

## 反復投与毒性・生殖発生毒性併合試験結果報告書

## 1. 一般的事項

新規化学物質等の名称 (IUPAC命名法による)	bumetizole [2-(2'-Hydroxy-3-tert-butyl-5'-methylphenyl)-5-chlorobenzotriazole] (ブメトリゾール)		
別 名	2-(2'-ヒドロキシ-3-tert-ブチル-5'-メチルフェニル)-5-クロロベンゾトリアゾール		
C A S 番号	3896-11-5		
構造式又は示性式 (いずれも不明の場合は、 その製法の概要)			
分子量	315.80		
試験に供した新規 化学物質の純度 (%)	99.9%		
試験に供した新規 化学物質のロット番号	01721IW4		
不純物の名称 及び含有率	—		
蒸気圧	$7.5 \times 10^{-7}$ Pa (20°C)		
対水溶解度	< 1 mg/L (20°C) EEC A6		
1-オクタノール/水分配係数	—		
融 点	138-141°C		
沸 点	—		
常温における性状	淡黄色粉末、臭いなし		
安定性	分解温度: 350°C以上		
溶媒に対する溶解度等	溶媒	溶解度	溶媒中の安定性
	—	—	—

[備考] 物理化学的性状は、可能な限り記入すること。

- 「蒸気圧」の欄には、被験物質の蒸気圧を記入すること。
- 「分配係数」の欄には、分配係数、測定温度及び分配係数の測定に用いた溶媒名を記入すること。
- 「安定性」の欄には、温度、光等に対する安定性を記入すること。
- 「溶媒に対する溶解度等」の欄には、被験物質の溶媒に対する溶解度及びその溶媒中での安定性を記入すること。

## 2. 急性毒性試験又は反復投与予備試験等

試験 №	試験の種類 及び期間	動物種	1群当たり の動物数	投与 経路	投与量 (mg/kg)	概略の致死量 又はNOEL (mg/kg)	実験場所
1	単回投与毒性試験	ラット Crj:CD (SD) IGS	雌6匹	強制経口 投与	2000	GHSのカテゴリー5に分類される。 死亡例は認められなかった。	(株)日本バイオ リサーチセンタ ー 羽島研究所
2	投与量設定試験 (14日間)	ラット Crj:CD (SD) IGS	雄 5匹	強制経口 投与	0、250、500、 1000	死亡例は認められなかっ た。 一般状態、体重、摂餌量 及び剖検所見に異常は みられなかった。	(株)日本バイオ リサーチセンタ ー 羽島研究所

\* NOEL: no observed effect level

## 4. 反復投与毒性・生殖発生毒性併合試験

## 1) 反復投与毒性

被験物質投与期間	雄:2005年6月1日～2005年7月12日[計42日間], 雌(試験群):2005年6月1日～2005年7月26日[計44～56日間] 雌(回復群):2005年6月2日～2005年7月13日[計42日間]																
使用動物種・系統	ラット, Crl:CD(SD)				1群当たりの動物数												
投与経路	強制経口投与				対照群, 低用量群, 中用量群, 高用量群: 雄各12匹, 雌各12匹 (回復群: 対照群, 中用量群, 高用量群; 雌雄各6匹, 低用量群; 雄6匹)												
被験物質の純度 99.9%	投与量 (mg/kg)	対照群		低用量群		中用量群		高用量群		0		62.5		250		1000	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀		
体重変化		—	—	—	—	—	—	—	—	—	*	—	—	—	—		
摂餌量		—	—	—	—	—	—	—	—	—	*	▽ <sup>a)</sup>	—	—	—		
一般状態	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
機能観察所見(N) FOB 立ち上がり	12	12	12	12	12	12	12	12	12	*	6	*	*	*	6	*	
感覚反応		—	—	—	—	—	—	—	—	*	*	*	*	*	*	*	
握力		—	—	—	—	—	—	—	—	*	*	*	*	*	*	*	
自発運動量		—	—	—	▽ <sup>a)</sup>	—	—	—	—	*	*	*	*	*	*	*	
尿所見		—	—	—	—	—	—	—	—	—	—	*	—	—	—	—	
血液学的所見(N) 平均赤血球色素濃度	6	6	6	6	6	6	5	6	6	6	6	*	6	6	6	6	
血小板数		—	—	—	▼ <sup>a)</sup>	—	▽ <sup>a)</sup>	—	—	—	—	*	—	—	—	—	
リンパ球率		—	—	—	—	—	—	—	—	—	—	*	—	—	—	△ <sup>a)</sup>	
好中球率		—	—	—	—	—	—	—	—	—	—	*	—	—	—	▽ <sup>a)</sup>	
血液生化学的所見(N) TP	6	6	6	6	6	6	6	6	6	6	6	*	6	6	6	6	
T-Bil		—	—	—	—	—	—	—	—	—	—	*	—	—	—	—	
Cl		—	—	—	—	—	—	—	—	—	—	*	—	—	—	—	
肉眼的所見 例数(N)	6	12	6	12	6	12	6	12	6	6	6	*	6	6	6	6	
精巣上体尾部		—	—	—	—	—	—	—	—	—	—	*	—	—	—	—	
黄白色結節	1	—	—	—	—	—	—	—	—	—	—	*	—	—	—	—	
器官重量変化(N) 絶対重量 卵巣	6	11	6	12	6	12	6	11	6	6	6	*	6	6	6	6	
相対重量 胸腺		—	—	—	△ <sup>a)</sup>	—	—	—	—	—	—	*	—	—	—	—	
卵巣		—	—	—	—	—	—	—	—	—	—	*	—	—	—	—	

\*: 検査せず.

