., *: significantly different from 0 mg/kg, $p < 0.05$, **: significantly different from 0 mg/kg, $p < 0.01$

Table 3 Blood chemical examination in 28-day repeat dose oral toxicity test of 4-ethylbiphenyl in rats

Dose(mg/kg)	End of administration period					End of recovery period		
	0	20	100	500	1000	0	500	1000
Male								
Number of animals	5	5	5	5	5	5	4	0
Total protein(g/dL)	5.1 ± 0.3	5.0 ± 0.1	4.9 ± 0.1	5.2 ± 0.5	5.2 ± 0.2	5.5 ± 0.1	5.2 ± 0.2	
Albumin(g/dL)	3.0 ± 0.2	3.0 ± 0.1	3.0 ± 0.1	3.3 ± 0.3	3.3 ± 0.1	3.0 ± 0.1	2.9 ± 0.1	
A/G	1.46 ± 0.14	1.43 ± 0.14	1.57 ± 0.09	1.71 ± 0.20*	1.79 ± 0.14**	1.19 ± 0.09	1.24 ± 0.16	
Glucose(mg/dL)	161 ± 18	137 ± 17*	122 ± 7**	113 ± 10**	121 ± 8**	141 ± 17	119 ± 7*	
Total cholesterol(mg/dL)	44 ± 4	37 ± 5	30 ± 5*	31 ± 4*	49 ± 12	42 ± 7	44 ± 3	
Triglyceride(mg/dL)	69 ± 35	72 ± 28	59 ± 18	81 ± 28	75 ± 50	69 ± 15	78 ± 9	
BUN(mg/dL)	13 ± 2	12 ± 3	11 ± 3	13 ± 2	15 ± 4	16 ± 2	15 ± 3	
Creatinine(mg/dL)	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.9 ± 0.1**	1.2 ± 0.2**	0.6 ± 0.1	0.7 ± 0.1	
Inorg. Phos.(mg/dL)	8.3 ± 0.7	7.8 ± 1.0	7.6 ± 0.3	8.3 ± 0.5	8.4 ± 0.9	7.1 ± 0.4	8.0 ± 0.3**	
Ca(mg/dL)	9.3 ± 0.5	8.9 ± 0.3	9.0 ± 0.2	9.6 ± 0.2	9.6 ± 0.5	9.1 ± 0.2	9.2 ± 0.3	
Na(mEq/L)	144.7 ± 0.7	145.1 ± 0.6	144.1 ± 0.8	145.2 ± 0.6	146.1 ± 1.3*	145.2 ± 0.7	144.7 ± 1.1	
K(mEq/L)	3.97 ± 0.31	3.86 ± 0.16	4.06 ± 0.18	3.97 ± 0.46	4.21 ± 0.32	3.78 ± 0.13	4.33 ± 0.80	
Cl(mEq/L)	105.3 ± 1.1	107.9 ± 1.4	108.6 ± 1.4*	108.7 ± 1.1**	110.5 ± 2.3**	107.3 ± 1.1	108.1 ± 1.4	
ALP(U/L)	370 ± 36	400 ± 95	344 ± 75	305 ± 65	399 ± 134	304 ± 79	311 ± 44	
LDH(U/L)	193 ± 93	154 ± 69	164 ± 75	147 ± 13	233 ± 135	135 ± 46	153 ± 58	
GPT(U/L)	26 ± 2	27 ± 6	28 ± 5	41 ± 12	70 ± 24*	29 ± 2	32 ± 2	
