

Table 15 Food consumption of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	250	1000	6
mg/kg				
Number of females				
Days of administration				
2	18 ± 3	19 ± 3	17 ± 3	3
5	19 ± 1	18 ± 3	20 ± 4	4
9	18 ± 2	17 ± 4	19 ± 3	3
12	17 ± 3	20 ± 3	16 ± 3	3
16	17 ± 3	19 ± 3	14 ± 3	3
19	20 ± 3	20 ± 4	17 ± 3	3
23	18 ± 2	18 ± 4	17 ± 2	2
26	20 ± 3	21 ± 4	19 ± 3	3
30	18 ± 4	18 ± 4	18 ± 2	2
33	21 ± 1	22 ± 2	23 ± 3	3
37	18 ± 2	17 ± 1	18 ± 2	2
40	18 ± 3	20 ± 3	18 ± 3	3
Number of females	6	6	6	6
Days of recovery				
2	20 ± 3	21 ± 3	18 ± 2	2
5	22 ± 4	19 ± 4	20 ± 2	2
9	21 ± 4	20 ± 4	19 ± 3	3
12	23 ± 6	19 ± 4	20 ± 4	4

Each value shows mean (g/day) ± S.D.

Table 16-1 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	62.5	250	1000
mg/kg				
Number of males	12	12	12	12
Observation of animals in cages				
Posture	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 28	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 35	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 41	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Palpebral closure	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Biting behavior	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Clonic convulsions	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows

- Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping
- Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.
- Biting behavior 1: Not observed, 2: observed.
- Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Table 16-2 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	62.5	250	1000
Number of males	12	12	12	12
Observation of animals in cages				
Tonic convulsions	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)				

Findings were graded as follows

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: salatory convulsions, 5: asphyxial convulsions.

Table 16-3 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	62.5	250	1000
Number of males	12	12	12	12
Observation of animals on observer's palm				
Ease of removal from cage				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 28	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 35	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 41	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Ease of handling				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 28	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 35	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 41	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Muscle tone				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 28	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 35	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 41	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Fur conditions				
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows

Ease of removal from cage

1: Docile and allowing itself to be handled, 2: rearing or covering, 3: running about; hard to catch.

Ease of handling

1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing, 3: struggling and trying to bite observer's hand.

Muscle tone

1: Decreased, 2: normal, 3: increased.

Fur conditions

1: Normal, 2: slightly soiled, 3: markedly soiled.

Table 16-4 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	62.5	250	1000
mg/kg				
Number of males	12	12	12	12
Observation of animals on observer's palm				
Lacrimation				
Mean (range)				
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Salivation				
Mean (range)				
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Respiration				
Mean (range)				
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows

- Lacrimation 1: None, 2: mild, 3: marked.
- Salivation 1: None, 2: mild, 3: marked.
- Respiration 1: Normal, 2: bradypnea, 3: dyspnea.

Table 16-5 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole		
	0	12	62.5	250	
mg/kg					
Number of males	12		12		
Open-field test					
Frequency of rearing Mean ± S.D.	Pre	8.8 ± 4.5	7.0 ± 4.0	7.3 ± 5.1	4.9 ± 4.1
	Day 7	3.3 ± 3.0	1.8 ± 2.1	2.7 ± 3.1	3.7 ± 4.9
	Day 14	2.0 ± 2.3	2.9 ± 3.3	1.0 ± 1.7	3.8 ± 3.7
	Day 21	2.3 ± 2.5	2.5 ± 2.5	2.1 ± 3.2	2.4 ± 2.5
	Day 28	3.3 ± 2.9	3.3 ± 4.9	4.1 ± 4.3	3.3 ± 2.6
	Day 35	3.4 ± 3.5	2.8 ± 3.1	3.2 ± 2.7	2.5 ± 2.5
Day 41	5.1 ± 4.3	2.7 ± 3.7	4.0 ± 3.5	5.0 ± 3.7	
Frequency of grooming Mean ± S.D.	Pre	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 7	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 14	0.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 21	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 28	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 35	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Day 41	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Gait Mean (range)	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
Palpebral closure Mean (range)	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 28	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 35	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 41	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	

Frequency of rearing (during a 2-minute period).
 Frequency of grooming (during a 2-minute period).
 Findings were graded as follows

- Gait
 Palpebral closure
- 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.
 - 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Table 16-6 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	62.5	250	1000
mg/kg	12		12	
Number of males	12		12	
Open-field test				
Consciousness Mean (range)	Pre	2.0 (2)	2.0 (2)	2.0 (2)
	Day 7	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)
	Day 28	2.0 (2)	2.0 (2)	2.0 (2)
	Day 35	2.0 (2)	2.0 (2)	2.0 (2)
Behavioral abnormalities Mean (range)	Pre	1.0 (1)	1.0 (1)	1.0 (1)
	Day 7	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)
	Day 28	1.0 (1)	1.0 (1)	1.0 (1)
	Day 35	1.0 (1)	1.0 (1)	1.0 (1)
Righting reflex Mean (range)	Pre	1.0 (1)	1.0 (1)	1.0 (1)
	Day 7	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)
	Day 28	1.0 (1)	1.0 (1)	1.0 (1)
	Day 35	1.0 (1)	1.0 (1)	1.0 (1)
Findings were graded as follows	Pre	1.0 (1)	1.0 (1)	1.0 (1)
	Day 7	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)
	Day 28	1.0 (1)	1.0 (1)	1.0 (1)
	Day 35	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows

- Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.
- Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.
- Righting reflex 1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Table 17-1 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		62.5		bumetrizole		1000	
	0	12	12	12	250	12	12	12
mg/kg								
Number of females								
Observation of animals in cages								
Posture								
Mean (range)								
Pre	2.0 (2)		2.0 (2)		2.0 (2)		2.0 (2)	
Day 8	2.0 (2)		2.0 (2)		2.0 (2)		2.0 (2)	
Day 15	2.0 (2)		2.0 (2)		2.0 (2)		2.0 (2)	
Day 1 of pregnancy	2.0 (2)	[11]	2.0 (2)		2.0 (2)		2.0 (2)	[11]
Day 8 of pregnancy	2.0 (2)	[11]	2.0 (2)		2.0 (2)		2.0 (2)	[11]
Day 15 of pregnancy	2.0 (2)	[11]	2.0 (2)		2.0 (2)		2.0 (2)	[11]
Day 3 of lactation	2.0 (2)	[11]	2.0 (2)		2.0 (2)		2.0 (2)	[11]
Palpebral closure								
Mean (range)								
Pre	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 8	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 15	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 1 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 8 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 15 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 3 of lactation	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Biting behavior								
Mean (range)								
Pre	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 8	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 15	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 1 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 8 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 15 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 3 of lactation	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Clonic convulsions								
Mean (range)								
Pre	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 8	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 15	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)	
Day 1 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 8 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 15 of pregnancy	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]
Day 3 of lactation	1.0 (1)	[11]	1.0 (1)		1.0 (1)		1.0 (1)	[11]

Figures in parentheses [] indicate number of females.

Findings were graded as follows

- Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.
- Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.
- Biting behavior 1: Not observed, 2: observed.
- Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Table 17-2 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	62.5	250	1000
Number of females	12	12	12	12
Observation of animals in cages				
Tonic convulsions	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 1 of pregnancy	[111]	1.0 (1)	1.0 (1)	1.0 (1)
Day 8 of pregnancy	[111]	1.0 (1)	1.0 (1)	1.0 (1)
Day 15 of pregnancy	[111]	1.0 (1)	1.0 (1)	1.0 (1)
Day 3 of lactation	[111]	1.0 (1)	1.0 (1)	1.0 (1)

Figures in parentheses [] indicate number of females.

Findings were graded as follows

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: salutory convulsions, 5: asphyxial convulsions.

Table 17-3 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	62.5	250	1000
Number of females	12	12	12	12
Observation of animals on observer's pain				
Ease of removal from cage				
Mean (range)				
Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 8	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 15	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 1 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 8 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 15 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 3 of lactation	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Ease of handling				
Mean (range)				
Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 8	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 15	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 1 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 8 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 15 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 3 of lactation	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Muscle tone				
Mean (range)				
Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 8	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 15	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 1 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 8 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 15 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 3 of lactation	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Fur conditions				
Mean (range)				
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 1 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 3 of lactation	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Figures in parentheses [] indicate number of females.

Findings were graded as follows

Ease of removal from cage

1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about, hard to catch.

Ease of handling

1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing, 3: struggling and trying to bite observer's hand.

Muscle tone

1: Decreased, 2: normal, 3: increased.

Fur conditions

1: Normal, 2: slightly soiled, 3: markedly soiled.

