Table 29 Hematological examination of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
RBC	(10^4/μL)	866 ± 45	874 ± 30	850 ± 19	861 ± 57
HGB	(g/dL)	15.9 ± 0.5	16.1 ± 0.5	16.2 ± 0.4	15.9 ± 0.8
HCT	(%)	46.8 ± 1.9	47.5 ± 1.8	47.4 ± 0.8	46.7 ± 2.4
MCV	(fL)	54.1 ± 1.4	54.3 ± 1.4	55.8 ± 1.0	54.3 ± 1.4
MCH	(pg)	18.4 ± 0.7	18.4 ± 0.5	19.1 ± 0.5	18.5 ± 0.6
MCHC	(g/dL)	33.9 ± 0.5	33.9 ± 0.5	34.3 ± 0.5	34.1 ± 0.2
PLT	(10^4/μL)	97.8 ± 10.3	97.3 ± 11.1	99.7 ± 13.4	94.0 ± 3.9
RET	(‰)	29 ± 1	34 ± 5	32 ± 5	29 ± 4
PT	(sec.)	19.8 ± 2.7	21.6 ± 3.3	20.1 ± 3.0	19.7 ± 4.2
APTT	(sec.)	22.9 ± 1.3	23.9 ± 2.5	23.1 ± 1.4	23.5 ± 3.8
Fbg	(mg/dL)	208.1 ± 14.7	210.4 ± 9.4	209.9 ± 6.6	196.3 ± 6.3
WBC	(10^2/μL)	56 ± 12	60 ± 10	59 ± 19	64 ± 11
Differential leukocyte (%)					
Lymphocyte		86.2 ± 3.0	87.3 ± 4.6	87.8 ± 3.5	87.5 ± 3.9
Neutrophil		13.0 ± 3.5	11.5 ± 3.6	11.7 ± 3.7	11.3 ± 4.0
Eosinophil		0.7 ± 0.8	0.7 ± 1.0	0.2 ± 0.4	0.5 ± 0.8
Basophil		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Monocyte		0.2 ± 0.4	0.5 ± 0.5	0.3 ± 0.5	0.7 ± 0.5

Each value shows mean ± S.D.

Table 30 Hematological examination of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of females		6	6	6	6
RBC	(10^4/μL)	722 ± 36	687 ± 34	719 ± 27	721 ± 38
HGB	(g/dL)	14.7 ± 0.4	14.2 ± 0.5	14.1 ± 0.7	14.6 ± 0.8
HCT	(%)	42.0 ± 1.3	40.2 ± 2.2	41.1 ± 1.7	42.0 ± 2.3
MCV	(fL)	58.3 ± 1.7	58.5 ± 2.1	57.2 ± 1.1	58.3 ± 1.5
MCH	(pg)	20.4 ± 0.7	20.6 ± 0.6	19.6 ± 0.3	20.2 ± 0.4
MCHC	(g/dL)	34.9 ± 0.7	35.3 ± 1.0	34.2 ± 0.7	34.7 ± 0.5
PLT	(10^4/μL)	109.3 ± 7.1	89.7 ± 12.1 **	95.0 ± 9.6 *	96.3 ± 7.4
RET	(‰)	59 ± 11	59 ± 7	68 ± 8	68 ± 14
PT	(sec.)	15.9 ± 0.6	16.2 ± 0.4	16.1 ± 0.4	16.0 ± 0.8
APTT	(sec.)	16.6 ± 0.7	16.8 ± 1.2	17.1 ± 0.8	17.1 ± 0.9
Fbg	(mg/dL)	224.3 ± 23.4	211.6 ± 33.7	214.8 ± 31.7	212.8 ± 20.9
WBC	(10^2/μL)	46 ± 14	39 ± 10	43 ± 7	39 ± 7
Differential leukocyte (%)					
Lymphocyte		84.0 ± 3.5	85.0 ± 7.2	83.7 ± 6.1	86.2 ± 2.9
Neutrophil		14.3 ± 4.6	13.8 ± 6.5	15.2 ± 4.9	12.2 ± 2.5
Eosinophil		0.8 ± 1.0	0.3 ± 0.8	0.3 ± 0.5	1.0 ± 0.9
Basophil		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Monocyte		0.8 ± 0.8	0.8 ± 0.8	0.8 ± 1.0	0.7 ± 0.5

Each value shows mean ± S.D.