GOT(U/L)	64 ± 12	63 ± 9	64 ± 6	58 ± 9	72 ± 14	59 ± 4	61 ± 9	
γ-GTP(U/L)	0 ± 0	0 ± 0	0 ± 0	0 ± 1	8 ± 5**	0 ± 0	0 ± 0	
Female								
Number of animals	5	5	5	5	5	5	5	5
Total protein(g/dL)	5.1 ± 0.1	5.2 ± 0.1	5.1 ± 0.1	5.3 ± 0.5	5.6 ± 0.4	5.6 ± 0.2	5.8 ± 0.3	5.2 ± 0.1*
Albumin(g/dL)	3 ± 0.4	3.2 ± 0.2	3.1 ± 0.1	3.2 ± 0.8	3.4 ± 0.3	3.5 ± 0.2	3.4 ± 0.3	3.2 ± 0.1
A/G	1.48 ± 0.40	1.58 ± 0.22	1.59 ± 0.12	1.54 ± 0.51	1.52 ± 0.10	1.61 ± 0.19	1.45 ± 0.18	1.65 ± 0.16
Glucose(mg/dL)	117 ± 8	110 ± 15	119 ± 6	120 ± 8	133 ± 14	125 ± 16	107 ± 14	101 ± 11
Total cholesterol(mg/dL)	47 ± 9	49 ± 8	47 ± 5	39 ± 10	57 ± 12	66 ± 12	64 ± 10	68 ± 9
Triglyceride(mg/dL)	42 ± 19	51 ± 9	80 ± 18	78 ± 28	83 ± 59	58 ± 15	74 ± 8	103 ± 31*
BUN(mg/dL)	17 ± 2	18 ± 6	18 ± 4	17 ± 2	24 ± 3	18 ± 3	19 ± 5	13 ± 1*
Creatinine(mg/dL)	0.5 ± 0.1	0.6 ± 0.1	0.6 ± 0	0.9 ± 0.1**	1.5 ± 0.2**	0.7 ± 0.1	0.8 ± 0.1	0.6 ± 0.1
Inorg. Phos.(mg/dL)	7.4 ± 0.8	7.8 ± 0.6	7.7 ± 0.6	7.6 ± 0.8	9.5 ± 1.5**	5.6 ± 0.6	7.0 ± 1.7	6.6 ± 0.7
Ca(mg/dL)	8.8 ± 0.1	9.0 ± 0.4	8.9 ± 0.1	9.0 ± 0.1	9.4 ± 0.4*	9.0 ± 0.3	9.2 ± 0.5	9.0 ± 0.2
Na(mEq/L)	144.9 ± 0.6	144.6 ± 0.6	145.5 ± 0.9	144.1 ± 2.7	145.7 ± 1.0	144.4 ± 0.6	144.4 ± 0.7	145.9 ± 0.2*
K(mEq/L)	3.62 ± 0.24	3.91 ± 0.23	3.74 ± 0.16	3.39 ± 0.47	3.68 ± 0.08	3.72 ± 0.41	4.55 ± 0.74	3.78 ± 0.73
Cl(mEq/L)	109.1 ± 1.2	108.8 ± 0.8	111.2 ± 1.6	110.9 ± 1.9	108.7 ± 2.1	107.9 ± 1.3	109.7 ± 3.1	111.5 ± 1.3
ALP(U/L)	245 ± 52	212 ± 27	200 ± 47	240 ± 66	265 ± 122	152 ± 42	166 ± 42	202 ± 28
LDH(U/L)	123 ± 40	120 ± 28	130 ± 44	147 ± 48	227 ± 66*	120 ± 39	119 ± 63	383 ± 353
GPT(U/L)	22 ± 3	23 ± 2	24 ± 7	39 ± 14	43 ± 7	22 ± 2	25 ± 5	118 ± 156
GOT(U/L)	62 ± 6	64 ± 5	63 ± 11	59 ± 8	57 ± 5	64 ± 6	57 ± 7	150 ± 148
γ-GTP(U/L)	0 ± 0	0 ± 0	0 ± 0	2 ± 0	10 ± 2*	0 ± 0	1 ± 1	2 ± 1**