Table 17-4 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	12	62.5	250
Number of females		12	12	12
1000				12
Observation of animals on observer's pain				
Lacrimation				
Mean (range)				
Pre	1.0 (1)		1.0 (1)	1.0 (1)
Day 8	1.0 (1)		1.0 (1)	1.0 (1)
Day 15	1.0 (1)		1.0 (1)	1.0 (1)
Day 1 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 8 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 15 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 3 of lactation	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Salivation				
Mean (range)				
Pre	1.0 (1)		1.0 (1)	1.0 (1)
Day 8	1.0 (1)		1.0 (1)	1.0 (1)
Day 15	1.0 (1)		1.0 (1)	1.0 (1)
Day 1 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 8 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 15 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 3 of lactation	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Respiration				
Mean (range)				
Pre	1.0 (1)		1.0 (1)	1.0 (1)
Day 8	1.0 (1)		1.0 (1)	1.0 (1)
Day 15	1.0 (1)		1.0 (1)	1.0 (1)
Day 1 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 8 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 15 of pregnancy	1.0 (1)	[11]	1.0 (1)	1.0 (1)
Day 3 of lactation	1.0 (1)	[11]	1.0 (1)	1.0 (1)

Figures in parentheses [] indicate number of females.

Findings were graded as follows

- Lacrimation 1: None, 2: mild, 3: marked.
- Salivation 1: None, 2: mild, 3: marked.
- Respiration 1: Normal, 2: bradypnea, 3: dyspnea.

Table 17-5 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	12	250	1000
mg/kg	62.5		12	
Number of females	12		12	
Open-field test				
Frequency of rearing				
Mean ± S.D.				
Pre	9.3 ± 4.8	8.8 ± 4.3	8.4 ± 5.2	9.8 ± 5.4
Day 8	7.5 ± 3.8	8.5 ± 2.9	6.2 ± 4.7	8.9 ± 5.7
Day 15	5.7 ± 4.9	7.4 ± 4.6	6.0 ± 3.2	9.0 ± 7.4
Day 1 of pregnancy	3.7 ± 2.6	6.3 ± 3.8	4.4 ± 3.9	5.2 ± 3.8
Day 8 of pregnancy	7.8 ± 4.8	6.1 ± 3.6	7.1 ± 3.2	6.7 ± 4.7
Day 15 of pregnancy	6.3 ± 5.8	6.4 ± 3.8	6.4 ± 4.9	8.5 ± 5.4
Day 3 of lactation	5.9 ± 4.6	5.7 ± 2.7	5.2 ± 3.7	5.2 ± 3.9
Frequency of grooming				
Mean ± S.D.				
Pre	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.6	0.1 ± 0.3
Day 8	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Day 15	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Day 1 of pregnancy	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Day 8 of pregnancy	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.6
Day 15 of pregnancy	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Day 3 of lactation	0.5 ± 0.9	0.3 ± 0.7	0.5 ± 0.9	0.1 ± 0.3
Gait				
Mean (range)				
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 1 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 3 of lactation	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Palpebral closure				
Mean (range)				
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 1 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 3 of lactation	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Figures in parentheses [] indicate number of females.

Frequency of rearing (during a 2-minute period).

Frequency of grooming (during a 2-minute period).

Findings were graded as follows

Gait

- 1: Normal, 2: unmovng, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

Palpebral closure

- 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Table 17-6 FOB of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	62.5	250	1000
mg/kg	12	12	12	12
Number of females	12	12	12	12
Open-field test				
Consciousness Mean (range)	Pre	2.0 (2)	2.0 (2)	2.0 (2)
	Day 8	2.0 (2)	2.0 (2)	2.0 (2)
Behavioral abnormalities Mean (range)	Day 15	2.0 (2)	2.0 (2)	2.0 (2)
	Day 1 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)
	Day 8 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)
	Day 15 of pregnancy	2.0 (2)	2.0 (2)	2.0 (2)
	Day 3 of lactation	2.0 (2)	2.0 (2)	2.0 (2)
Righting reflex Mean (range)	Pre	1.0 (1)	1.0 (1)	1.0 (1)
	Day 8	1.0 (1)	1.0 (1)	1.0 (1)
	Day 15	1.0 (1)	1.0 (1)	1.0 (1)
	Day 1 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)
	Day 8 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)
Righting reflex Mean (range)	Day 15 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)
	Day 3 of lactation	1.0 (1)	1.0 (1)	1.0 (1)
	Pre	1.0 (1)	1.0 (1)	1.0 (1)
	Day 8	1.0 (1)	1.0 (1)	1.0 (1)
	Day 15	1.0 (1)	1.0 (1)	1.0 (1)
Righting reflex Mean (range)	Day 1 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)
	Day 8 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)
	Day 15 of pregnancy	1.0 (1)	1.0 (1)	1.0 (1)
	Day 3 of lactation	1.0 (1)	1.0 (1)	1.0 (1)
	Pre	1.0 (1)	1.0 (1)	1.0 (1)

Figures in parentheses [] indicate number of females.

Findings were graded as follows

Consciousness

Behavioral abnormalities

Righting reflex

1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

1: Not observed, 2: Straub's reaction, 3: moving backward, 4: writhing.

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Table 18-1 FOB of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	250	1000	6
Number of females	6	6	6	6
Observation of animals in cages				
Posture	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 8	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 15	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 22	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 29	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 36	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 42	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Palpebral closure	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Biting behavior	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Clonic convulsions	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows

- Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.
- Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.
- Biting behavior 1: Not observed, 2: observed.
- Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Table 18-2 FOB of female rats (recovery group) 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
Observation of animals in cages			
Tonic convulsions	1.0 (1)	1.0 (1)	1.0 (1)
Pre	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)			

Findings were graded as follows

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: salatory convulsions, 5: asphyxial convulsions.

Table 18-3 FOB of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	1000	250	1000
Number of females	6	6	6	6
Observation of animals on observer's palm				
Ease of removal from cage	Pre	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 8	2.0 (2)	2.0 (2)	2.0 (2)
	Day 15	2.0 (2)	2.0 (2)	2.0 (2)
	Day 22	2.0 (2)	2.0 (2)	2.0 (2)
	Day 29	2.0 (2)	2.0 (2)	2.0 (2)
	Day 36	2.0 (2)	2.0 (2)	2.0 (2)
	Day 42	2.0 (2)	2.0 (2)	2.0 (2)
Ease of handling				
Mean (range)	Pre	2.0 (2)	2.0 (2)	2.0 (2)
	Day 8	2.0 (2)	2.0 (2)	2.0 (2)
	Day 15	2.0 (2)	2.0 (2)	2.0 (2)
	Day 22	2.0 (2)	2.0 (2)	2.0 (2)
	Day 29	2.0 (2)	2.0 (2)	2.0 (2)
	Day 36	2.0 (2)	2.0 (2)	2.0 (2)
	Day 42	2.0 (2)	2.0 (2)	2.0 (2)
Muscle tone				
Mean (range)	Pre	2.0 (2)	2.0 (2)	2.0 (2)
	Day 8	2.0 (2)	2.0 (2)	2.0 (2)
	Day 15	2.0 (2)	2.0 (2)	2.0 (2)
	Day 22	2.0 (2)	2.0 (2)	2.0 (2)
	Day 29	2.0 (2)	2.0 (2)	2.0 (2)
	Day 36	2.0 (2)	2.0 (2)	2.0 (2)
	Day 42	2.0 (2)	2.0 (2)	2.0 (2)
Fur conditions				
Mean (range)	Pre	1.0 (1)	1.0 (1)	1.0 (1)
	Day 8	1.0 (1)	1.0 (1)	1.0 (1)
	Day 15	1.0 (1)	1.0 (1)	1.0 (1)
	Day 22	1.0 (1)	1.0 (1)	1.0 (1)
	Day 29	1.0 (1)	1.0 (1)	1.0 (1)
	Day 36	1.0 (1)	1.0 (1)	1.0 (1)
	Day 42	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows

- Ease of removal from cage
1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about, hard to catch.
- Muscle tone
1: Decreased, 2: normal, 3: increased.
- Fur conditions
1: Normal, 2: slightly soiled, 3: markedly soiled.

Table 18-4 FOB of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	1000	250	1000
Number of females	6	6	6	6
Observation of animals on observer's palm				
Lacrimation	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Salivation	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Respiration	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows

- Lacrimation 1: None, 2: mild, 3: marked.
- Salivation 1: None, 2: mild, 3: marked.
- Respiration 1: Normal, 2: bradypnea, 3: dyspnea.

