

Table 17-4 FOB of 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	12
Observation of animals on observer's palm						
Lacrimation	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 8	1.0 (1)	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)	1.0 (1)
	Day 1 of pregnancy	1.0 (1) [11]	1.0 (1)	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)	1.0 (1) [11]
	Day 15 of pregnancy	1.0 (1) [11]	1.0 (1)	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)	1.0 (1) [11]
Salivation	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 8	1.0 (1)	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)	1.0 (1)
	Day 1 of pregnancy	1.0 (1) [11]	1.0 (1)	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)	1.0 (1) [11]
	Day 15 of pregnancy	1.0 (1) [11]	1.0 (1)	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)	1.0 (1) [11]
Respiration	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 8	1.0 (1)	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)	1.0 (1)
	Day 1 of pregnancy	1.0 (1) [11]	1.0 (1)	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)	1.0 (1) [11]
	Day 15 of pregnancy	1.0 (1) [11]	1.0 (1)	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)	1.0 (1) [11]

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		62.5		bumetrizole		250		1000		
mg/kg		0		12		12		12		12		
Number of females		12		12		12		12		12		
Open-field test												
Frequency of rearing	Pre	9.3 ± 4.8		8.8 ± 4.3		8.4 ± 5.2		9.8 ± 5.4				
	Mean ± S.D.											
Mean ± S.D.	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	[11]	6.3 ± 3.8		4.4 ± 3.9		5.2 ± 3.8	[11]			
	Day 8 of pregnancy	7.8 ± 4.8	[11]	6.1 ± 3.6		7.1 ± 3.2		6.7 ± 4.7	[11]			
	Day 15 of pregnancy	6.3 ± 5.8	[11]	6.4 ± 3.8		6.4 ± 4.9		8.5 ± 5.4	[11]			
	Day 3 of lactation	5.9 ± 4.6	[11]	5.7 ± 2.7		5.2 ± 3.7		5.2 ± 3.9	[11]			
	Frequency of grooming	Pre	0.0 ± 0.0		0.0 ± 0.0		0.2 ± 0.6		0.1 ± 0.3			
		Mean ± S.D.										
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	[11]	0.0 ± 0.0		0.0 ± 0.0		0.0 ± 0.0	[11]			
Day 8 of pregnancy		0.0 ± 0.0	[11]	0.0 ± 0.0		0.0 ± 0.0		0.3 ± 0.6	[11]			
Day 15 of pregnancy		0.0 ± 0.0	[11]	0.0 ± 0.0		0.0 ± 0.0		0.0 ± 0.0	[11]			
Day 3 of lactation		0.5 ± 0.9	[11]	0.3 ± 0.7		0.5 ± 0.9		0.1 ± 0.3	[11]			
Gait	Pre	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)				
	Mean (range)											
	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]			
Palpebral closure	Pre	1.0 (1)		1.0 (1)		1.0 (1)		1.0 (1)				
	Mean (range)											
	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.

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 17-6 FOB of 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			
Open-field test									
Consciousness	Pre	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)
Behavioral abnormalities	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)	[11]
	Day 8 of pregnancy	2.0	(2)	[11]	2.0	(2)	2.0	(2)	[11]
	Day 15 of pregnancy	2.0	(2)	[11]	2.0	(2)	2.0	(2)	[11]
	Day 3 of lactation	2.0	(2)	[11]	2.0	(2)	2.0	(2)	[11]
	Pre	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)	
Righting reflex	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)	[11]
	Day 8 of pregnancy	1.0	(1)	[11]	1.0	(1)	1.0	(1)	[11]
	Day 15 of pregnancy	1.0	(1)	[11]	1.0	(1)	1.0	(1)	[11]
	Day 3 of lactation	1.0	(1)	[11]	1.0	(1)	1.0	(1)	[11]
	Pre	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)	
Righting reflex	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)	[11]
	Day 8 of pregnancy	1.0	(1)	[11]	1.0	(1)	1.0	(1)	[11]
	Day 15 of pregnancy	1.0	(1)	[11]	1.0	(1)	1.0	(1)	[11]
	Day 3 of lactation	1.0	(1)	[11]	1.0	(1)	1.0	(1)	[11]
	Pre	1.0	(1)	1.0	(1)	1.0	(1)	1.0	(1)

Figures in parentheses [] indicate number of females.

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 18-1 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				
Posture 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)
	Palpebral closure Mean (range)	Pre	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)
Biting behavior Mean (range)		Pre	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)
	Clonic convulsions Mean (range)	Pre	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

- 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	Pre	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory 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		Control	bumetrizole	
mg/kg		0	250	1000
Number of females		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)			
Ease of handling	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)
	Pre	2.0 (2)	2.0 (2)	2.0 (2)
	Mean (range)			
Muscle tone	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)
	Pre	2.0 (2)	2.0 (2)	2.0 (2)
	Mean (range)			
Fur conditions	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)
	Pre	1.0 (1)	1.0 (1)	1.0 (1)
	Mean (range)			

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 18-4 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 on observer's palm				
Lacrimation	Pre	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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)
Salivation	Pre	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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)
Respiration	Pre	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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