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

Table 31 Hematological examination of male rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
RBC	(10^4/μL)	868 ± 33	841 ± 39	859 ± 24	846 ± 44
HGB	(g/dL)	15.9 ± 0.4	15.5 ± 0.8	15.8 ± 0.6	15.4 ± 0.7
HCT	(%)	46.8 ± 1.3	45.6 ± 2.0	46.9 ± 1.8	45.8 ± 2.4
MCV	(fL)	53.9 ± 0.7	54.3 ± 1.9	54.6 ± 1.1	54.2 ± 1.7
MCH	(pg)	18.3 ± 0.4	18.5 ± 1.0	18.4 ± 0.4	18.2 ± 0.7
MCHC	(g/dL)	33.9 ± 0.5	34.0 ± 0.6	33.7 ± 0.3	33.6 ± 0.5
PLT	(10^4/μL)	99.3 ± 8.8	102.0 ± 9.3	104.3 ± 10.3	100.0 ± 13.2
RET	(‰)	28 ± 4	27 ± 4	33 ± 8	29 ± 7
PT	(sec.)	19.4 ± 2.2	17.4 ± 1.5	18.3 ± 1.7	20.0 ± 1.2
APTT	(sec.)	22.2 ± 2.7	21.9 ± 1.0	21.9 ± 1.1	23.0 ± 1.0
Fbg	(mg/dL)	199.1 ± 10.1	195.9 ± 11.6	190.2 ± 13.1	186.8 ± 9.9
WBC	(10^2/μL)	58 ± 11	61 ± 12	63 ± 18	61 ± 12
Differential leukocyte (%)					
Lymphocyte		88.7 ± 3.2	86.5 ± 4.6	87.0 ± 6.4	87.8 ± 4.4
Neutrophil		10.2 ± 2.6	12.0 ± 5.0	11.8 ± 6.0	10.5 ± 3.6
Eosinophil		0.5 ± 0.5	0.7 ± 0.5	0.7 ± 0.8	0.8 ± 1.0
Basophil		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Monocyte		0.7 ± 0.5	0.8 ± 0.8	0.5 ± 0.5	0.8 ± 0.8

Each value shows mean ± S.D.

Table 32 Hematological examination of female rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole	
mg/kg		0	250	1000
Number of females		6	6	6
RBC	(10^4/μL)	761 ± 19	743 ± 38	760 ± 25
HGB	(g/dL)	15.0 ± 0.5	14.6 ± 0.7	14.8 ± 0.5
HCT	(%)	43.3 ± 1.2	41.2 ± 1.9	42.7 ± 1.5
MCV	(fL)	56.9 ± 1.4	55.4 ± 1.4	56.3 ± 0.7
MCH	(pg)	19.7 ± 0.5	19.7 ± 0.7	19.5 ± 0.3
MCHC	(g/dL)	34.6 ± 0.4	35.5 ± 0.3 **	34.7 ± 0.3
PLT	(10^4/μL)	94.5 ± 19.0	94.8 ± 3.8	92.9 ± 9.7
RET	(‰)	27 ± 6	27 ± 5	26 ± 4
PT	(sec.)	15.2 ± 1.1	15.1 ± 0.4	15.2 ± 0.3
APTT	(sec.)	17.9 ± 1.2	17.3 ± 1.2	17.0 ± 1.0
Fbg	(mg/dL)	159.3 ± 8.6	162.8 ± 5.7	163.9 ± 5.8
WBC	(10^2/μL)	31 ± 6	33 ± 11	33 ± 8
Differential leukocyte (%)				
Lymphocyte		83.8 ± 3.9	86.3 ± 4.3	89.5 ± 3.2 *
Neutrophil		15.2 ± 4.4	12.2 ± 4.2	9.2 ± 3.5 *
Eosinophil		0.2 ± 0.4	0.8 ± 0.4	0.8 ± 1.0
Basophil		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Monocyte		0.8 ± 0.8	0.7 ± 0.5	0.5 ± 0.5

Each value shows mean ± S.D.

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

Table 33 Blood chemical examination of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
AST	(IU/L)	79.2 ± 11.8	82.5 ± 8.1	83.2 ± 11.2	91.1 ± 22.5
ALT	(IU/L)	22.0 ± 5.0	23.9 ± 4.3	23.1 ± 6.8	27.9 ± 11.0
ALP	(IU/L)	329.4 ± 69.2	370.4 ± 47.8	380.3 ± 79.4	339.6 ± 52.3
γ-GTP	(IU/L)	0.36 ± 0.22	0.30 ± 0.12	0.32 ± 0.25	0.46 ± 0.21
TP	(g/dL)	5.72 ± 0.16	5.41 ± 0.26 *	5.52 ± 0.16	5.49 ± 0.19
Alb	(g/dL)	2.84 ± 0.13	2.76 ± 0.15	2.86 ± 0.13	2.82 ± 0.14
A/G		0.99 ± 0.06	1.05 ± 0.08	1.08 ± 0.07	1.05 ± 0.04
T-Bil	(mg/dL)	0.13 ± 0.01	0.12 ± 0.01 *	0.12 ± 0.01	0.12 ± 0.01 *
UN	(mg/dL)	18.4 ± 1.6	18.0 ± 1.5	17.7 ± 2.1	18.2 ± 1.2
CRE	(mg/dL)	0.30 ± 0.04	0.30 ± 0.03	0.29 ± 0.01	0.29 ± 0.02
Glu	(mg/dL)	115.1 ± 7.2	116.2 ± 6.0	117.0 ± 15.1	119.2 ± 13.0
T-Cho	(mg/dL)	57.9 ± 13.3	51.5 ± 13.0	55.9 ± 11.5	54.0 ± 13.2
TG	(mg/dL)	39.7 ± 14.7	36.3 ± 11.7	41.2 ± 17.0	54.6 ± 29.1
Na	(mEq/L)	144.5 ± 1.2	145.9 ± 0.5	145.2 ± 0.8	145.1 ± 1.2
K	(mEq/L)	4.32 ± 0.23	4.42 ± 0.16	4.26 ± 0.21	4.23 ± 0.12
Cl	(mEq/L)	105.6 ± 1.1	107.0 ± 0.4 *	106.4 ± 0.8	106.2 ± 0.7
Ca	(mg/dL)	9.7 ± 0.2	9.5 ± 0.2	9.6 ± 0.1	9.6 ± 0.3
IP	(mg/dL)	7.2 ± 0.7	7.3 ± 0.7	7.5 ± 0.5	7.5 ± 0.8