Table 18-5 FOB of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	6	250	1000
mg/kg				
Number of females	6	6	6	6
Open-field test				
Frequency of rearing Mean ± S.D.	Pre 5.5 ± 2.9	2.9 *	10.7 ± 6.0	2.9 ± 3.3
	Day 8 4.8 ± 5.3	3.7	6.0 ± 8.8	3.3 ± 2.3
	Day 15 6.0 ± 4.6	5.7	7.0 ± 7.0	6.0 ± 3.9
	Day 22 5.0 ± 4.3	4.6	8.8 ± 8.8	5.7 ± 2.9
	Day 29 4.5 ± 3.3	4.5	0.0 ± 0.0	7.5 ± 3.8
	Day 36 3.5 ± 1.9	4.4 **	0.2 ± 0.2	7.7 ± 3.1
	Day 42 9.0 ± 2.0	4.1	0.3 ± 0.0	8.5 ± 5.2
Frequency of grooming Mean ± S.D.	Pre 0.0 ± 0.0	0.0	0.0 ± 0.0	0.2 ± 0.4
	Day 8 0.0 ± 0.0	0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 15 0.0 ± 0.0	0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 22 0.0 ± 0.0	0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 29 0.0 ± 0.0	0.4	0.0 ± 0.0	0.0 ± 0.0
	Day 36 0.0 ± 0.0	0.8	0.3 ± 0.3	0.3 ± 0.8
	Day 42 0.0 ± 0.0	0.0	0.0 ± 0.0	0.0 ± 0.0
Gait				
Mean (range)	Pre 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 8 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 15 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 22 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 29 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 36 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 42 1.0 (1)	(1)	1.0 (1)	1.0 (1)
Palpebral closure				
Mean (range)	Pre 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 8 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 15 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 22 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 29 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 36 1.0 (1)	(1)	1.0 (1)	1.0 (1)
	Day 42 1.0 (1)	(1)	1.0 (1)	1.0 (1)

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

Frequency of rearing (during a 2-minute period).

Frequency of grooming (during a 2-minute period).

Findings were graded as follows

Gait

1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended,

6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

Palpebral closure

1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Table 18-6 FOB of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	250	1000	6
mg/kg				
Number of females	6	6	6	6
Open-field test				
Consciousness				
Mean (range)				
Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 8	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 15	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 22	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 29	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 36	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Day 42	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Behavioral abnormalities				
Mean (range)				
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Righting reflex				
Mean (range)				
Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 8	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 15	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 22	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 29	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 36	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Day 42	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows

- Consciousness
 - Behavioral abnormalities
 - Righting reflex
- 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.
 1: Not observed, 2: Straub's reaction, 3: moving backward, 4: writhing.
 1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Table 19 Sensory response 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	
	0	62.5	250	1000
mg/kg				
Number of males	6	6	6	6
Pupillary reflex				
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Approaching behavior				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Response to touch				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Auditory reflex				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Pain reflex				
Mean (range)	3.0 (3)	3.0 (3)	3.0 (3)	3.0 (3)

Findings were graded as follows.

- Pupillary reflex
 - 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
- Approaching behavior
 - 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.
- Response to touch
 - 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.
- Auditory reflex
 - 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
- Pain reflex
 - 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus, 3: quickly moving forward to escape from stimulus or biting at it immediately after looking back, 4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Table 20 Sensory response 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	
	0	6	62.5	250
mg/kg				
Number of females	6	6	6	6
Pupillary reflex				
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Approaching behavior				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Response to touch				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Auditory reflex				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Pain reflex				
Mean (range)	3.0 (3)	3.0 (3)	3.0 (3)	3.0 (3)

Findings were graded as follows.

Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.

Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing.

Response to touch 4: jumping at or biting at stimulus.

Auditory reflex 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing,

Pain reflex 4: jumping at or biting at stimulus.

1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.

2: slowly looking back or slowly moving forward to escape from stimulus,

3: quickly moving forward to escape from stimulus or biting at it immediately after looking back,

4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Table 21 Grip strength of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	62.5	250	1000
Number of males	6	6	6	6
Forelimb	1029 ± 325	1122 ± 255	1120 ± 301	954 ± 252
Hindlimb	118 ± 44	148 ± 103	137 ± 58	117 ± 40

Each value shows mean (g) ± S.D.

Table 22 Grip strength 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	2.50	1000
Number of females	6	6	6
Forelimb			
	959 ± 185	799 ± 145	860 ± 240
Hindlimb			
	121 ± 48	74 ± 18	118 ± 58

Each value shows mean (g) ± S.D.

Table 23 Spontaneous motor activity of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group mg/kg	Control		bumetrizole	
	0	6	250	1000
Number of males	6	6	6	6
Ambulatory counts				
Minutes after administration				
10	1188 ± 561	1044 ± 517	878 ± 436	678 ± 325
20	395 ± 386	1168 ± 2109	328 ± 261	871 ± 1568
30	127 ± 120	467 ± 792	260 ± 239	238 ± 292
40	181 ± 240	188 ± 166	191 ± 233	156 ± 288
50	59 ± 95	151 ± 182	108 ± 108	190 ± 327
60	204 ± 239	169 ± 273	2 ± 4 *	152 ± 273
Total	2153 ± 825	3187 ± 3493	1765 ± 1020	2285 ± 3007
Vertical counts				
Minutes after administration				
10	62 ± 20	59 ± 28	58 ± 12	40 ± 18
20	22 ± 14	23 ± 17	28 ± 18	15 ± 10
30	7 ± 9	17 ± 23	15 ± 12	6 ± 8
40	10 ± 13	10 ± 14	12 ± 16	2 ± 2
50	6 ± 12	4 ± 5	6 ± 7	2 ± 6
60	11 ± 13	5 ± 7	0 ± 0 *	2 ± 3
Total	118 ± 64	118 ± 77	119 ± 37	66 ± 33

Each value shows mean ± S.D.
Significantly different from control group (*: P<0.05).

Table 24 Spontaneous motor activity 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	
	0	6	62.5	250
mg/kg				1000
Number of females		6	6	6
Ambulatory counts				
Minutes after administration				
10	1015 ± 496	301	922 ± 301	891 ± 450
20	331 ± 500	363	262 ± 363	329 ± 472
30	73 ± 156	180	75 ± 180	192 ± 298
40	107 ± 179	161	67 ± 161	164 ± 224
50	68 ± 125	80	35 ± 80	964 ± 2065
60	9 ± 22	227	94 ± 227	52 ± 123
Total	1604 ± 1068	1246	1455 ± 1246	2592 ± 2969
Vertical counts				
Minutes after administration				
10	30 ± 9	26	42 ± 26	27 ± 15
20	9 ± 12	12	9 ± 12	11 ± 13
30	5 ± 12	5	2 ± 5	7 ± 11
40	3 ± 5	4	2 ± 4	6 ± 11
50	2 ± 3	2	1 ± 2	4 ± 6
60	0 ± 0	6	2 ± 6	2 ± 4
Total	48 ± 31	43	58 ± 43	57 ± 53
				149 ± 265

Each value shows mean ± S.D.

Table 25-1 Urinary 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	
	0	62.5	250	1000
mg/kg				
Number of males	6	6	6	6
Volume (mL): Mean \pm S.D.	17.0 \pm 4.8	23.3 \pm 7.5	17.2 \pm 4.4	14.6 \pm 3.7
Specific gravity: Mean \pm S.D.	1.044 \pm 0.005	1.032 \pm 0.010	1.047 \pm 0.008	1.054 \pm 0.014
Color				
Light yellow	6	6	6	6
pH				
8.5	6	6	3	6
9.0	0	0	3	0
Protein				
10~20 mg/dL	1	1	0	0
30 mg/dL	4	4	4	2
100 mg/dL	1	1	2	4
Glucose				
Negative	6	6	6	6
Ketone body				
Negative	6	5	5	4
Slight	0	1	1	2
Bilirubin				
Negative	6	6	6	6
Occult blood				
Negative	4	5	5	3
Trace	2	1	0	3
Slight	0	0	1	0
Urobilinogen				
Normal	6	6	6	5
1 mg/dL	0	0	0	1

Table 2-5-2 Urinary 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		
	0	62.5	250	1000	
mg/kg					
Number of males	6	6	6	6	6
Urinary sediments					
Epithelial cells					
0~20 cells/100 fields	6	6	6	6	6
Erythrocytes					
0~20 cells/100 fields	6	6	6	6	6
Leukocytes					
0~20 cells/100 fields	6	6	6	6	6
Casts					
Not observed	6	6	6	6	6
Crystals					
Not observed	4	3	4	3	3
Observed	2	3	2	3	3