—: 変化なし, あるいは対照群との間に有意差なし.

△▽: 5%有意差. ▲▼: 1%有意差.

a): 毒性学的影響ではないと判断.

投与量 (mg/kg)	対照群			低用量群			中用量群			高用量群		
性別	♂			♂			♂			♂		
Grade	—	±	+~	—	±	+~	—	±	+~	—	±	+~
病理組織学的所見												
投与期間終了時												
肺 泡沫細胞の集簇 (N)	4	2	0	*	*	*	*	*	*	5	1 <sup>a)</sup>	0
空腸 パイエル氏板の鉱質沈着 (N)	6	0	0	*	*	*	*	*	*	5	1 <sup>a)</sup>	0
精巣上体 リンパ細胞浸潤 (N)	5	1	0	*	*	*	*	*	*	6	0	0
	片側性精子肉芽腫 (N)	5	1	0	*	*	*	*	*	6	0	0
前立腺 リンパ細胞浸潤 (N)	6	0	0	*	*	*	*	*	*	5	1 <sup>a)</sup>	0
性別	♀			♀			♀			♀		
Grade	—	±	+~	—	±	+~	—	±	+~	—	±	+~
病理組織学的所見												
投与期間終了時												
空腸 パイエル氏板の鉱質沈着 (N)	6	0	0	*	*	*	*	*	*	5	1 <sup>a)</sup>	0
脾臓 隹外造血 (N)	3	3	0	*	*	*	*	*	*	5	1 <sup>a)</sup>	0
眼球 右網膜異形成 (N)	6	0	0	*	*	*	*	*	*	5	1 <sup>a)</sup>	0
NOEL	雄: 1000 mg/kg/day を超える. 雌: 1000 mg/kg/day を超える.											
NOEL の推定根拠 とした変化	雄では、1000 mg/kg 投与でいずれの項目にも影響が認められなかったため. 雌では、1000 mg/kg 投与でいずれの項目にも影響が認められなかったため.											

\* NOEL: no observed effect level

—: 変化なし, ±: ごく軽度, +~: 軽度, 中等度, 高度.

a): 毒性学的影響ではないと判断.

## 2) 生殖発生毒性

投与量 (mg/kg)	対照群 0	低用量群 62.5	中用量群 250	高用量群 1000
親動物				
発情回数	3.1	3.5	3.4	3.3
交尾率(%)	100.0	100.0	100.0	100.0
受胎率(%)	91.7	100.0	100.0	91.7
妊娠黄体数	16.4	15.6	17.3	16.5
着床数	14.4	15.0	15.7	15.4
着床率(%)	88.0	96.3△ <sup>a)</sup>	90.3	93.7
妊娠母獣数	11	12	12	11
生児出産母獣数	11	12	12	11
出産率(%)	100.0	100.0	100.0	100.0
妊娠期間	22.3	22.5	22.3	22.3
新生児				
総出産児数	13.8	13.8	14.0	14.7
分娩率(%)	95.2	89.7	85.5▽ <sup>a)</sup>	93.5
児の出産率(%)	95.3	89.7	85.5▽ <sup>a)</sup>	93.5
生存児数（哺育 0 日）	13.6	13.4	13.4	14.4
出生率(%)	98.9	97.0	95.8	97.5
性比 (♂/♀, 哺育 0 日)	1.06	1.34	2.24	1.21
生存児数（哺育 4 日）	13.5	13.1	13.3	14.2
生存率(%)	98.6	97.5	98.9	98.7
性比 (♂/♀, 哺育 4 日)	1.06	1.43	2.25	1.21
体重（哺育 0 日）		-/-	-/-	-/-
体重（哺育 4 日）		-/-	-/-	-/-
外表異常所見 (N)	-	-	-	無尾 (1) <sup>b)</sup>
剖検所見 (N)	-	-	腹腔内器官の欠損 (1) <sup>b)</sup>	-
NOEL	親動物: 雌雄ともに 1000 mg/kg/day を超える。 児動物: 1000 mg/kg/day を超える。			
NOEL の推定根拠 とした変化	雄では、1000 mg/kg 投与でいずれの項目にも影響が認められなかったため。 雌では、1000 mg/kg 投与でいずれの項目にも影響が認められなかったため。 児動物では、1000 mg/kg 投与で生存性及び体重などに影響が認められなかったため。			

\* NOEL: no observed effect level

-/-: ♂/♀

交尾率(%) = (交尾確認動物数/交配動物数) × 100

受胎率(%) = (妊娠確認動物数/交尾確認動物数) × 100

着床率(%) = (着床数/妊娠黄体数) × 100

出産率(%) = (新生児出産母獣数/妊娠母獣数) × 100

妊娠期間 = 哺育 0 日[分娩確認日] (年月日) - 妊娠 0 日 (年月日)