Each value shows mean ± S.D.

Significantly different from control group (*: $P<0.05$).

Table 34 Blood chemical examination of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of females		6	6	6	6
AST	(IU/L)	85.4 ± 12.0	80.3 ± 10.0	78.8 ± 6.2	79.3 ± 10.6
ALT	(IU/L)	17.6 ± 2.5	19.8 ± 6.6	16.1 ± 1.9	19.3 ± 4.3
ALP	(IU/L)	134.8 ± 15.7	182.7 ± 41.4	150.4 ± 47.1	165.6 ± 23.3
γ-GTP	(IU/L)	0.55 ± 0.16	0.57 ± 0.15	0.50 ± 0.17	0.55 ± 0.16
TP	(g/dL)	5.98 ± 0.30	6.21 ± 0.24	6.11 ± 0.33	6.15 ± 0.22
Alb	(g/dL)	2.99 ± 0.28	3.10 ± 0.23	3.07 ± 0.19	3.10 ± 0.24
A/G		1.00 ± 0.11	1.01 ± 0.13	1.01 ± 0.05	1.02 ± 0.09
T-Bil	(mg/dL)	0.12 ± 0.01	0.13 ± 0.01	0.12 ± 0.01	0.13 ± 0.01
UN	(mg/dL)	23.5 ± 2.8	23.2 ± 1.3	23.5 ± 3.7	20.5 ± 3.2
CRE	(mg/dL)	0.40 ± 0.03	0.38 ± 0.02	0.37 ± 0.03	0.39 ± 0.02
Glu	(mg/dL)	111.9 ± 9.8	117.8 ± 5.5	109.8 ± 5.0	121.7 ± 7.9
T-Cho	(mg/dL)	71.0 ± 4.8	77.5 ± 13.4	82.3 ± 24.6	80.5 ± 15.2
TG	(mg/dL)	30.7 ± 6.8	31.9 ± 11.6	34.8 ± 23.4	34.3 ± 14.6
Na	(mEq/L)	139.4 ± 0.5	139.9 ± 1.3	140.2 ± 1.5	140.3 ± 0.5
K	(mEq/L)	4.27 ± 0.23	4.05 ± 0.20	4.26 ± 0.24	4.16 ± 0.30
Cl	(mEq/L)	103.7 ± 1.8	103.6 ± 2.6	104.2 ± 1.4	104.0 ± 1.2
Ca	(mg/dL)	10.3 ± 0.1	10.4 ± 0.3	10.3 ± 0.5	10.4 ± 0.3
IP	(mg/dL)	6.5 ± 0.4	6.8 ± 0.6	7.0 ± 0.7	6.6 ± 0.9

Each value shows mean ± S.D.