Table 26-1 Urinary 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	
	0	62.5	250	1000
mg/kg				
Number of females	6	6	6	6
Volume (mL): Mean ± S.D.	29.9 ± 3.8	24.2 ± 3.9	28.2 ± 6.8	35.9 ± 9.9
Specific gravity: Mean ± S.D.	1.032 ± 0.005	1.036 ± 0.005	1.033 ± 0.005	1.027 ± 0.005
Color				
Light yellow	6	6	6	6
pH				
5.5	0	2	1	0
6.0	1	0	0	0
6.5	3	2	0	3
7.0	0	0	3	1
7.5	1	2	0	2
8.0	1	0	1	0
8.5	0	0	1	0
Protein				
Negative	2	3	5	6
10~20 mg/dL	4	1	0	0
30 mg/dL	0	1	1	0
100 mg/dL	0	1	0	0
Glucose				
Negative	6	6	6	6
Ketone body				
Negative	6	6	5	6
Slight	0	0	1	0
Bilirubin				
Negative	6	6	6	6
Occult blood				
Negative	6	6	6	6
Urobilinogen				
Normal	6	5	5	6
1 mg/dL	0	1	1	0

Table 26-2 Urinary 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		
	0	62.5	250	1000	
mg/kg	0	62.5	250	1000	
Number of females	6	6	6	6	6
Urinary sediments					
Epithelial cells	6	6	6	6	6
0~20 cells/100 fields	6	6	6	6	6
Erythrocytes	6	6	6	6	6
0~20 cells/100 fields	6	6	6	6	6
Leukocytes	6	6	6	6	6
0~20 cells/100 fields	6	6	6	6	6
Casts	6	6	6	6	6
Not observed	1	3	2	1	1
Crystals	5	3	4	5	5
Not observed					
Observed					

Table 27-1 Urinary 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	
	0	62.5	250	1000
mg/kg				
Number of males	6	6	6	6
Volume (mL): Mean ± S.D.	20.0 ± 9.2	19.8 ± 6.5	15.2 ± 5.4	12.7 ± 2.2
Specific gravity: Mean ± S.D.	1.043 ± 0.020	1.042 ± 0.011	1.052 ± 0.015	1.056 ± 0.008
Color				
Light yellow	6	6	6	6
pH				
7.5	0	0	1	0
8.0	0	0	1	0
8.5	6	6	3	6
9.0	0	0	1	0
Protein				
10~20 mg/dL	0	1	0	0
30 mg/dL	3	2	4	1
100 mg/dL	3	3	2	5
Glucose				
Negative	6	6	6	6
Ketone body				
Negative	6	6	6	4
Slight	0	0	0	2
Bilirubin				
Negative	6	6	6	6
Occult blood				
Negative	5	5	6	6
Trace	1	1	0	0
Urobilinogen				
Normal	6	6	6	6

Table 27-2 Urinary 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		
	0	62.5	250	1000	
mg/kg					
Number of males	6	6	6	6	6
Urinary sediments					
Epithelial cells	6	6	6	6	6
0~20 cells/100 fields					
Erythrocytes	6	6	6	6	6
0~20 cells/100 fields					
Leukocytes	6	6	6	6	6
0~20 cells/100 fields					
Casts	6	6	6	6	6
Not observed					
Crystals	4	4	4	4	3
Not observed					
Observed	2	2	2	2	3

Table 28-1 Urinary 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	
	0	250	250	1000
mg/kg				
Number of females	6	6	6	6
Volume (mL): Mean ± S.D.	12.4 ± 4.1	13.3 ± 3.1	10.0 ± 3.4	
Specific gravity: Mean ± S.D.	1.050 ± 0.013	1.046 ± 0.005	1.058 ± 0.009	
Color				
Light yellow	6	6	6	6
pH				
7.0	0	0	1	
8.5	5	4	2	
9.0	1	2	3	
Protein				
Negative	3	3	3	
10~20 mg/dL	2	2	3	
30 mg/dL	1	1	0	
Glucose				
Negative	6	6	6	
Ketone body				
Negative	6	6	6	
Bilirubin				
Negative	6	6	6	
Occult blood				
Negative	5	5	6	
Trace	1	1	0	
Urobilinogen				
Normal	6	6	6	

Table 28-2 Urinary 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	
	0	250	1000	
mg/kg				
Number of females	6	6	6	6
Urinary sediments				
Epithelial cells	6	6	6	6
0~20 cells/100 fields				
Erythrocytes	6	6	6	6
0~20 cells/100 fields				
Leukocytes	6	6	6	6
0~20 cells/100 fields				
Casts				
Not observed	6	6	6	6
Crystals				
Not observed	2	3	3	3
Observed	4	3	3	3