分娩率(%) = (総出産児数/着床数) × 100

児の出産率(%) = (哺育 0 日新生児数/着床数) × 100

出生率(%) = (哺育 0 日生存児数/総出産児数) × 100

生存率(%) = (哺育 4 日生存児数/哺育 0 日生存児数) × 100

-: 変化なし、あるいは対照群との間に有意差なし。

△▽: 5%有意差。

a): 毒性学的影響ではないと判断。

b): 偶発例と判断。

## 4. その他

	名 称	[REDACTED]
試験実施施設	所在地	株式会社日本バイオリサーチセンター 羽島研究所 岐阜県羽島市福寿町間島6-104 電話058 (392) 6222 FAX 058 (392) 1284
試験責任者	職氏名	試験管理部主席研究員
	経験年数	36年
試験番号	100624	
試験期間	2005年 5月 6日から2007年 1月30日まで	

届出様式作成責任者

&lt;所属&gt; 株式会社日本バイオリサーチセンター 羽島研究所

&lt;電話&gt; 058-392-6222

&lt;職氏名&gt; 試験管理部主席研究員 [REDACTED]

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ブメトリゾールのラットを用いる  
経口投与による反復投与毒性・生殖発生毒性併合試験

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## 最 終 報 告 書

作成日 2007年1月30日

株式会社日本バイオリサーチセンター  
羽島研究所

本報告書は最終報告書を複写したものに  
相違ありません。

2007年1月30日

試験責任者

## 信頼性保証書

試験番号：100624

表 題：ブメトリゾールのラットを用いる経口投与による反復投与毒性・生殖発生毒性  
併合試験

当試験に関して、2005年5月9日から2007年1月30日にかけて調査を実施し、その結果は運営管理者及び試験責任者に報告した。

当試験が「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成15年11月21日、薬食発第1121003号、平成15・11・17製局第3号、環保企発第031121004号)及びOECD PRINCIPLES OF GOOD LABORATORY PRACTICE(OECD化学物質の安全性試験の実施に関する基準)に従って実施され、この最終報告書には試験の方法が正確に記載され、かつ生データが正確に反映されていることを保証する。

(調査の状況は、別紙1及び2のとおりである。)

2007年1月30日

株式会社日本バイオリサーチセンター 羽島研究所

信頼性保証部門責任者

別紙1

## 調査の状況

調査項目	調査実施日	調査結果の報告日
1. 試験計画書及び主計画表	2005年 5月 9日	2005年 5月 11日
2. コンピュータプロトコール	2005年 5月 11日	2005年 5月 11日
3. 動物の受け入れ	2005年 5月 11日	2005年 5月 11日
4. 試験計画書変更書(No. 1)	2005年 5月 19日	2005年 5月 19日
5. 被験物質の管理	2005年 5月 31日	2005年 6月 2日
6. 検体の調製	2005年 5月 31日	2005年 6月 2日
7. 群分け及び個体識別(試験群雄・雌)	2005年 6月 1日	2005年 6月 2日
8. 投与(試験群雄・雌)	2005年 6月 1日	2005年 6月 2日
9. 動物飼育管理(試験群雄・雌)	2005年 6月 1日	2005年 6月 2日
10. 投与(回復群雌)	2005年 6月 2日	2005年 6月 2日
11. 体重測定・摂餌量測定(試験群雄・雌)	2005年 6月 8日	2005年 6月 8日
12. 一般状態観察(試験群雄・雌)	2005年 6月 8日	2005年 6月 8日
13. 行動機能(FOB)観察(試験群雌)	2005年 6月 8日	2005年 6月 8日
14. 同居	2005年 6月 15日	2005年 6月 23日
15. 交尾確認	2005年 6月 16日	2005年 6月 23日
16. 体重測定・摂餌量測定(回復群雌)	2005年 6月 16日	2005年 6月 23日
17. 行動機能(FOB)観察(回復群雌)	2005年 6月 16日	2005年 6月 23日
18. 摂餌量測定(試験群雌)	2005年 6月 20日	2005年 6月 23日
19. 投与(試験群雌)	2005年 6月 20日	2005年 6月 23日
20. 動物飼育管理(試験群雌)	2005年 6月 20日	2005年 6月 23日
21. 行動機能(FOB)観察(試験群雌)	2005年 6月 20日	2005年 6月 23日
22. 体重測定(試験群雌)	2005年 6月 23日	2005年 6月 23日
23. 尿検査(投与期間終了前・雄)	2005年 7月 7日 ～ 7月 8日	2005年 7月 11日
24. 分娩(試験群雌)	2005年 7月 8日	2005年 7月 11日
25. 体重測定(試験群雌)	2005年 7月 8日	2005年 7月 11日
26. 摂餌量測定(試験群雌)	2005年 7月 10日	2005年 7月 11日
27. 自発運動量測定(投与 40 日・雄)	2005年 7月 10日	2005年 7月 11日
28. 行動機能(FOB)観察(投与 41 日・雄)	2005年 7月 11日	2005年 7月 11日
29. 感覚反応検査(投与 41 日・雄)	2005年 7月 11日	2005年 7月 11日
30. 握力測定(投与 41 日・雄)	2005年 7月 11日	2005年 7月 11日
31. 体重測定・摂餌量測定(雄)	2005年 7月 13日	2005年 7月 13日
32. 一般状態観察(雄)	2005年 7月 13日	2005年 7月 13日
33. 投与(試験群雌)	2005年 7月 13日	2005年 7月 13日
34. 動物飼育管理(試験群雌)	2005年 7月 13日	2005年 7月 13日
35. 自発運動量測定(哺育 4 日, 試験群雌)	2005年 7月 13日	2005年 7月 13日
36. 行動機能(FOB)観察(哺育 3 日, 試験群雌)	2005年 7月 13日	2005年 7月 13日
37. 感覚反応検査(哺育 3 日, 試験群雌)	2005年 7月 13日	2005年 7月 13日