Table 35 Blood chemical examination of male rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
AST	(IU/L)	82.4 ± 12.3	78.2 ± 8.4	79.5 ± 4.1	83.5 ± 9.3
ALT	(IU/L)	32.2 ± 3.8	31.4 ± 3.9	32.4 ± 3.4	33.9 ± 4.8
ALP	(IU/L)	287.5 ± 41.7	275.2 ± 37.1	313.2 ± 36.2	311.2 ± 40.9
γ-GTP	(IU/L)	0.46 ± 0.18	0.33 ± 0.15	0.39 ± 0.08	0.37 ± 0.11
TP	(g/dL)	5.45 ± 0.19	5.45 ± 0.30	5.41 ± 0.26	5.34 ± 0.20
Alb	(g/dL)	2.72 ± 0.14	2.67 ± 0.13	2.71 ± 0.03	2.68 ± 0.17
A/G		1.00 ± 0.08	0.96 ± 0.07	1.01 ± 0.11	1.01 ± 0.10
T-Bil	(mg/dL)	0.11 ± 0.01	0.11 ± 0.02	0.12 ± 0.01	0.11 ± 0.01
UN	(mg/dL)	18.7 ± 2.9	17.5 ± 1.4	19.0 ± 2.2	18.6 ± 2.0
CRE	(mg/dL)	0.31 ± 0.02	0.30 ± 0.02	0.32 ± 0.02	0.31 ± 0.03
Glu	(mg/dL)	124.4 ± 12.7	116.8 ± 7.9	119.9 ± 18.8	119.4 ± 14.3
T-Cho	(mg/dL)	56.1 ± 6.1	53.7 ± 3.4	59.0 ± 10.5	44.9 ± 13.3
TG	(mg/dL)	47.9 ± 20.7	43.1 ± 14.6	48.4 ± 14.4	38.4 ± 13.2
Na	(mEq/L)	144.4 ± 1.3	145.1 ± 1.3	144.3 ± 0.9	144.6 ± 1.2
K	(mEq/L)	4.34 ± 0.30	4.46 ± 0.22	4.45 ± 0.18	4.56 ± 0.18
Cl	(mEq/L)	105.4 ± 1.1	105.4 ± 1.0	105.5 ± 1.2	105.8 ± 0.9
Ca	(mg/dL)	9.5 ± 0.3	9.5 ± 0.3	9.4 ± 0.3	9.4 ± 0.3
IP	(mg/dL)	6.7 ± 1.2	6.8 ± 0.6	6.5 ± 0.5	6.8 ± 0.5

Each value shows mean ± S.D.

Table 36 Blood chemical examination of female rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole	
mg/kg		0	250	1000
Number of females		6	6	6
AST	(IU/L)	71.2 ± 11.5	76.9 ± 13.4	75.5 ± 7.0
ALT	(IU/L)	26.8 ± 4.5	27.2 ± 10.4	27.8 ± 5.6
ALP	(IU/L)	147.9 ± 31.8	142.1 ± 24.4	122.4 ± 15.7
γ-GTP	(IU/L)	0.58 ± 0.31	0.58 ± 0.11	0.52 ± 0.18
TP	(g/dL)	6.37 ± 0.39	6.26 ± 0.49	6.25 ± 0.38
Alb	(g/dL)	3.58 ± 0.29	3.45 ± 0.36	3.56 ± 0.29
A/G		1.29 ± 0.11	1.23 ± 0.11	1.33 ± 0.12
T-Bil	(mg/dL)	0.14 ± 0.02	0.13 ± 0.02	0.14 ± 0.02
UN	(mg/dL)	17.7 ± 2.8	20.1 ± 2.9	19.2 ± 4.3
CRE	(mg/dL)	0.39 ± 0.08	0.38 ± 0.02	0.39 ± 0.03
Glu	(mg/dL)	125.0 ± 14.0	123.9 ± 6.1	115.4 ± 8.1
T-Cho	(mg/dL)	77.3 ± 18.5	70.8 ± 8.5	70.0 ± 9.9
TG	(mg/dL)	35.4 ± 10.2	29.2 ± 15.6	23.9 ± 12.0
Na	(mEq/L)	142.5 ± 0.6	142.6 ± 1.2	143.3 ± 1.4
K	(mEq/L)	4.12 ± 0.09	4.20 ± 0.21	4.20 ± 0.25
Cl	(mEq/L)	106.5 ± 0.6	106.7 ± 0.5	107.1 ± 1.5
Ca	(mg/dL)	9.8 ± 0.4	9.6 ± 0.3	9.9 ± 0.3
IP	(mg/dL)	5.1 ± 1.0	5.5 ± 1.7	5.8 ± 1.2

Each value shows mean ± S.D.

Table 37 Necropsy findings of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control	bumetrizole		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Normal	5	6	6	6
Epididymis				
Yellowish white nodule, left cauda	1	0	0	0

Table 38 Necropsy findings of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control	bumetrizole		
mg/kg	0	62.5	250	1000
Number of dams	11	12	12	11
Normal	11	12	12	11
Number of non-pregnant females	1	0	0	1
Normal	1	-	-	1

Table 39 Necropsy findings of male rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control	bumetrizole		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Normal	6	6	6	6

Table 40 Necropsy findings of female rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control	bumetrizole	
mg/kg	0	250	1000
Number of females	6	6	6
Normal	6	6	6