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	
	0	6	250	1000
mg/kg				
Number of males	45	6	6	6
RBC (10 ⁶ /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 ³ /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	
	0	6	250	1000
mg/kg				
Number of females	6	6	6	6
RBC (10 ⁶ /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 ⁶ /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 mg/kg	Control		bumetrizole	
	0	6	62.5	250
Number of males	6		6	
RBC (10 ⁶ /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 ³ /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 ³ /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	
	0	250	1000	
mg/kg				
Number of females	6	6	6	6
RBC (10 ⁶ /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 ³ /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 ³ /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 mg/kg	Control		bumetrizole	
	0	6	62.5	250
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-Chol (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 (mg/dL)	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 mg/kg	Control		bumetrizole				
	0	6	62.5		250		1000
	Number of females		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 mg/kg	Control		bumetrizole	
	0	6	62.5	250
	6		6	
Number of males	0	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-Chol (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 mg/kg	Control		bumetrizole	
	0	6	250	1000
	Number of females		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		
	0	62.5	250	250	1000	1000
mg/kg						
Number of males	6	6	6	6	6	6
Normal	5	6	6	6	6	6
Epididymis						
Yellowish white nodule, left cauda	1	0	0	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	mg/kg	bumetrizole			
		Control	62.5	250	1000
Number of dams		0	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		
	0	62.5	250	250	1000	1000
mg/kg						
Number of males	6	6	6	6	6	6
Normal	6	6	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	mg/kg	bumetrizole	
		Control	bumetrizole
		0	250
Number of females		6	6
Normal		6	6
			1000
			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	
	0	6	62.5	250
mg/kg				
Number of males				
Body weight	459 ± 29	461 ± 25	457 ± 13	461 ± 16
Brain	2.11 ± 0.10	2.12 ± 0.10	2.13 ± 0.05	2.06 ± 0.08
	0.46 ± 0.02	0.46 ± 0.03	0.47 ± 0.02	0.45 ± 0.02
Pituitary	14.4 ± 1.7	13.0 ± 2.2	12.6 ± 0.7	12.4 ± 1.9
	3.2 ± 0.3	2.8 ± 0.5	2.8 ± 0.2	2.7 ± 0.4
Thyroids	21.4 ± 4.7	22.7 ± 2.6	20.7 ± 3.9	19.0 ± 2.4
	4.7 ± 0.9	4.9 ± 0.6	4.6 ± 0.9	4.1 ± 0.5
Thymus	244 ± 50	285 ± 103	228 ± 41	216 ± 79
	53 ± 9	61 ± 19	50 ± 10	47 ± 17
Heart	1.37 ± 0.11	1.52 ± 0.16	1.39 ± 0.08	1.47 ± 0.09
	0.30 ± 0.02	0.33 ± 0.03	0.30 ± 0.02	0.32 ± 0.02
Liver	11.17 ± 0.71	11.38 ± 1.06	11.23 ± 0.94	11.44 ± 0.68
	2.44 ± 0.13	2.47 ± 0.12	2.45 ± 0.15	2.48 ± 0.14
Spleen	0.72 ± 0.08	0.71 ± 0.13	0.77 ± 0.10	0.67 ± 0.10
	0.16 ± 0.01	0.15 ± 0.02	0.17 ± 0.02	0.15 ± 0.02
Kidneys	2.97 ± 0.26	2.86 ± 0.16	2.98 ± 0.17	3.00 ± 0.28
	0.65 ± 0.05	0.62 ± 0.04	0.65 ± 0.03	0.65 ± 0.06
Adrenals	63.5 ± 7.4	62.1 ± 8.9	59.3 ± 13.8	64.3 ± 7.6
	13.9 ± 1.2	13.5 ± 1.8	13.0 ± 3.0	14.0 ± 1.7
Testes	3.33 ± 0.25	3.31 ± 0.37	3.47 ± 0.08	3.23 ± 0.34
	0.73 ± 0.04	0.72 ± 0.06	0.76 ± 0.03	0.70 ± 0.06
Epididymides	1.29 ± 0.09	1.26 ± 0.12	1.29 ± 0.12	1.20 ± 0.07
	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		
	0	11	62.5	250	1000
mg/kg					
Number of females		11	12	12	11
Body weight	307 ± 20		304 ± 21	303 ± 25	300 ± 28
Brain	1.97 ± 0.08	(g)	1.97 ± 0.06	2.01 ± 0.10	1.97 ± 0.09
	0.64 ± 0.04	(g%)	0.65 ± 0.03	0.67 ± 0.05	0.66 ± 0.07
Pituitary	18.2 ± 2.2	(mg)	17.9 ± 3.0	18.0 ± 1.7	16.4 ± 1.6
	6.0 ± 0.7	(mg%)	5.9 ± 0.9	6.0 ± 0.6	5.5 ± 0.8
Thyroids	18.3 ± 2.2	(mg)	18.1 ± 3.7	18.0 ± 1.9	17.9 ± 2.5
	6.0 ± 0.8	(mg%)	6.0 ± 1.2	6.0 ± 0.7	6.0 ± 0.8
Thymus	270 ± 84	(mg)	327 ± 63	267 ± 56	266 ± 60
	87 ± 24	(mg%)	107 ± 19*	88 ± 15	89 ± 19
Heart	1.04 ± 0.11	(g)	1.00 ± 0.08	1.00 ± 0.08	1.03 ± 0.08
	0.34 ± 0.02	(g%)	0.33 ± 0.02	0.33 ± 0.02	0.35 ± 0.03
Liver	9.29 ± 0.77	(g)	9.70 ± 1.19	9.95 ± 1.33	9.77 ± 0.89
	3.03 ± 0.20	(g%)	3.18 ± 0.21	3.28 ± 0.37	3.26 ± 0.25
Spleen	0.68 ± 0.12	(g)	0.74 ± 0.11	0.75 ± 0.11	0.70 ± 0.08
	0.22 ± 0.03	(g%)	0.24 ± 0.03	0.25 ± 0.03	0.24 ± 0.03
Kidneys	2.00 ± 0.14	(g)	2.05 ± 0.15	2.05 ± 0.19	2.03 ± 0.16
	0.65 ± 0.04	(g%)	0.67 ± 0.04	0.68 ± 0.06	0.68 ± 0.07
Adrenals	76.6 ± 11.5	(mg)	75.6 ± 5.8	77.4 ± 11.8	75.6 ± 10.2
	25.0 ± 3.8	(mg%)	24.9 ± 1.8	25.6 ± 3.5	25.3 ± 3.2
Ovaries	98.7 ± 13.9	(mg)	94.2 ± 11.0	99.9 ± 9.6	103.5 ± 9.8
	32.2 ± 4.1	(mg%)	31.0 ± 3.2	33.1 ± 3.9	34.7 ± 3.4
Uterus	0.54 ± 0.10	(g)	0.59 ± 0.14	0.57 ± 0.04	0.56 ± 0.10
	0.18 ± 0.04	(g%)	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 mg/kg	Control		bumetrizole	
	0	6	62.5	250
Number of males			6	6
Body weight (g)	504 ± 30		508 ± 27	494 ± 37
Brain (g)	2.12 ± 0.05		2.10 ± 0.08	2.08 ± 0.08
(g%)	0.42 ± 0.03		0.41 ± 0.03	0.42 ± 0.03
Pituitary (mg)	13.6 ± 1.2		15.0 ± 1.6	13.5 ± 1.7
(mg%)	2.7 ± 0.2		3.0 ± 0.4	2.7 ± 0.3
Thyroids (mg)	20.7 ± 3.8		25.5 ± 4.2	21.4 ± 4.6
(mg%)	4.1 ± 0.9		5.0 ± 0.7	4.3 ± 0.9
Thymus (mg)	262 ± 77		257 ± 55	276 ± 59
(mg%)	52 ± 15		51 ± 12	56 ± 10
Heart (g)	1.55 ± 0.16		1.47 ± 0.17	1.45 ± 0.15
(g%)	0.31 ± 0.04		0.29 ± 0.03	0.29 ± 0.03
Liver (g)	12.18 ± 0.91		12.43 ± 0.90	11.99 ± 1.60
(g%)	2.42 ± 0.09		2.45 ± 0.09	2.42 ± 0.16
Spleen (g)	0.79 ± 0.11		0.77 ± 0.07	0.77 ± 0.13
(g%)	0.16 ± 0.02		0.15 ± 0.02	0.16 ± 0.02
Kidneys (g)	2.96 ± 0.23		3.10 ± 0.23	2.85 ± 0.26
(g%)	0.59 ± 0.05		0.61 ± 0.06	0.58 ± 0.02
Adrenals (mg)	59.1 ± 5.3		57.1 ± 9.5	53.1 ± 8.0
(mg%)	11.8 ± 1.4		11.3 ± 1.9	10.7 ± 1.3
Testes (g)	3.24 ± 0.11		3.36 ± 0.46	3.59 ± 0.35
(g%)	0.65 ± 0.04		0.66 ± 0.11	0.73 ± 0.09
Epididymides (g)	1.31 ± 0.10		1.30 ± 0.05	1.36 ± 0.14
(g%)	0.26 ± 0.02		0.26 ± 0.01	0.28 ± 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 mg/kg	Control		bumetrizole	
	0	250	1000	6
Number of females	6	6	6	6
Body weight (g)	316 ± 24	323 ± 25	303 ± 8	8
Brain (g)	1.98 ± 0.07	2.02 ± 0.14	2.01 ± 0.06	
Pituitary (g%)	0.63 ± 0.05	0.63 ± 0.08	0.67 ± 0.01	
Thyroids (mg)	17.0 ± 2.6	18.2 ± 1.6	18.7 ± 2.8	
Thymus (mg%)	5.4 ± 1.1	5.7 ± 0.7	6.2 ± 0.8	
Heart (mg)	19.0 ± 3.7	19.2 ± 5.7	17.7 ± 3.7	
Liver (mg%)	6.1 ± 1.2	5.9 ± 1.5	5.8 ± 1.2	
Spleen (mg)	303 ± 43	326 ± 60	282 ± 40	
Kidneys (mg%)	96 ± 14	101 ± 18	93 ± 12	
Adrenals (g)	0.97 ± 0.07	0.97 ± 0.11	0.98 ± 0.05	
Ovaries (g%)	0.31 ± 0.02	0.30 ± 0.02	0.33 ± 0.02	
Uterus (g)	7.81 ± 0.68	7.58 ± 0.66	7.45 ± 0.32	
Brain (g%)	2.47 ± 0.10	2.35 ± 0.12	2.46 ± 0.11	
Pituitary (g)	0.56 ± 0.09	0.57 ± 0.09	0.59 ± 0.09	
Thyroids (g%)	0.18 ± 0.02	0.18 ± 0.03	0.20 ± 0.03	
Thymus (g)	1.93 ± 0.10	1.88 ± 0.11	1.93 ± 0.11	
Heart (g%)	0.61 ± 0.05	0.59 ± 0.04	0.64 ± 0.04	
Liver (mg)	72.0 ± 9.5	66.0 ± 6.8	71.2 ± 2.9	
Spleen (mg%)	22.8 ± 1.8	20.6 ± 2.4	23.5 ± 1.3	
Kidneys (mg)	85.8 ± 9.7	74.1 ± 5.9 *	79.9 ± 7.6	
Adrenals (mg%)	27.2 ± 2.5	23.1 ± 2.3 *	26.4 ± 2.7	
Ovaries (g)	0.54 ± 0.18	0.62 ± 0.16	0.60 ± 0.12	
Uterus (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 mg/kg	Control						bumetrizole					
	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 mg/kg	Control						bumetrizole					
	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	
	0	62.5	250	1000
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 (F₁) in combined repeat dose and reproductive/development toxicity screening test of bumetrizole by oral administration

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

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.

c): Number of male pups/number of female pups.

e): (Number of live pups born/number of implantation scars)×100.

g): (Number of live pups on Day 4/number of live pups born)×100.

b): (Number of dams with live pups/number of pregnant dams)×100.

d): (Number of pups born/number of implantation scars)×100.

f): (Number of live pups born/number of 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	
		Normal	11	11	11	11	11	
bumetrizole	62.5	Number of dams	12	12	12	12	12	
		Normal	12	12	12	12	12	
	250	Number of dams	12	12	12	12	12	
		Normal	12	12	12	12	12	
1000	Number of dams	11	11	11	11	11		
	Normal	11	11	11	11	11		

Table 50 General signs of pups (F₁) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration.