Parameter, mean±S.D., *: significantly different from 0 mg/kg, p<0.05, **: significantly different from 0 mg/kg, p<0.01

Table 4 Organ weights in 28-day repeat dose oral toxicity test of 4-ethylbiphenyl in rats

Dose (mg/kg)	End of administration period					End of recovery period		
	0	20	100	500	1000	0	500	1000
Male								
Number of animals	5	5	5	5	5	5	4	0
Body weight (g)	336.2 ± 23.4	334.1 ± 26.0	324.0 ± 6.7	269.3 ± 25.5**	217.7 ± 34.7**	412.9 ± 37.4	340.4 ± 34.4*	
Absolute organ weights (mg)								
Brain	1852.4 ± 44.9	1888.6 ± 35.3	1920 ± 33.1	1808.6 ± 69.1	1757.5 ± 82.5*	2007.5 ± 57.7	1916.4 ± 79.1	
Thymus	771.7 ± 89.1	703.5 ± 97.5	714.4 ± 236.0	428.7 ± 89.0**	237.6 ± 103.0**	559.9 ± 52.8	529.2 ± 60.3	
Heart	1123.4 ± 61.4	1138.3 ± 74.9	1149.6 ± 47.8	892.8 ± 87.2**	737.3 ± 117.6**	1362.7 ± 121.7	1112.2 ± 101.3*	
Liver	12147.7 ± 1870.8	11592.0 ± 1180.1	12437.8 ± 547.7	15379.9 ± 2045.8*	14580.2 ± 2523.0	13752.5 ± 2181.6	11013.3 ± 1499.8	
Kidneys	2631.9 ± 256.9	2667.2 ± 203.6	2668.4 ± 43.8	2856.6 ± 302.1	2431.0 ± 341.3	2902.7 ± 99.5	2785.6 ± 302.5	
Spleen	717.5 ± 35.6	611.0 ± 69.5	674.4 ± 104.5	537.0 ± 78.7**	429.3 ± 82.4**	803.8 ± 124.1	761.1 ± 186.0	
Adrenal glands	44.5 ± 8.1	50.0 ± 4.5	43.1 ± 4.5	44.9 ± 3.1	48.5 ± 5.7	54.6 ± 5.3	51.7 ± 15.7	
Testes	2891.3 ± 181.3	3056.8 ± 160.8	2845.5 ± 186.2	2929.2 ± 111.8	2282.6 ± 378.5**	3268.2 ± 214.3	3241.6 ± 103.3	
Epididymides	570.9 ± 70.5	594.4 ± 31.0	586.5 ± 14.3	570.1 ± 48.0	373.7 ± 136.1	946.3 ± 53.0	881.9 ± 71.2	
Relative organ weights (mg/g)								
Brain	5.528 ± 0.348	5.674 ± 0.361	5.928 ± 0.166	6.751 ± 0.488	8.225 ± 1.235**	4.902 ± 0.572	5.658 ± 0.395	
Thymus	2.309 ± 0.344	2.105 ± 0.252	2.204 ± 0.724	1.578 ± 0.191*	1.051 ± 0.333**	1.367 ± 0.208	1.579 ± 0.328	
Heart	3.349 ± 0.207	3.410 ± 0.121	3.548 ± 0.119	3.318 ± 0.161	3.39 ± 0.144	3.304 ± 0.169	3.273 ± 0.167	
Liver	36.017 ± 3.606	34.659 ± 1.413	38.398 ± 1.788	56.940 ± 2.539**	67.082 ± 5.198**	33.168 ± 2.568	32.279 ± 1.597	
Kidneys	7.817 ± 0.316	8.014 ± 0.780	8.238 ± 0.193	10.695 ± 1.681*	11.211 ± 0.676*	7.064 ± 0.503	8.208 ± 0.767*	
Spleen	2.146 ± 0.246	1.831 ± 0.181	2.086 ± 0.358	1.990 ± 0.166	1.971 ± 0.213	1.964 ± 0.377	2.216 ± 0.361	
Adrenal glands	0.132 ± 0.019	0.151 ± 0.019	0.133 ± 0.015	0.168 ± 0.022	0.228 ± 0.048**	0.133 ± 0.012	0.151 ± 0.036	