Table 41 Organ weights of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
Body weight	(g)	459 ± 29	461 ± 25	457 ± 13	461 ± 16
Brain	(g)	2.11 ± 0.10	2.12 ± 0.10	2.13 ± 0.05	2.06 ± 0.08
	(g%)	0.46 ± 0.02	0.46 ± 0.03	0.47 ± 0.02	0.45 ± 0.02
Pituitary	(mg)	14.4 ± 1.7	13.0 ± 2.2	12.6 ± 0.7	12.4 ± 1.9
	(mg%)	3.2 ± 0.3	2.8 ± 0.5	2.8 ± 0.2	2.7 ± 0.4
Thyroids	(mg)	21.4 ± 4.7	22.7 ± 2.6	20.7 ± 3.9	19.0 ± 2.4
	(mg%)	4.7 ± 0.9	4.9 ± 0.6	4.6 ± 0.9	4.1 ± 0.5
Thymus	(mg)	244 ± 50	285 ± 103	228 ± 41	216 ± 79
	(mg%)	53 ± 9	61 ± 19	50 ± 10	47 ± 17
Heart	(g)	1.37 ± 0.11	1.52 ± 0.16	1.39 ± 0.08	1.47 ± 0.09
	(g%)	0.30 ± 0.02	0.33 ± 0.03	0.30 ± 0.02	0.32 ± 0.02
Liver	(g)	11.17 ± 0.71	11.38 ± 1.06	11.23 ± 0.94	11.44 ± 0.68
	(g%)	2.44 ± 0.13	2.47 ± 0.12	2.45 ± 0.15	2.48 ± 0.14
Spleen	(g)	0.72 ± 0.08	0.71 ± 0.13	0.77 ± 0.10	0.67 ± 0.10
	(g%)	0.16 ± 0.01	0.15 ± 0.02	0.17 ± 0.02	0.15 ± 0.02
Kidneys	(g)	2.97 ± 0.26	2.86 ± 0.16	2.98 ± 0.17	3.00 ± 0.28
	(g%)	0.65 ± 0.05	0.62 ± 0.04	0.65 ± 0.03	0.65 ± 0.06
Adrenals	(mg)	63.5 ± 7.4	62.1 ± 8.9	59.3 ± 13.8	64.3 ± 7.6
	(mg%)	13.9 ± 1.2	13.5 ± 1.8	13.0 ± 3.0	14.0 ± 1.7
Testes	(g)	3.33 ± 0.25	3.31 ± 0.37	3.47 ± 0.08	3.23 ± 0.34
	(g%)	0.73 ± 0.04	0.72 ± 0.06	0.76 ± 0.03	0.70 ± 0.06
Epididymides	(g)	1.29 ± 0.09	1.26 ± 0.12	1.29 ± 0.12	1.20 ± 0.07
	(g%)	0.28 ± 0.02	0.27 ± 0.02	0.28 ± 0.02	0.26 ± 0.02

Each value shows mean ± S.D.

Table 42 Organ weights of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of females		11	12	12	11
Body weight	(g)	307 ± 20	304 ± 21	303 ± 25	300 ± 28
Brain	(g)	1.97 ± 0.08	1.97 ± 0.06	2.01 ± 0.10	1.97 ± 0.09
	(g%)	0.64 ± 0.04	0.65 ± 0.03	0.67 ± 0.05	0.66 ± 0.07
Pituitary	(mg)	18.2 ± 2.2	17.9 ± 3.0	18.0 ± 1.7	16.4 ± 1.6
	(mg%)	6.0 ± 0.7	5.9 ± 0.9	6.0 ± 0.6	5.5 ± 0.8
Thyroids	(mg)	18.3 ± 2.2	18.1 ± 3.7	18.0 ± 1.9	17.9 ± 2.5
	(mg%)	6.0 ± 0.8	6.0 ± 1.2	6.0 ± 0.7	6.0 ± 0.8
Thymus	(mg)	270 ± 84	327 ± 63	267 ± 56	266 ± 60
	(mg%)	87 ± 24	107 ± 19 *	88 ± 15	89 ± 19
Heart	(g)	1.04 ± 0.11	1.00 ± 0.08	1.00 ± 0.08	1.03 ± 0.08
	(g%)	0.34 ± 0.02	0.33 ± 0.02	0.33 ± 0.02	0.35 ± 0.03
Liver	(g)	9.29 ± 0.77	9.70 ± 1.19	9.95 ± 1.33	9.77 ± 0.89
	(g%)	3.03 ± 0.20	3.18 ± 0.21	3.28 ± 0.37	3.26 ± 0.25
Spleen	(g)	0.68 ± 0.12	0.74 ± 0.11	0.75 ± 0.11	0.70 ± 0.08
	(g%)	0.22 ± 0.03	0.24 ± 0.03	0.25 ± 0.03	0.24 ± 0.03
Kidneys	(g)	2.00 ± 0.14	2.05 ± 0.15	2.05 ± 0.19	2.03 ± 0.16
	(g%)	0.65 ± 0.04	0.67 ± 0.04	0.68 ± 0.06	0.68 ± 0.07
Adrenals	(mg)	76.6 ± 11.5	75.6 ± 5.8	77.4 ± 11.8	75.6 ± 10.2
	(mg%)	25.0 ± 3.8	24.9 ± 1.8	25.6 ± 3.5	25.3 ± 3.2
Ovaries	(mg)	98.7 ± 13.9	94.2 ± 11.0	99.9 ± 9.6	103.5 ± 9.8
	(mg%)	32.2 ± 4.1	31.0 ± 3.2	33.1 ± 3.9	34.7 ± 3.4
Uterus	(g)	0.54 ± 0.10	0.59 ± 0.14	0.57 ± 0.04	0.56 ± 0.10
	(g%)	0.18 ± 0.04	0.19 ± 0.05	0.19 ± 0.02	0.19 ± 0.04

Each value shows mean ± S.D.