Group	mg/kg	Number of pups and general signs	Days of lactation				
			0	1	2	3	4
Control	0	Number of pups	152	150	150	149	149
		Normal	150	150	149	149	148
		Death	2	0	1	0	1
bumetrizole	62.5	Number of pups	166	161	160	159	159
		Normal	161	160	159	159	157
	Death	5	1	1	0	2	
	250	Number of pups	168	161	159	159	159
Normal		161	159	159	159	159	
		Death	7	2	0	0	0
	1000	Number of pups	162	158	157	157	156
Normal		158	157	157	156	156	
		Death	4	1	0	1	0

Table 51 Body weights of pups (F₁) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	62.5	250	1000
Number of dams	11	12	12	11
Male weight				
Days of lactation	0	7.2 ± 0.7	7.0 ± 0.6	6.8 ± 0.4
	4	11.2 ± 0.8	11.4 ± 1.4	10.8 ± 0.7
Female weight				
Days of lactation	0	6.8 ± 0.6	6.6 ± 0.7	6.4 ± 0.7
	4	10.4 ± 0.8	10.8 ± 1.5	10.3 ± 0.9
Mean pups weight				
Days of lactation	0	7.0 ± 0.7	6.9 ± 0.6	6.6 ± 0.6
	4	10.6 ± 0.8	11.1 ± 1.4	10.6 ± 0.7
Litter weight				
Days of lactation	0	90.5 ± 9.3	93.8 ± 16.4	94.8 ± 10.9
	4	143.8 ± 15.1	142.0 ± 19.4	145.5 ± 20.6

Each value shows mean (g) ± S.D. per dam.

Table 52 Necropsy findings of dead pups (F₁) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole		
	0	62.5	250	1000	
mg/kg	0	62.5	250	1000	
Number of dams	1	4	5	4	
Number of dead pups	1	4	6	4	
Normal	1	4	5	4	
Abnormal	0	0	1	0	
Lack of abdominal organs	0	0	1	0	

Table 53 Necropsy findings of pups (F₁) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

Group	Control		bumetrizole	
	0	62.5	250	1000
mg/kg	0	62.5	250	1000
Number of dams	11	12	12	11
Number of male pups	75	84	90	81
Normal	75	84	90	81
Abnormal	0	0	0	0
Number of dams	11	12	12	11
Number of female pups	73	73	69	75
Normal	73	73	69	75
Abnormal	0	0	0	0