別紙2

## 調査の状況

調査項目	調査実施日	調査結果の報告日
38. 握力測定(哺育3日, 試験群雌)	2005年 7月13日	2005年 7月13日
39. 剖検(最終投与の翌日・雄)	2005年 7月13日	2005年 7月15日
40. 剖検(新生児 F <sub>1</sub> )	2005年 7月13日	2005年 7月15日
41. 血液学検査(最終投与の翌日・雄)	2005年 7月13日	2005年 7月15日
42. 血液生化学検査(最終投与の翌日・雄)	2005年 7月13日	2005年 7月15日
43. 尿検査(哺育5~6日, 試験群雌)	2005年 7月13日 ~ 7月14日	2005年 7月15日
44. 体重測定・摂餌量測定(回復群雌)	2005年 7月14日	2005年 7月15日
45. 一般状態観察(回復群雌)	2005年 7月14日	2005年 7月15日
46. 剖検(哺育7日, 試験群雌)	2005年 7月15日	2005年 7月15日
47. 尿検査(回復期間終了前・雄)	2005年 7月21日 ~ 7月22日	2005年 7月29日
48. 尿検査(回復群雌)	2005年 7月22日 ~ 7月23日	2005年 7月29日
49. 剖検(回復期間終了後・雄)	2005年 7月27日	2005年 7月29日
50. 剖検(回復群雌)	2005年 7月28日	2005年 7月29日
51. 血液学検査(回復群雌)	2005年 7月28日	2005年 7月29日
52. 血液生化学検査(回復群雌)	2005年 7月28日	2005年 7月29日
53. 標本作製(病理: 切り出し)	2005年 7月29日	2005年 7月29日
54. 血液生化学検査(回復群雌)	2005年 8月 2日	2005年 8月 2日
55. 標本作製(病理: 薄切)	2005年 8月 2日	2005年 8月 2日
56. 生データ	2005年10月24日 ~11月 9日	2005年11月17日
57. 標本	2005年11月 8日	2005年11月17日
58. 最終報告書(一次案)	2005年11月 7日 ~11月16日	2005年11月17日
59. 生データ(再調査)	2005年11月29日	2005年11月29日
60. 最終報告書(一次案)(再調査)	2005年11月29日	2005年11月29日
61. 試験計画書変更書(No. 2)	2006年 3月 1日	2006年 3月 1日
62. 最終報告書	2007年 1月30日	2007年 1月30日

# 最終報告書作成者署名

試験番号：100624

表題：ブメトリゾールのラットを用いる経口投与による反復投与毒性・生殖発生毒性  
併合試験

2007年 1月 30日

株式会社日本バイオリサーチセンター 羽島研究所

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被験物質名：ブメトリゾール(CAS No.3896-11-5)

試験系：Cr1:CD(SD)雌雄ラット(SPF)

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試験目的：当試験は、ブメトリゾールが継続的に人に摂取された場合の健康への影響を推定するために、ブメトリゾールを雌雄ラットに反復経口投与し、毒性学的影響を検討するとともに、性腺機能、交尾行動、受胎及び分娩などの雌雄動物の生殖行動に及ぼす影響を検討した。

準拠したガイドライン：

OECD Guideline for Testing of Chemicals for Combined Repeat Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (422)

遵守した GLP：

新規化学物質等に係る試験を実施する試験施設に関する基準

(平成 15 年 11 月 21 日、薬食発第 1121003 号、平成 15・11・17 製局第 3 号、環保企発第 031121004 号)

OECD PRINCIPLES OF GOOD LABORATORY PRACTICE

(OECD 化学物質の安全性試験の実施に関する基準)

遵守した動物の福祉に関する法令など：

「動物の愛護及び管理に関する法律」(昭和 48 年 10 月 1 日法律第 105 号、平成 11 年 12 月 22 日改正)、「実験動物の飼養及び保管等に関する基準」(昭和 55 年 3 月 27 日総理府告示第 6 号、平成 14 年 5 月 28 日一部改正)、「動物実験に関する指針」(昭和 62 年 5 月 22 日社団法人日本実験動物学会)及び株式会社日本バイオリサーチセンター 羽島研究所「動物実験倫理委員会規則」

試験開始日：2005 年 5 月 6 日

試験終了日：2007 年 1 月 30 日

## 試験実施日 :

雄動物入手日	2005年5月11日
雌動物入手日	2005年5月11日
実験開始日(雌雄試験群の投与開始日)	2005年6月1日
雌回復群の投与開始日	2005年6月2日
交配開始日	2005年6月15日
新生児の剖検開始日	2005年7月12日
雄投与期間終了時の剖検日	2005年7月13日
母動物の剖検開始日	2005年7月15日
雄回復期間終了時の剖検日	2005年7月27日
雌回復群の剖検日	2005年7月28日
病理組織所見最終化日	2005年8月31日
実験終了日(臨床検査標本観察終了日)	2005年9月8日