Significantly different from control group (*: $P<0.05$).

Table 43 Organ weights of male rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
Body weight	(g)	504 ± 30	508 ± 27	494 ± 37	490 ± 33
Brain	(g)	2.12 ± 0.05	2.10 ± 0.08	2.08 ± 0.08	2.13 ± 0.06
	(g%)	0.42 ± 0.03	0.41 ± 0.03	0.42 ± 0.03	0.44 ± 0.03
Pituitary	(mg)	13.6 ± 1.2	15.0 ± 1.6	13.5 ± 1.7	13.8 ± 0.5
	(mg%)	2.7 ± 0.2	3.0 ± 0.4	2.7 ± 0.3	2.9 ± 0.1
Thyroids	(mg)	20.7 ± 3.8	25.5 ± 4.2	21.4 ± 4.6	20.8 ± 1.9
	(mg%)	4.1 ± 0.9	5.0 ± 0.7	4.3 ± 0.9	4.3 ± 0.5
Thymus	(mg)	262 ± 77	257 ± 55	276 ± 59	270 ± 54
	(mg%)	52 ± 15	51 ± 12	56 ± 10	55 ± 11
Heart	(g)	1.55 ± 0.16	1.47 ± 0.17	1.45 ± 0.15	1.44 ± 0.10
	(g%)	0.31 ± 0.04	0.29 ± 0.03	0.29 ± 0.03	0.29 ± 0.02
Liver	(g)	12.18 ± 0.91	12.43 ± 0.90	11.99 ± 1.60	12.42 ± 1.39
	(g%)	2.42 ± 0.09	2.45 ± 0.09	2.42 ± 0.16	2.53 ± 0.16
Spleen	(g)	0.79 ± 0.11	0.77 ± 0.07	0.77 ± 0.13	0.77 ± 0.10
	(g%)	0.16 ± 0.02	0.15 ± 0.02	0.16 ± 0.02	0.16 ± 0.02
Kidneys	(g)	2.96 ± 0.23	3.10 ± 0.23	2.85 ± 0.26	3.04 ± 0.16
	(g%)	0.59 ± 0.05	0.61 ± 0.06	0.58 ± 0.02	0.62 ± 0.01
Adrenals	(mg)	59.1 ± 5.3	57.1 ± 9.5	53.1 ± 8.0	56.4 ± 4.2
	(mg%)	11.8 ± 1.4	11.3 ± 1.9	10.7 ± 1.3	11.6 ± 1.3
Testes	(g)	3.24 ± 0.11	3.36 ± 0.46	3.59 ± 0.35	3.31 ± 0.21
	(g%)	0.65 ± 0.04	0.66 ± 0.11	0.73 ± 0.09	0.68 ± 0.07
Epididymides	(g)	1.31 ± 0.10	1.30 ± 0.05	1.36 ± 0.14	1.33 ± 0.10
	(g%)	0.26 ± 0.02	0.26 ± 0.01	0.28 ± 0.03	0.27 ± 0.03

Each value shows mean ± S.D.

Table 44 Organ weights of female rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group		Control	bumetrizole	
mg/kg		0	250	1000
Number of females		6	6	6
Body weight	(g)	316 ± 24	323 ± 25	303 ± 8
Brain	(g)	1.98 ± 0.07	2.02 ± 0.14	2.01 ± 0.06
	(g%)	0.63 ± 0.05	0.63 ± 0.08	0.67 ± 0.01
Pituitary	(mg)	17.0 ± 2.6	18.2 ± 1.6	18.7 ± 2.8
	(mg%)	5.4 ± 1.1	5.7 ± 0.7	6.2 ± 0.8
Thyroids	(mg)	19.0 ± 3.7	19.2 ± 5.7	17.7 ± 3.7
	(mg%)	6.1 ± 1.2	5.9 ± 1.5	5.8 ± 1.2
Thymus	(mg)	303 ± 43	326 ± 60	282 ± 40
	(mg%)	96 ± 14	101 ± 18	93 ± 12
Heart	(g)	0.97 ± 0.07	0.97 ± 0.11	0.98 ± 0.05
	(g%)	0.31 ± 0.02	0.30 ± 0.02	0.33 ± 0.02
Liver	(g)	7.81 ± 0.68	7.58 ± 0.66	7.45 ± 0.32
	(g%)	2.47 ± 0.10	2.35 ± 0.12	2.46 ± 0.11
Spleen	(g)	0.56 ± 0.09	0.57 ± 0.09	0.59 ± 0.09
	(g%)	0.18 ± 0.02	0.18 ± 0.03	0.20 ± 0.03
Kidneys	(g)	1.93 ± 0.10	1.88 ± 0.11	1.93 ± 0.11
	(g%)	0.61 ± 0.05	0.59 ± 0.04	0.64 ± 0.04
Adrenals	(mg)	72.0 ± 9.5	66.0 ± 6.8	71.2 ± 2.9
	(mg%)	22.8 ± 1.8	20.6 ± 2.4	23.5 ± 1.3
Ovaries	(mg)	85.8 ± 9.7	74.1 ± 5.9 *	79.9 ± 7.6
	(mg%)	27.2 ± 2.5	23.1 ± 2.3 *	26.4 ± 2.7
Uterus	(g)	0.54 ± 0.18	0.62 ± 0.16	0.60 ± 0.12
	(g%)	0.17 ± 0.05	0.20 ± 0.05	0.20 ± 0.04

Each value shows mean ± S.D.