Testes	8.628 ± 0.726	9.186 ± 0.756	8.781 ± 0.500	10.949 ± 1.007**	10.481 ± 0.442**	7.965 ± 0.836	9.576 ± 0.731*	
Epididymides	1.701 ± 0.202	1.792 ± 0.222	1.811 ± 0.047	2.125 ± 0.185	1.669 ± 0.424	2.311 ± 0.284	2.597 ± 0.147	
Female								
Number of animals	5	5	5	5	3	5	5	3
Body weight (g)	232.7 ± 11.9	223.3 ± 6.7	221.1 ± 21.0	201.8 ± 22.7*	178.9 ± 11.9**	259.0 ± 19.9	223.5 ± 12.2*	225.5 ± 16.0*
Absolute organ weights (mg)								
Brain	1758.3 ± 48.6	1803.0 ± 33.1	1753.6 ± 40.5	1772.5 ± 35.5	1657.3 ± 55.9*	1823.3 ± 30.0	1728.9 ± 88.7	1722.6 ± 51.0
Thymus	552.8 ± 90.5	430.0 ± 84.2	515.5 ± 93.3	338.2 ± 22.4**	272.4 ± 41.6**	438.3 ± 94.0	373.3 ± 42.9	405.8 ± 105.5
Heart	787.6 ± 55.0	754.1 ± 45.7	750.7 ± 73.4	675.1 ± 66.8	669.7 ± 116.9	903.7 ± 40.1	781.8 ± 50.9**	826.1 ± 45.5
Liver	7427.1 ± 954.7	6964.8 ± 324.6	8291.8 ± 913.4	11840.6 ± 2035.3*	13242.9 ± 1431.2*	7787.4 ± 815.4	7834.2 ± 913.4	8320.1 ± 369.3
Kidneys	1780.5 ± 96.2	1804.2 ± 117.0	1757.8 ± 142.4	2054.2 ± 373.4	2273.9 ± 261.7*	1792.6 ± 130.9	1925.0 ± 131.4	1957.9 ± 81.4
Spleen	582.7 ± 81.5	451.5 ± 60.9	503.1 ± 107.7	536.5 ± 141.2	376.6 ± 39.5	532.1 ± 39.8	525.5 ± 58.0	539.9 ± 90.0
Adrenal glands	60.5 ± 4.7	58.2 ± 7.6	59.4 ± 5.1	60.6 ± 11.8	55.4 ± 8.2	73.1 ± 7.6	59.4 ± 7.9*	54.0 ± 7.8*
Ovaries	86.4 ± 18.5	92.6 ± 15.3	83.4 ± 5.2	84.2 ± 5.4	69.2 ± 21.6	93.7 ± 15.0	94.4 ± 8.4	75.0 ± 23.8
Relative organ weights (mg/g)								
Brain	7.574 ± 0.497	8.079 ± 0.260	7.989 ± 0.788	8.860 ± 0.844*	9.291 ± 0.707**	7.075 ± 0.596	7.743 ± 0.321	7.669 ± 0.699
Thymus	2.375 ± 0.365	1.921 ± 0.340	2.329 ± 0.317	1.686 ± 0.122**	1.528 ± 0.276**	1.689 ± 0.332	1.674 ± 0.218	1.791 ± 0.391
Heart	3.386 ± 0.209	3.377 ± 0.178	3.403 ± 0.277	3.359 ± 0.278	3.733 ± 0.484	3.499 ± 0.202	3.502 ± 0.201	3.667 ± 0.131
Liver	31.854 ± 3.080	31.194 ± 1.218	37.493 ± 2.158*	58.391 ± 3.921**	73.895 ± 3.303**	30.039 ± 1.711	34.979 ± 2.416**	36.947 ± 1.368**
Kidneys	7.656 ± 0.354	8.080 ± 0.462	7.961 ± 0.266	10.171 ± 1.436*	12.728 ± 1.503*	6.936 ± 0.490	8.620 ± 0.489**	8.729 ± 1.015**
Spleen	2.503 ± 0.331	2.029 ± 0.330	2.272 ± 0.383	2.629 ± 0.449	2.105 ± 0.192	2.058 ± 0.135	2.357 ± 0.282	2.385 ± 0.260
Adrenal glands	0.260 ± 0.024	0.260 ± 0.029	0.271 ± 0.035	0.300 ± 0.047	0.309 ± 0.025	0.282 ± 0.016	0.265 ± 0.030	0.241 ± 0.049
Ovaries	0.370 ± 0.072	0.415 ± 0.072	0.379 ± 0.027	0.421 ± 0.049	0.387 ± 0.121	0.362 ± 0.063	0.422 ± 0.024	0.337 ± 0.124