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			
mg/kg		0		250		1000	
Number of females		6		6		6	
Open-field test							
Frequency of rearing	Pre	5.5 ±	2.9	10.7 ±	2.9 *	6.2 ±	3.3
	Mean ± S.D.						
Mean ± S.D.	Day 8	4.8 ±	5.3	6.0 ±	3.7	3.3 ±	2.3
	Day 15	6.0 ±	4.6	8.8 ±	5.7	6.0 ±	3.9
	Day 22	5.0 ±	4.3	7.0 ±	4.6	5.7 ±	2.9
	Day 29	4.5 ±	3.3	8.8 ±	4.5	7.5 ±	3.8
	Day 36	3.5 ±	1.9	11.2 ±	4.4 **	7.7 ±	3.1
	Day 42	9.0 ±	2.0	11.5 ±	4.1	8.5 ±	5.2
Frequency of grooming	Pre	0.0 ±	0.0	0.0 ±	0.0	0.2 ±	0.4
	Mean ± S.D.						
Mean ± S.D.	Day 8	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
	Day 22	0.0 ±	0.0	0.0 ±	0.0	0.0 ±	0.0
	Day 29	0.0 ±	0.0	0.2 ±	0.4	0.0 ±	0.0
	Day 36	0.0 ±	0.0	0.3 ±	0.8	0.3 ±	0.8
	Day 42	0.0 ±	0.0	0.0 ±	0.0	0.0 ±	0.0
Gait	Pre	1.0	(1)	1.0	(1)	1.0	(1)
	Mean (range)						
Mean (range)	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)
Palpebral closure	Pre	1.0	(1)	1.0	(1)	1.0	(1)
	Mean (range)						
Mean (range)	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)

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	
mg/kg		0	250	1000
Number of females		6	6	6
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)
	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)
	Behavioral abnormalities Mean (range)	Pre	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)
Righting reflex Mean (range)		Pre	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

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 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			
mg/kg	0		62.5	250		1000
Number of males	6		6	6		6
Pupillary reflex						
Mean (range)	1.0	(1)	1.0	(1)	1.0	(1)
Approaching behavior						
Mean (range)	2.0	(2)	2.0	(2)	2.0	(2)
Response to touch						
Mean (range)	2.0	(2)	2.0	(2)	2.0	(2)
Auditory reflex						
Mean (range)	2.0	(2)	2.0	(2)	2.0	(2)
Pain reflex						
Mean (range)	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 mg/kg	Control		bumetrizole					
	0		62.5		250		1000	
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,
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 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	Control	bumetrizole		
mg/kg	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	62.5	250	1000
Number of females	6	6	6	6
Forelimb	959 ± 185	791 ± 90	799 ± 145	860 ± 240
Hindlimb	121 ± 48	93 ± 41	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	Control		bumetrizole					
mg/kg	0		62.5		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					
mg/kg	0		62.5		250		1000	
Number of females	6		6		6		6	
Ambulatory counts								
Minutes after administration								
10	1015 ±	496	922 ±	301	891 ±	450	1222 ±	1334
20	331 ±	500	262 ±	363	329 ±	472	1600 ±	2466
30	73 ±	156	75 ±	180	192 ±	298	850 ±	1599
40	107 ±	179	67 ±	161	164 ±	224	726 ±	1256
50	68 ±	125	35 ±	80	964 ±	2065	656 ±	1255
60	9 ±	22	94 ±	227	52 ±	123	685 ±	1259
Total	1604 ±	1068	1455 ±	1246	2592 ±	2969	5740 ±	9110
Vertical counts								
Minutes after administration								
10	30 ±	9	42 ±	26	27 ±	15	38 ±	36
20	9 ±	12	9 ±	12	11 ±	13	98 ±	215
30	5 ±	12	2 ±	5	7 ±	11	10 ±	18
40	3 ±	5	2 ±	4	6 ±	11	2 ±	4
50	2 ±	3	1 ±	2	4 ±	6	1 ±	2
60	0 ±	0	2 ±	6	2 ±	4	0 ±	0
Total	48 ±	31	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 mg/kg	Control		bumetrizole					
	0		62.5		250		1000	
Number of males	6		6		6		6	
Volume (mL): Mean ± S.D.	17.0 ± 4.8		23.3 ± 7.5		17.2 ± 4.4		14.6 ± 3.7	
Specific gravity: Mean ± S.D.	1.044 ± 0.005		1.032 ± 0.010		1.047 ± 0.008		1.054 ± 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 25-2 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		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Urinary sediments				
Epithelial cells				
0~20 cells/100 fields	6	6	6	6
Erythrocytes				
0~20 cells/100 fields	6	6	6	6
Leukocytes				
0~20 cells/100 fields	6	6	6	6
Casts				
Not observed	6	6	6	6
Crystals				
Not observed	4	3	4	3
Observed	2	3	2	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 mg/kg	Control		bumetrizole					
	0		62.5		250		1000	
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		
mg/kg	0	62.5	250	1000
Number of females	6	6	6	6
Urinary sediments				
Epithelial cells				
0~20 cells/100 fields	6	6	6	6
Erythrocytes				
0~20 cells/100 fields	6	6	6	6
Leukocytes				
0~20 cells/100 fields	6	6	6	6
Casts				
Not observed	6	6	6	6
Crystals				
Not observed	1	3	2	1
Observed	5	3	4	5

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