## 資料、標本及び被験物質の保存場所 :

当試験の実施により得られたすべての資料は株式会社日本バイオリサーチセンター 羽島研究所の資料保管室に保存し、すべての標本及び保存すべき被験物質は標本保管室に保存する。保存期間は、最終報告書提出後10年間とする。その後は、試験委託者と協議の上で決定する。

## SOP 及び試験計画書に従わなかったこと :

1) 被験物質保管庫の湿度の許容範囲はSOPで40~70%としていたが、逸脱が2005年3月13日の午前3時00分頃~午前6時00分頃(最低37.6%)、2005年3月19日の午前1時00分頃~午前6時00分頃(最低39.8%)、2005年3月24日の午後11時00分頃~3月25日の午前6時00分頃(最低36.0%)及び2005年3月29日の午前10時00分頃(最低39.3%)に認められた。しかし、湿度の逸脱幅はいずれもわずかであること、他の期間の湿度は許容範囲内であることから、試験成績への影響はないと判断した。

2) 0.5 w/v%メチルセルロース溶液及び投与検体を保管した被験物質冷蔵保管庫の温度の許容範囲は2~8 °Cとしていたが、温度の逸脱が2005年6月16日の午後4時15分頃~午後4時20分頃(最高8.2 °C)に認められた。しかし、温度の逸脱幅はわずかであること、他の期間の温度は許容範囲内であることから、試験成績への影響はないと判断した。

その他には、当試験ではSOP又は試験計画書に従わなかったことはなかった。

## 予見することができなかつた試験の信頼性に影響を及ぼす疑いのある事態 :

当試験の実施期間中に、予見することができなかつた試験の信頼性に影響を及ぼす疑いのある事態は認められなかつた。

試験従事者及び業務分担

試験責任者 : [REDACTED]

(試験計画書の作成, 試験実施の指示, 剖検, データの確認,  
最終報告書の作成)

試験従事者 : [REDACTED]

(検体の投与, 一般状態観察, 動物の一般飼育管理, FOB, 感覚反応検査,  
握力測定, 自発運動量測定)

[REDACTED]

(剖検, 病理組織標本作製, 病理組織学検査)

[REDACTED]

(被験物質の管理, 投与検体の調製)

[REDACTED]

(被験物質の安定性確認, 投与検体中の被験物質濃度測定)

[REDACTED]

(統計解析)

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## 要約

ブメトリゾールのラットを用いる経口投与による反復投与毒性・生殖発生毒性併合試験を行い、雌雄動物に対する一般毒性学的影響を検討するとともに、性腺機能、交尾行動、受胎及び分娩などの生殖行動に及ぼす影響について検討した。投与量は、1000 mg/kg を高用量とし、以下 250 及び 62.5 mg/kg とした。対照として媒体(0.5 w/v% メチルセルロース溶液)投与群を設けた。各群の使用動物数は試験群を雌雄各 12 例とし、雄では各群ともそのうち半数を回復群とした。雌では、試験群とは別に対照群、250 及び 1000 mg/kg 群に各 6 例の回復群を設けた。

### I. 反復投与毒性

#### 1. 一般状態及び死亡状況

死亡例及び瀕死例は、いずれの群にも認められなかった。

一般状態の異常は、いずれの群にもみられなかった。

#### 2. 体重及び摂餌量

体重及び摂餌量では、雌雄とも投与に起因する変化はみられなかった。

#### 3. 行動機能 (FOB) 観察、感覚反応検査、握力測定及び自発運動量測定

行動機能 (FOB)、感覚反応、握力及び自発運動量では、雌雄とも投与に起因する変化はみられなかった。

#### 4. 尿検査、血液学検査及び血液生化学検査

尿検査、血液学検査及び血液生化学検査において、雌雄とも投与に起因する変化はみられなかった。

#### 5. 剖検所見及び器官重量

剖検及び器官重量において、雌雄とも投与に起因する変化はみられなかった。

#### 6. 病理組織学検査

病理組織学検査において、雌雄とも投与に起因する変化はみられなかった。

### II. 生殖発生毒性

#### 1. 親動物の生殖発生に及ぼす影響

交配開始前の投与期間(14 日間)の発情回数、交尾率、交尾所要日数、受胎雌数、受胎率、妊娠期間、出産率、分娩状態、哺育状態、妊娠黄体数、着床数及び着床率には、投与に起因する変化はみられなかった。

## 2. 児動物 ( $F_1$ ) に及ぼす影響

総出産児数, 死産児数, 哺育 0 日の新生児数, 哺育 0 日の性比, 分娩率, 児の産出率及び出生率には, 投与に起因する変化はみられなかった.

一般状態, 哺育 4 日の生存児数, 哺育 4 日の性比及び哺育 4 日の生存率には, 投与に起因する変化はみられなかった.

外表, 体重及び剖検において, 投与に起因する変化はみられなかった.