Parameter, mean ± S.D., *: significantly different from 0 mg/kg, p < 0.05, **: significantly different from 0 mg/kg, p < 0.01

Table 5 Histopathological examination in 28-day repeat dose oral toxicity test of 4-ethylbiphenyl in rats

Sex	Dose (mg/kg)	Male					Female					End of recovery period				
		End of administration period					End of recovery period		End of administration period					End of recovery period		
		0	20	100	500	1000	0	500	0	20	100	500	1000	0	500	1000
Number of animals (Liver)		5	5	5	5	5	5	4	5	5	5	5	3	5	5	3
Hypertrophy, eosinophilic and granular cytoplasm, hepatocyte	±	0	0	3	0	0	0	0	0	0	3	0	0	0	0	0
	1+	0	0	0	5	0	0	0	0	0	0	5	0	0	0	0
	2+	0	0	0	0	5	0	0	0	0	0	0	3	0	0	0
					**	**					**	**				
Necrosis, focal	Pos.	0	0	3	5##	5##	0	0	0	0	3	5##	3#	0	0	0
	±	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
	1+	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
	Pos.	0	0	0	1	2	0	0	0	0	1	0	0	0	0	0
Deposit, hemosiderin, Kupffer cell	±	0	0	0	2	1	0	2	0	0	0	2	1	0	2	3
	1+	0	0	0	1	3	0	0	0	0	0	0	2	0	1	0
											**	**			**	
Hypertrophy, Kupffer cell	Pos.	0	0	0	3	4#	0	2	0	0	0	2	3#	0	3	3#
	±	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Fibrosis, focal	Pos.	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
	Pos.	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Fibrosis, capsule	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	Pos.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Fatty change, periportal	±	4	3	2	2	4	3	4	2	3	4	4	2	2	4	1
	1+	1	1	0	0	0	2	0	3	2	0	0	0	3	1	2
	Pos.	5	4	2	2	4	5	4	5	5	4	4	2	5	5	3
(Thymus) Atrophy	±	0	0	0	2	4	0	0	0	0	0	2	3	0	0	0
	1+	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
					**	**					**	**				
Hemorrhage	Pos.	0	0	0	2	5##	0	0	0	0	0	2	3#	0	0	0
	±	1	0	0	1	1	1	0	0	0	0	0	0	0	0	0
	Pos.	1	0	0	1	1	1	0	0	0	0	0	0	0	0	0
(Spleen) Hematopoiesis, extramedullary	±	0	1	0	2	5	1	0	4	5	5	5	3	4	4	2
	1+	5	4	5	3	0	4	4	1	0	0	0	0	1	1	1
					**	**					**	**				
Deposit, hemosiderin	Pos.	5	5	5	5	5	5	4	5	5	5	5	3	5	5	3
	±	5	4	5	2	0	0	0	2	1	1	0	0	0	0	0
	1+	0	1	0	3	5	4	1	3	4	4	3	0	2	0	0
	2+	0	0	0	0	0	1	3	0	0	0	2	3	3	5	3
					**	**					**	**				
Necrosis, focal	Pos.	5	5	5	5	5	5	4	5	5	5	5	3	5	5	3
	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
	Pos.	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
(Kidney) Necrosis, papilla	±	0	0	0	0	0	0	1	0	0	0	1	0	0	1	0
	1+	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	2+	0	0	0	1	1	0	0	0	0	0	0	1	0	0	1
	Pos.	0	0	0	1	1	0	1	0	0	0	1	2	0	1	2
Mineralization, papilla	±	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	1	0	0	0	0	0	0	0	1	0	0	2
	Pos.	0	0	0	1	1	0	0	0	0	0	0	1	0	0	2
Basophilic tubule, cortex	±	2	3	0	0	0	3	0	5	4	0	0	0	3	1	0
	1+	0	0	4	2	1	0	1	0	0	0	0	0	0	0	0
	2+	0	0	1	3	4	0	3	0	0	5	4	2	0	4	1
	3+	0	0	0	0	0	0	0	0	0	0	1	1	0	0	2
					**	**				**	**	**	**	*	**	
Basophilic tubule, medulla	Pos.	2	3	5	5	5	3	4	5	4	5	5	3	3	5	3
	±	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
	1+	0	0	0	1	2	0	0	0	0	0	0	2	0	3	2
	2+	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1
					**	**					**	**	**	**	**	
Dilatation, tubule, cortex	Pos.	0	0	0	1	2	0	0	0	0	0	2	3#	0	3	3#
	±	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	1	2	0	0	0	0	0	2	2	0	1	0
	2+	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
					**	**					**	**	**	*	**	
	Pos.	0	0	0	2	2	0	0	0	0	0	2	3#	0	1	0