Significantly different from control group (*: $P<0.05$).

Table 45 Histopathological findings of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control						bumetrizole					
mg/kg	0						1000					
Grade	N[a)]	A[b)]	±	+	2+	3+	N[a)]	A[b)]	±	+	2+	3+
Findings												
Heart	[6][c)]						[6]					
Lung												
Accumulation, foam cell	4	2	2	0	0	0	5	1	1	0	0	0
Trachea	[6]						[6]					
Liver	[6]						[6]					
Pancreas	[6]						[6]					
Sublingual gland	[6]						[6]					
Submandibular gland	[6]						[6]					
Esophagus	[6]						[6]					
Stomach	[6]						[6]					
Duodenum	[6]						[6]					
Jejunum	[6]						[6]					
Mineralization, Peyer's patch	6	0	0	0	0	0	5	1	1	0	0	0
Ileum	[6]						[6]					
Cecum	[6]						[6]					
Colon	[6]						[6]					
Rectum	[6]						[6]					
Thymus	[6]						[6]					
Spleen	[6]						[6]					
Submandibular lymph node	[6]						[6]					
Mesenteric lymph node	[6]						[6]					
Kidney	[6]						[6]					
Urinary bladder	[6]						[6]					
Testis	[6]						[6]					
Epididymis	[6]						[6]					
Cellular infiltration, lymphoid cell	5	1	1	0	0	0	6	0	0	0	0	0
Granuloma, spermatic, lateral	5	1	1	0	0	0	6	0	0	0	0	0
Seminal vesicle	[6]						[6]					
Prostate	[6]						[6]					
Cellular infiltration, lymphoid cell	6	0	0	0	0	0	5	1	1	0	0	0
Pituitary	[6]						[6]					
Adrenal	[6]						[6]					
Thyroid	[6]						[6]					
Parathyroid	[6]						[6]					
Cerebrum	[6]						[6]					
Cerebellum	[6]						[6]					
Medulla oblongata	[6]						[6]					
Spinal code	[6]						[6]					
Sciatic nerve	[6]						[6]					
Eyeball	[6]						[6]					
Harderian gland	[6]						[6]					
Bone marrow (sternum or femur)	[6]						[6]					
Bone (sternum or femur)	[6]						[6]					

a): No abnormality detected.
b): Abnormality detected.
c): Number in brackets is number of males examined.
Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Table 46 Histopathological findings of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control						bumetrizole					
mg/kg	0						1000					
Grade	N[a)]	A[b)]	±	+	2+	3+	N[a)]	A[b)]	±	+	2+	3+
Findings												
Heart	[6][c)]											
Lung	[6]						[6]					
Trachea	[6]						[6]					
Liver	[6]						[6]					
Pancreas	[6]						[6]					
Sublingual gland	[6]						[6]					
Submandibular gland	[6]						[6]					
Esophagus	[6]						[6]					
Stomach	[6]						[6]					
Duodenum	[6]						[6]					
Jejunum	[6]						[6]					
Mineralization, Peyer's patch	6	0	0	0	0	0	5	1	1	0	0	0
Ileum	[6]						[6]					
Cecum	[6]						[6]					
Colon	[6]						[6]					
Rectum	[6]						[6]					
Thymus	[6]						[6]					
Spleen	[6]						[6]					
Hematopoiesis, extramedullary	3	3	3	0	0	0	5	1	1	0	0	0
Submandibular lymph node	[6]						[6]					
Mesenteric lymph node	[6]						[6]					
Kidney	[6]						[6]					
Urinary bladder	[6]						[6]					
Ovary	[6]						[6]					
Uterus	[6]						[6]					
Vagina	[6]						[6]					
Pituitary	[6]						[6]					
Adrenal	[6]						[6]					
Thyroid	[6]						[6]					
Parathyroid	[6]						[6]					
Cerebrum	[6]						[6]					
Cerebellum	[6]						[6]					
Medulla oblongata	[6]						[6]					
Spinal code	[6]						[6]					
Sciatic nerve	[6]						[6]					
Eyeball	[6]						[6]					
Dysplasia, retina, right	6	0	0	0	0	0	5	1	1	0	0	0
Harderian gland	[6]						[6]					
Bone marrow (sternum or femur)	[6]						[6]					
Bone (sternum or femur)	[6]						[6]					
Mammary gland	[6]						[6]					