以上のように, ブメトリゾールの無影響量は, 雌雄とも  $1000 \text{ mg/kg}$  投与でいずれの項目にも影響が認められなかつたことから  $1000 \text{ mg/kg/day}$  を越えると考えられる. また, 生殖発生毒性学的な無影響量は, 雌雄とも  $1000 \text{ mg/kg}$  投与でいずれの項目にも影響が認められなかつたことから  $1000 \text{ mg/kg/day}$  を越えると考えられる. 児動物への無影響量は,  $1000 \text{ mg/kg}$  投与で生存性及び体重などに影響が認められなかつたことから  $1000 \text{ mg/kg/day}$  を越えると考えられる.

## 緒言

ブメトリゾールが経口的に継続して人に摂取された場合の健康への影響を推定するために, OECD Guideline for Testing of Chemicals for Combined Repeat Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (422)に基づいてブメトリゾールを雄ラットに 1 日 1 回, 42 日間及び雌ラットに 1 日 1 回, 44~56 日間反復経口投与し, 毒性学的影響を検討するとともに, 性腺機能, 交尾行動, 受胎及び分娩などの雌雄動物の生殖行動に及ぼす影響を検討した. 一部の動物には 14 日間の回復期間を設け, 回復性についても検討した.

## 方法

### 1. 被験物質及び媒体

被験物質のブメトリゾール[日本語別名:2-(2'-ヒドロキシ-3-tert-ブチル-5'-メチルフェニル)-5-クロロベンゾトリアゾール, 英語名称:bumetrizole, 英語別名:2-(2'-Hydroxy-3-tert-butyl-5'-methylphenyl)-5-chlorobenzotriazole, CAS No. 3896-11-5]は, Fig.1 に示す化学構造を有し, 淡黄色粉末で臭いはなく, 分子量:315.80, 蒸気圧:7.5×10E-7Pa(20 °C), 融点:138-141 °C, 相対密度:1.32 g/cm<sup>3</sup>(25 °C)である. 当試験には, [REDACTED] から入手したもの用いた[製造元: [REDACTED] Lot No. 01721IW4, 含量:99.9%]. 入手後は, 試験施設の被験物質保管室の保管庫(設定温度:23 °C, 実測値:20.0~25.3 °C)に室温・密閉の条件下で保管した. 入手後に当試験施設で被験物質を分析した結果, 含量は 99.5%であった. 当試験の投与期間終了後に当試験施設で被験物質を再分析した結果, 含量は 100.6%であり, 使用期間中の安定性が確認された(Attachment 1-1 及び 1-2).

媒体 0.5 w/v%メチルセルロース溶液の調製には, メチルセルロース[メトローズ®SM-100, 局方, Lot No. 110654, 使用期限 2007 年 4 月 4 日, 信越化学工業株式会社, 被験物質保管室の保管庫(設定温度:23°C, 実測値:20.4~24.7 °C)に室温保管]及び注射用水[局方, Lot No. 3F86, 使用期限 2008 年 6 月, 株式会社大塚製薬工場, 被験物質保管室(設定温度:23°C, 実測値:20.4~24.7 °C)に室温保管]を用いた.

### 2. 投与検体及び濃度確認

0.5 w/v%メチルセルロース溶液は, メチルセルロースの必要量を秤取(電子天秤: AT250 及び PM2500, メトラー・トレド株式会社)後, 注射用水に溶解し, 調製した. 0.5 w/v%メチルセルロース溶液は, 被験物質保管室の保管庫(冷蔵庫:RC-M501, 株式会社日立製作所)で冷蔵(設定温度:4°C, 実測値:3.4~8.2 °C)の条件下で保管し, 調製後 10 日以内に使用した.

ブメトリゾールは, 各濃度ごとに必要量を秤取(電子天秤:AT250 及び PM2500, メトラー・トレド株式会社)後, コンディショニングミキサー(AR-250, 株式会社シンキー)を用いて 0.5 w/v%メチルセルロース溶液に懸濁させ, 所定濃度とした. なお, 調製に際して被験物質の含量による補正は行わず, 投与量は原末重量で表示した.

ブメトリゾールの 0.2, 2 及び 20 w/v%懸濁液は、調製後 7 日間冷蔵・遮光の条件下で保管し、その後室温・遮光で 6 時間保管しても安定性及び均一性に問題のないことが確認されている(Attachment 2)<sup>1)</sup>。投与検体は、週 1 回以上の頻度で調製し、被験物質保管室の保管庫(冷蔵庫:RC-M501, 株式会社日立製作所)に冷蔵(設定温度:4 °C, 実測値:3.4~8.2 °C)・遮光条件下で保管後、7 日以内に使用した。なお、投与検体は、保管庫から持ち出し後 6 時間以内に使用した。残余投与検体は廃棄した。

雌雄試験群投与開始日及び雄投与終了日に使用した投与検体中の被験物質濃度を HPLC(株式会社島津製作所)で測定した。その結果、被験物質含量は表示濃度の 101.5~102.7%であり、規定された濃度の範囲内(100±10%)であった。また、その CV 値は 5%以内であった。従って、各投与検体中の含量及び均一性に問題はなかった(Attachment 3-1 及び 3-2)。