-: negative, ±: very slight, 1+: slight, 2+: moderate, 3+: severe, Pos.: total of positive grade

** : Significantly different from 0 mg/kg, p<0.01 (Two-tailed Mann-Whitney U test)

: Significantly different from 0 mg/kg, p<0.05 (One-tailed Fisher exact test)

: Significantly different from 0 mg/kg, p<0.01 (One-tailed Fisher exact test)

Table 5 (Continued)

Sex	Dose (mg/kg)	Male						Female								
		— End of administration period —			— End of recovery period —			— End of administration period —			— End of recovery period —					
		0	20	100	500	1000	0	500	0	20	100	500	1000	0	500	1000
Number of animals (Kidney)		5	5	5	5	5	5	4	5	5	5	5	3	5	5	3
Dilatation, tubule, medulla	±	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	1	0	0	0	0	0	0	2	1	0	0	0
	2+	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	Pos.	0	0	0	1	1	0	0	0	0	0	2	2	0	0	0
Cast, proteinous	±	0	0	0	2	2	0	0	0	0	0	2	1	0	0	0
	1+	0	0	0	3	1	0	2	0	0	0	1	0	0	2	1
					**											
	Pos.	0	0	0	5##	3	0	2	0	0	0	3	1	0	2	1
Mineralization, cortico-medullary junction	±	0	0	0	4	0	0	0	3	1	2	0	0	0	0	0
	1+	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0
	Pos.	0	0	1	4#	0	0	0	4	1	2	0#	0	0	0	0
Eosinophilic body	±	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	1+	1	0	0	0	0	2	0	0	0	0	0	0	0	0	0
	2+	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Pos.	3	0	0	0	0	3	0	0	0	0	0	0	0	0	0
Cyst	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	Pos.	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
(Forestomach)																
Erosion	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0
	Pos.	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0
Hyperplasia, epithelium	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	1	4	0	0	0	0	0	2	0	0	0	0
	2+	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
	Pos.	0	0	0	1	4#	0	0	0	0	0	1	2	0	0	0
Edema, submucosa	±	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0
	2+	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	Pos.	0	0	0	1	2	0	0	0	0	1	0	0	0	0	0
Hemorrhage, submucosa	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	Pos.	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Fibrosis, serosa	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	Pos.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
(Glandular stomach)																
Erosion	±	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	1	0	0	0	0	1	1	3	0	0	0
													**			
	Pos.	0	0	0	0	2	0	0	0	0	1	1	3#	0	0	0
Ulcer	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
	Pos.	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Edema, submucosa	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
	Pos.	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Inflammation, serosa and submucosa	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1+	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
	Pos.	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
(Prostate)																
Atrophy	±	0	0	0	1	2	0	0								
	1+	0	0	0	0	1	0	0								
	2+	0	0	0	0	1	0	0								
	Pos.	0	0	0	1	4#	0	0								
Cellular infiltration, lymphocyte	±	0	2	0	1	0	2	1								
	1+	0	0	2	0	0	1	1								
	Pos.	1	2	2	1	0	3	2								
(Seminal vesicle)																
Atrophy	±	0	0	0	0	2	0	0								
	1+	0	0	0	0	1	0	0								
	2+	0	0	0	0	1	0	0								
	Pos.	0	0	0	0	4#	0	0								

-: negative, ±: very slight, 1+: slight, 2+: moderate, 3+: severe, Pos.: total of positive grade
 **: Significantly different from 0 mg/kg, p<0.01 (Two-tailed Mann-Whitney U test)
 #: Significantly different from 0 mg/kg, p<0.05 (One-tailed Fisher exact test)
 ##: Significantly different from 0 mg/kg, p<0.01 (One-tailed Fisher exact test)