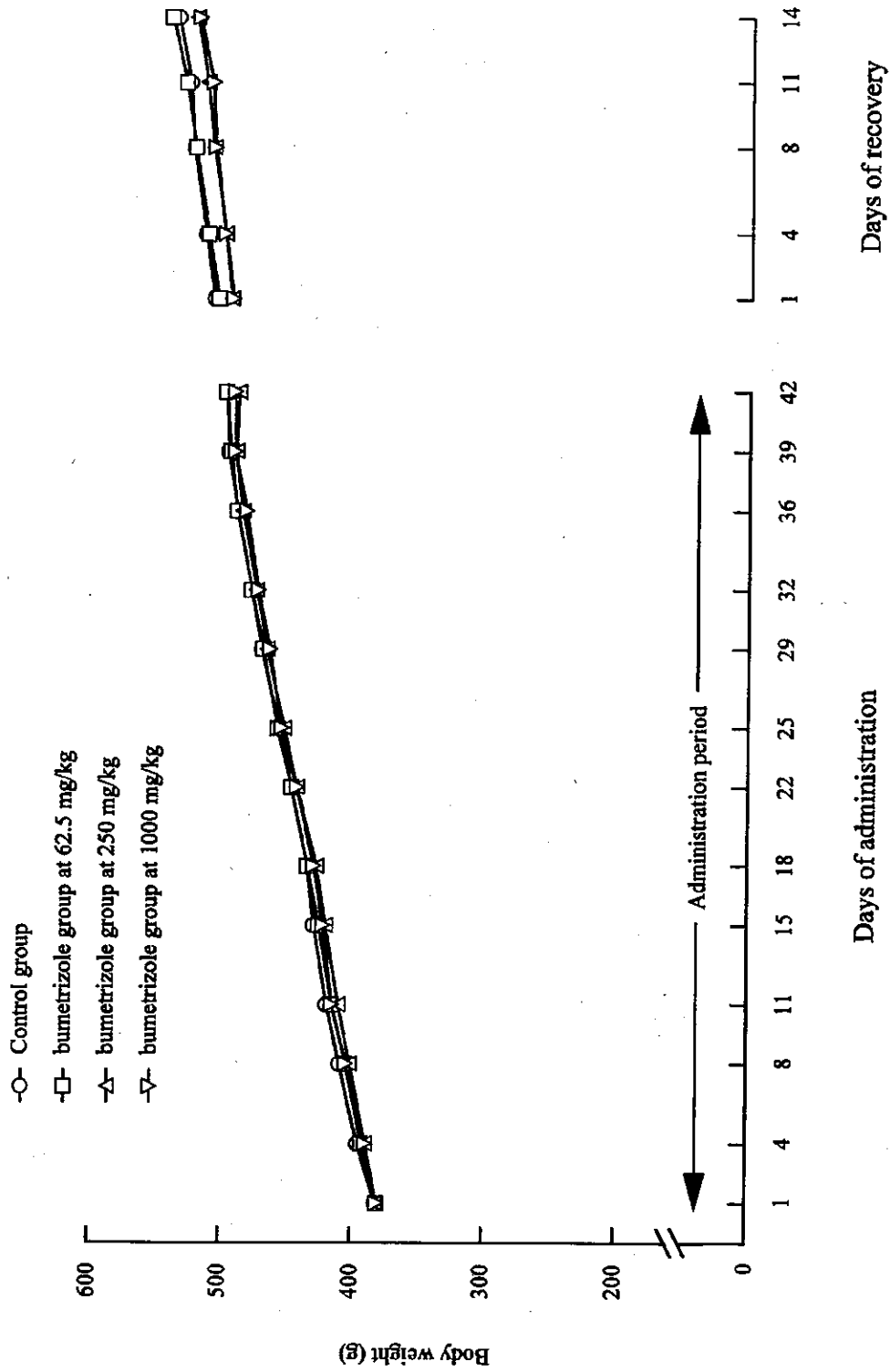


Fig. 2 Body weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

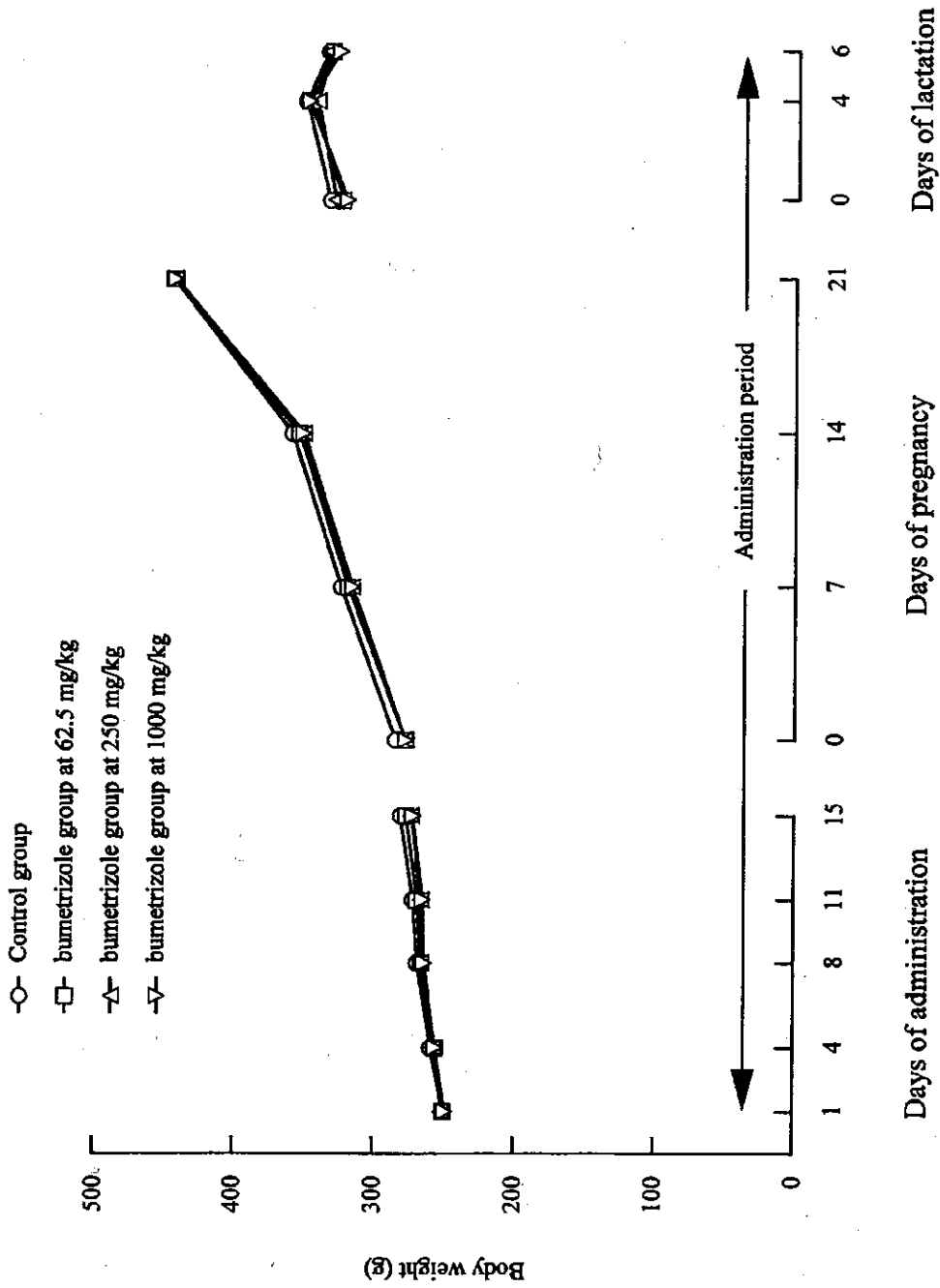


Fig. 3 Body weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

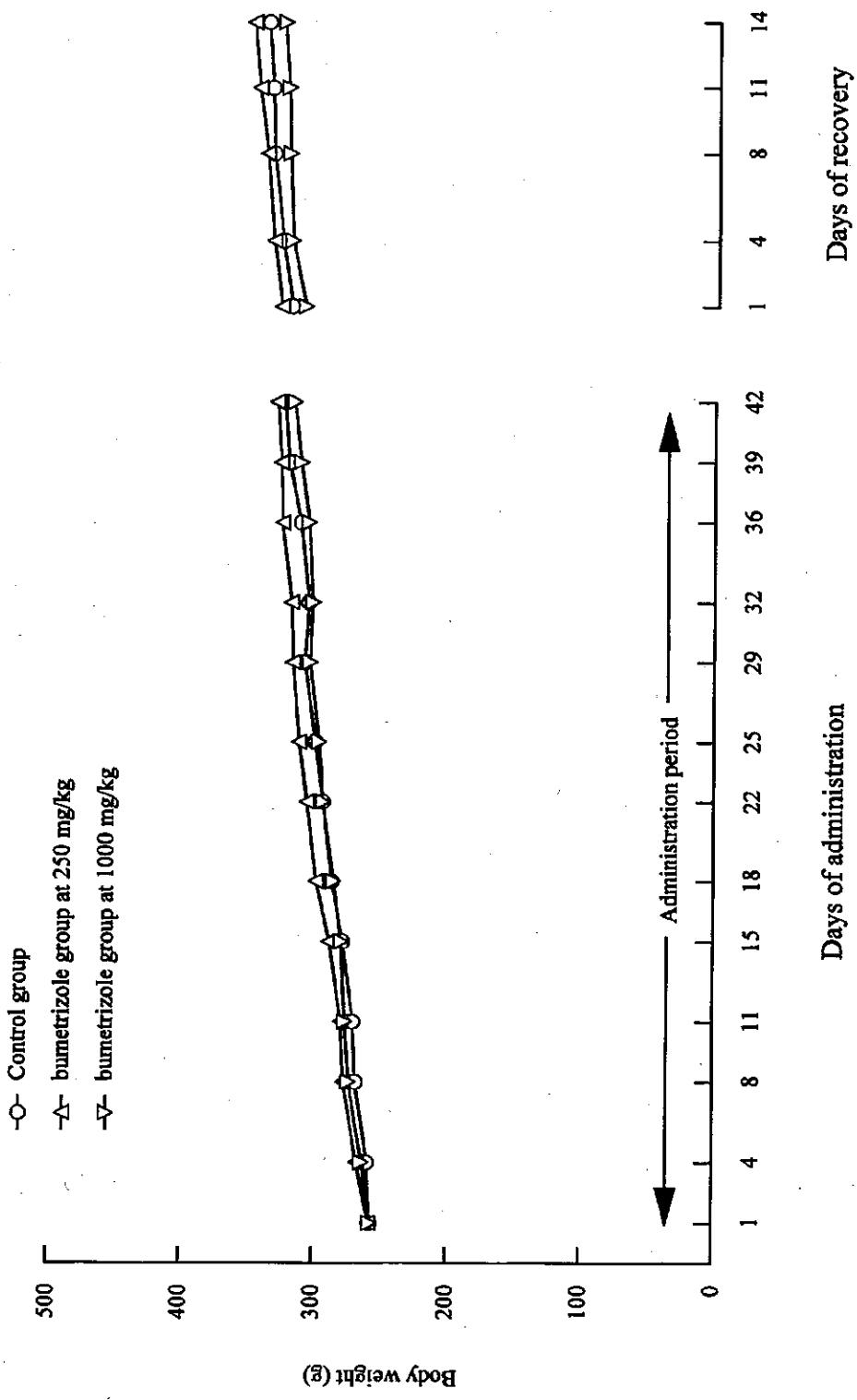


Fig. 4 Body weights of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

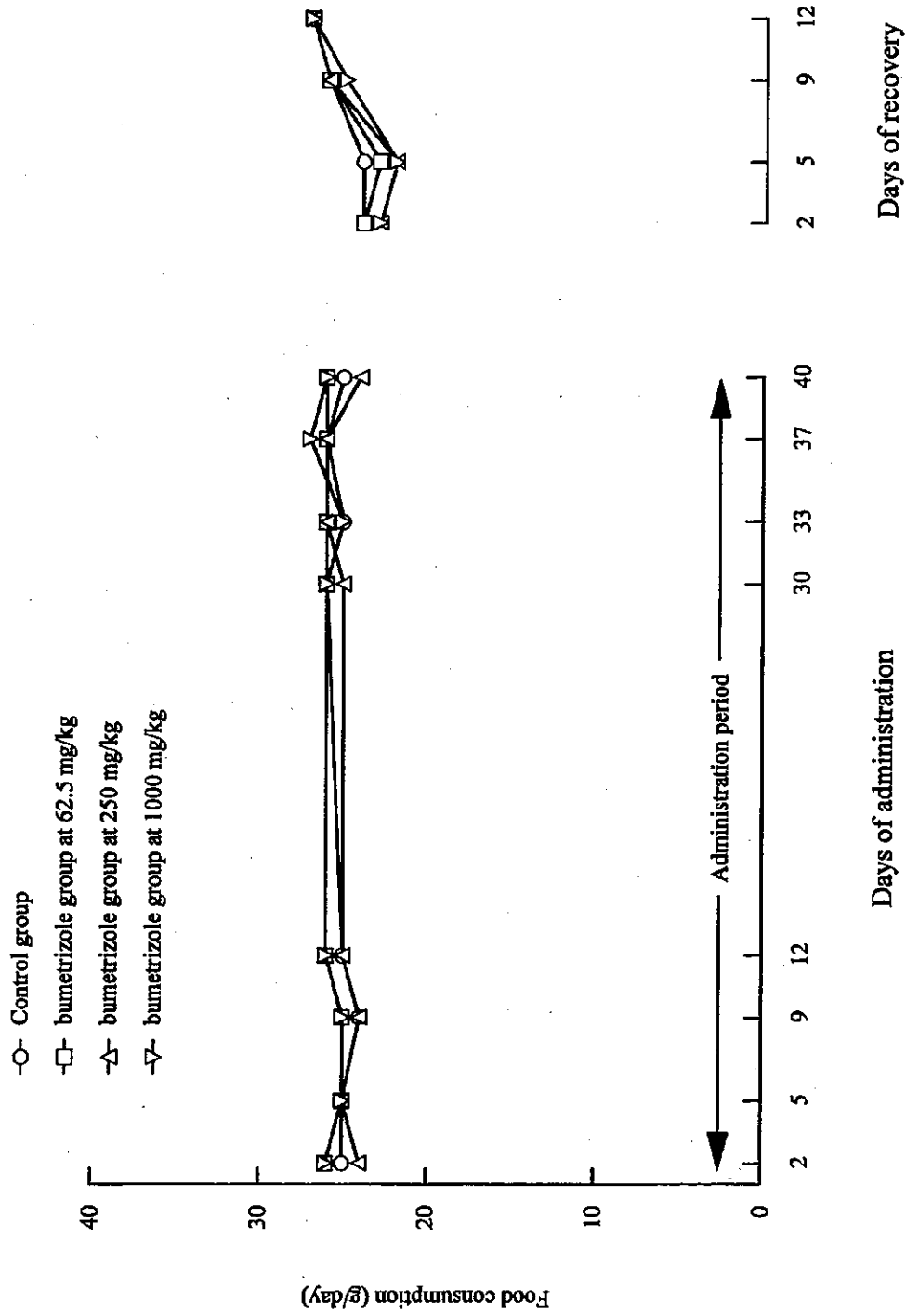