a): No abnormality detected.
b): Abnormality detected.
c): Number in brackets is number of females examined.
Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Table 47 Reproductive functions of male rats and female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control	bumetrizole		
mg/kg	0	62.5	250	1000
Number of females	12	12	12	12
Number of estrous cases before pairing (14 days) Mean±S.D.	3.1 ± 0.8	3.5 ± 0.5	3.4 ± 0.5	3.3 ± 0.5
Number of pairs	12	12	12	12
Number of pairs with successful copulation	12	12	12	12
Copulation index (%) [a)]	100.0	100.0	100.0	100.0
Number of conceiving days				
Mean±S.D.	2.9 ± 1.2	1.9 ± 1.0	2.8 ± 1.2	3.1 ± 3.3
Conceiving days 1-5	12	12	12	11
Conceiving days ≥6	0	0	0	1
Number of pregnant females	11	12	12	11
Fertility index (%) [b)]	91.7	100.0	100.0	91.7

a): (Number of pairs with successful copulation / number of pairs)×100.

b): (Number of pregnant females / number of pairs with successful copulation)×100.

Table 48 Observation of pups (F_1) in combined repeat dose and reproductive/development toxicity screening test of bumetrizole by oral administration

Group	Control	bumetrizole		
mg/kg	0	62.5	250	1000
Number of dams	11	12	12	11
Length of gestation (days)	22.3 ± 0.5	22.5 ± 0.5	22.3 ± 0.5	22.3 ± 0.5
Pregnancy days ≦ 21	0	0	0	0
Pregnancy days = 22	8	6	8	8
Pregnancy days ≧ 23	3	6	4	3
Corpora lutea	16.4 ± 1.6	15.6 ± 2.2	17.3 ± 1.7	16.5 ± 1.4
Implantation scars	14.4 ± 1.3	15.0 ± 2.0	15.7 ± 2.1	15.4 ± 1.4
Implantation index (%) [a]	88.0 ± 4.6	96.3 ± 5.0 *	90.3 ± 6.2	93.7 ± 9.3
Gestation index (%) [b]	100.0	100.0	100.0	100.0
Pups born	13.8 ± 1.2	13.8 ± 1.9	14.0 ± 2.6	14.7 ± 1.6
Stillbirths	0.2 ± 0.6	0.4 ± 0.5	0.6 ± 0.7	0.4 ± 0.5
Live pups born	13.6 ± 0.9	13.4 ± 1.9	13.4 ± 2.6	14.4 ± 1.6
Sex ratio at birth [c]	1.06 ± 0.29	1.34 ± 1.04	2.24 ± 3.14	1.21 ± 0.70
(Total male/total female)	76／74	84／77	90／71	82／76
Delivery index (%) [d]	95.2 ± 5.1	89.7 ± 7.5	85.5 ± 11.5 *	93.5 ± 7.0
Birth index (%) [e]	95.3 ± 5.0	89.7 ± 7.5	85.5 ± 11.7 *	93.5 ± 7.0
Live birth index (%) [f]	98.9 ± 3.6	97.0 ± 3.8	95.8 ± 4.6	97.5 ± 3.4
Live pups on Day 4 of lactation	13.5 ± 1.2	13.1 ± 1.9	13.3 ± 2.5	14.2 ± 1.7
Sex ratio on Day 4 of lactation [c]	1.06 ± 0.29	1.43 ± 1.08	2.25 ± 3.13	1.21 ± 0.71
(Total male/total female)	75／73	84／73	90／69	81／75
Viability index (%) [g]	98.6 ± 4.6	97.5 ± 3.7	98.9 ± 3.8	98.7 ± 2.8
External abnormalities (%) [h]	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.1
Acaudate	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.1

Each value shows mean ± S.D. per dam.
Significantly different from control group (*: P<0.05).
a): (Number of implantation scars/number of corpora lutea)×100.
b): (Number of dams with live pups/number of pregnant dams)×100.
c): Number of male pups/number of female pups.
d): (Number of pups born/number of implantation scars)×100.
e): (Number of live pups born/number of implantation scars)×100.
f): (Number of live pups born/number of pups born)×100.
g): (Number of live pups on Day 4/number of live pups born)×100.
h): (Number of pups with external abnormalities/number of live pups)×100.

Table 49 Delivery conditions and nursing conditions of dams in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	mg/kg	Number of dams and delivery conditions/nursing conditions	Delivery conditions	Nursing conditions				
				Days of lactation				
				0	1	2	3	4
Control	0	Number of dams	11	11	11	11	11	11
		Normal	11	11	11	11	11	11
bumetrizole	62.5	Number of dams	12	12	12	12	12	12
		Normal	12	12	12	12	12	12
	250	Number of dams	12	12	12	12	12	12
		Normal	12	12	12	12	12	12
	1000	Number of dams	11	11	11	11	11	11
		Normal	11	11	11	11	11	11