### 3. 使用動物及び飼育条件

#### 3.1. 動物種及び系統

試験には、毒性試験に一般的に用いられている動物種で、その系統維持が明らかである Crl:CD(SD)雌雄ラット(SPF)を用いた。動物は、2005 年 5 月 11 日に日本チャールス・リバー株式会社(日野飼育センター)から 7 週齢で試験群として雌雄各 73 匹及び回復群として雌 26 匹を入手した。入手後 1 日の体重範囲は、雄が 230~249 g, 試験群雌が 176~202 g, 回復群雌が 179 ~198 g であった。

#### 3.2. 検疫及び馴化、群分け法並びに個体識別法

入手した動物は、5 日間の検疫期間及びその後 16 日間(ただし、回復群雌は 17 日間)の馴化期間を設けた。この間に、体重測定(電子天秤:PM2000, PB3002 及び PG2002-S, メトラー・トレド株式会社)を 5 回、一般状態の観察を毎日 1 回、行動機能(FOB)観察を投与開始前に 1 回行い、さらに試験群雌は馴化期間中に性周期観察を 14 日間毎日 1 回行った。一般状態、体重推移あるいは FOB 観察に異常がみられず、また性周期観察で異常が認められなかった動物(発情期が認められ、4 日あるいは 5 日周期と考えられた動物)を群分けした。

群分けは、コンピュータを用いて体重を層別に分けた後に無作為抽出法により各群の平均体重及び分散がほぼ等しくなるように投与開始日に行った。群分け後の残余動物のうち、検疫・馴化動物番号の若い順に雄 2 例を選び、飼育期間終了日の微生物モニタリング検査に用いた。その他の群分け残余動物は、投与開始日にジエチルエーテル麻酔下で腹大動脈から放血致死させた後に廃棄した。

動物の個体識別は、入手日に油性インクによる尾への記入法を用いて行った。さらに、検疫・馴化期間中の各ケージには試験番号、入手年月日及び検疫・馴化動物番号を記入したラベルを、群分け後の各ケージには試験番号、投与量、検疫・馴化動物番号、動物番号、交尾成立日(試験群雌のみ)及び分娩日(試験群雌のみ)を記入し、群ごとに色分けしたラベルを取り付けた。なお、行動機能(FOB)観察を Blind で検査する場合には、試験番号、入手年月日及び検疫・馴化動物番号を記入したラベルを取り付けた。児動物(F<sub>1</sub>)の各ケージには、試験番号、投与量、動物番号及び出生日を記入し、群ごとに色分けしたラベルを取り付けた。

### 3.3. 環境条件及び飼育管理

動物は、設定温度 23 °C(実測値：22～25 °C)、設定湿度 55%(実測値：40～56%)、明暗各 12 時間(照明：午前 6 時～午後 6 時)、換気回数 12 回／時(フィルターにより除菌した新鮮空気)に維持された飼育室(E 棟 3 号室、但し、検疫は E 棟 7 号室)で飼育した。

検疫・馴化期間中及び群分け後ともステンレス製懸垂式ケージ(W:240×D:380×H:200 mm)を用いて個別飼育した。交配は、雄のケージ内で行った。母動物は、妊娠 18 日以降オートクレーブ処理した床敷(サンフレーク、日本チャールス・リバー株式会社)を入れたプラスチック製ケージ(W:310×D:360×H:175 mm)で個別飼育し、自然分娩及び哺育させ、哺育 4 日以降ステンレス製懸垂式ケージを用いて個別飼育した。ケージの受け皿、給水瓶及びプラスチック製ケージの交換は 1 週間に 2 回以上、ステンレス製懸垂式ケージ及び給餌器の交換は 2 週間に 1 回以上行った。なお、動物飼育室の清掃(床の掃き掃除)及び 0.02%次亜塩素酸ナトリウム水溶液での床のモップ拭きによる消毒は毎日行った。

飼育期間終了日に採血したモニタリング動物の血清検査において、感染を示唆するような異常はみられなかった。

床敷の微量金属及び汚染物質の分析結果は、ほぼ 6 ヶ月ごとに財団法人日本食品分析センターで実施した成績を日本チャールス・リバー株式会社から入手した。その分析結果は、試験施設で定めた基準値の範囲内であった。

### 3.4. 飼料及び飲料水

飼料は、製造後 5 カ月以内の固型飼料(CRF-1、オリエンタル酵母工業株式会社)を給餌器に入れ、自由に摂取させた。剖検前日の午後 4 時から絶食させた。使用した飼料と同一ロットの飼料の分析結果は、財団法人日本食品分析センター及びオリエンタル酵母工業株式会社から入手した。

飲料水は、水道水を給水瓶を用いて自由に摂取させた。飲料水の水質検査結果は、ほぼ 6 カ月ごとに東西化学産業株式会社 東日本分析センター又は株式会社環境公害センターで実施した成績を入手した。