Fig. 5 Food consumption of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

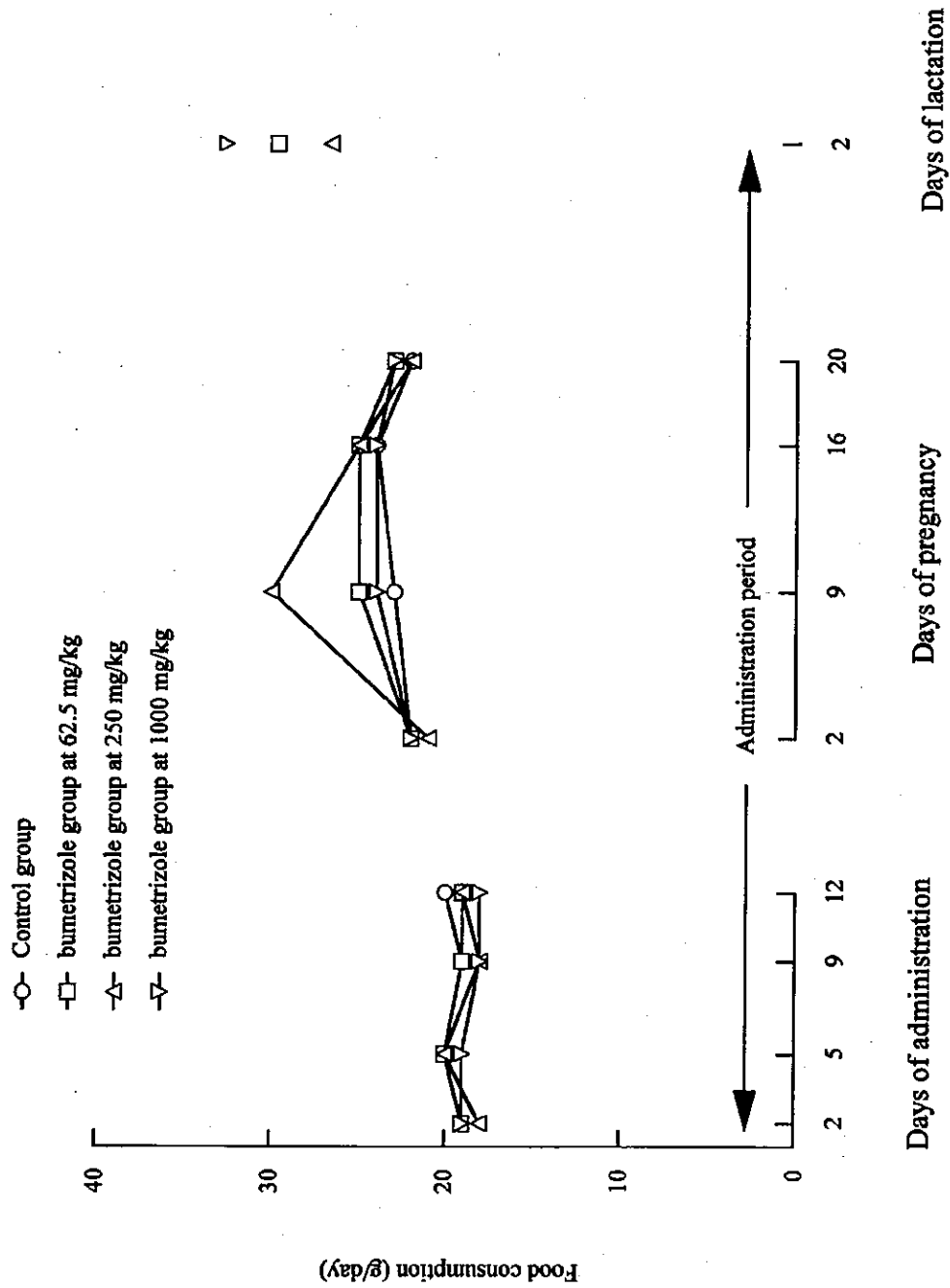


Fig. 6 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration

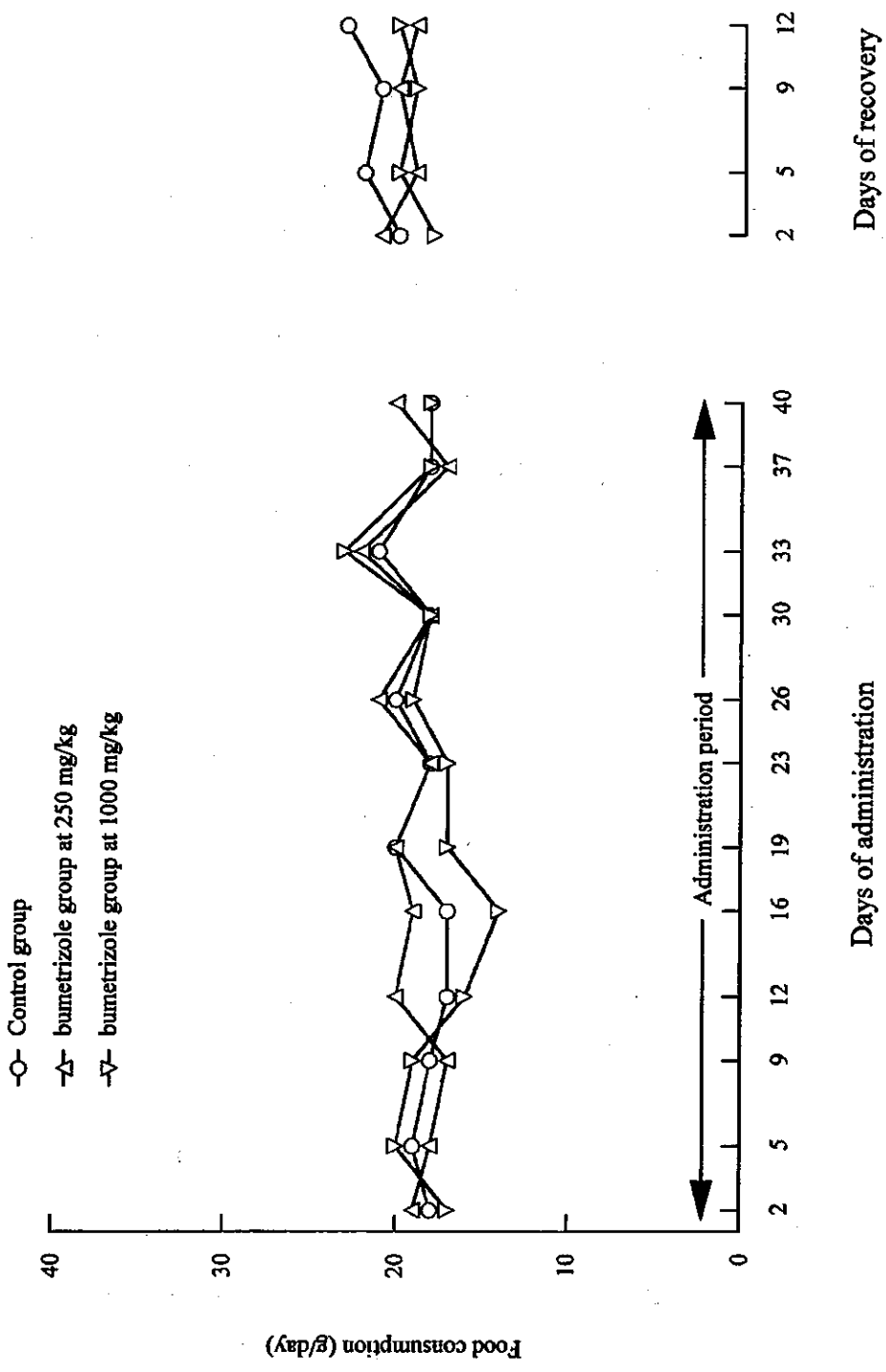


Fig. 7 Food consumption of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetrizole by oral administration