飼料及び飲料水の分析結果は、いずれも試験施設で定めた基準値の範囲内であった。

## 4. 投与経路、投与方法、群構成、投与量及び投与期間

### 4.1. 投与経路及び投与方法

ブメトリゾールは、継続して経口的に人に摂取される可能性が考えられるため、投与経路として経口投与を選択した。

投与に際しては、金属製経口胃ゾンデ(有限会社フチガミ器械)を取り付けたポリプロピレン製ディスポーザブル注射筒(テルモ株式会社)を用いて、強制経口投与した。

投与液量は、雄では投与日あるいは投与日に最も近い測定日の体重を基準とし、5 mL/kg で算出した。試験群雌の投与液量は、交配前及び交配期間は投与日あるいは投与日に最も近い測定日の体重を、妊娠期間は妊娠 0, 7, 14 及び 21 日の体重を、哺育期間は哺育 0, 4 及び 6 日の

体重を基準とし、5 mL/kg で算出した。回復群雌の投与液量は、投与日あるいは投与日に最も近い測定日の体重を基準とし、5 mL/kg で算出した。

投与時刻は午前 9 時 00 分～午後 1 時 55 分の間で、投与回数は 1 日 1 回とした。

投与開始日の週齢は雌雄とも 10 週齢であり、体重範囲は雄が 358～405 g、試験群雌が 236～262 g、回復群雌が 247～267 g であった。

#### 4.2. 群構成及び投与量

群構成は、以下に示したように被験物質投与群として 3 群を設定し、その他に対照群を設けた。各群の動物数は、試験群を雌雄各 12 例、対照群、250 及び 1000 mg/kg 群の回復群を雌各 6 例とした。

群	投与量 (含量)	動物数(動物番号)		
		試験群雄	試験群雌	回復群雌
第 1 群 対照 (0.5 w/v% メチルセルロース溶液)	0 mg/kg ( 0 w/v%)	6 <sup>1)</sup> +6 <sup>2)</sup> (M01101～ M01112)	12 <sup>1)</sup> (F01151 ～F01162)	6 <sup>2)</sup> (F01171～ F01176)
第 2 群 ブメトリゾール	62.5 mg/kg ( 1.25 w/v%)	6 <sup>1)</sup> +6 <sup>2)</sup> (M02201～ M02212)	12 <sup>1)</sup> (F02251 ～F02262)	—
第 3 群 ブメトリゾール	250 mg/kg ( 5 w/v%)	6 <sup>1)</sup> +6 <sup>2)</sup> (M03301～ M03312)	12 <sup>1)</sup> (F03351 ～F03362)	6 <sup>2)</sup> (F03371～ F03376)
第 4 群 ブメトリゾール	1000 mg/kg ( 20 w/v%)	6 <sup>1)</sup> +6 <sup>2)</sup> (M04401～ M04412)	12 <sup>1)</sup> (F04451 ～F04462)	6 <sup>2)</sup> (F04471～ F04476)

- 1) 投与期間終了時に剖検
- 2) 回復期間終了時に剖検

投与量は、ブメトリゾールのラットを用いる経口投与による反復投与毒性・生殖発生毒性併合試験の予備試験<sup>2)</sup> (投与段階 : 0, 250, 500 及び 1000 mg/kg, 各群雄 5 例) の結果により決定した。すなわち、いずれの群にも死亡例は認めらず、1000 mg/kg 群でも一般状態、体重、摂餌量及び剖検所見に異常はみられなかった。そこで、当試験の投与量は、1000 mg/kg を高用量とし、以下公比 4 により 250 及び 62.5 mg/kg とした。また、対照として媒体(0.5 w/v%メチルセルロース溶液)のみを同容量投与する群を設けた。

#### 4.3. 投与期間

投与期間は、OECD Guideline for Testing of Chemicals for Combined Repeat Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (422)に基づいて、雄では交配前 14 日間とその後 28 日間の合計 42 日間とし、試験群雌では交配前 14 日間、交配期間中、妊娠期間及び哺育 6 日までの合計 44～56 日間とした。雄については、42 日間の投与後に各群とも半数の動物について 14 日間の回復期間を設けた。また、回復群雌については、42 日間の投与後に 14 日間の回復期間を設けた。なお、投与開始日を投与 1 日とし、最終投与の翌日を回復 1 日とした。

## 5. 観察及び検査項目

### 5.1. 一般状態

#### 5.1.1. 雄

一般状態及び死亡の有無は、投与期間中に投与前・後の1日2回、回復期間中に毎日1回及び剖検日に1回観察した。

#### 5.1.2. 試験群雌

一般状態及び死亡の有無は、投与期間中に投与前・後の1日2回及び剖検日に1回観察した。

#### 5.1.3. 回復群雌

一般状態及び死亡の有無は、投与期間中に投与前・後の1日2回、回復期間中に毎日1回及び剖検日に1回観察した。

### 5.2. 体重測定

#### 5.2.1. 雄

体重は、1週間に2回測定した[測定日:投与1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 42及び43日(回復1日), 回復4, 8, 11, 14及び15日(電子天秤:PM2000, メトラー・トレド株式会社)]。

#### 5.2.2. 試験群雌

体重は、交配開始前14日間及び交配期間中は1週間に2回(測定日:投与1, 4, 8, 11, 15, 18, 22及び25日), 妊娠期間中は妊娠0, 7, 14及び21日に, 哺育期間中は哺育0, 4, 6及び7日に測定した(電子天秤:PM2000及びPB3002, メトラー・トレド株式会社)。

#### 5.2.3. 回復群雌

体重は、1週間に2回測定した[測定日:投与1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39及び42日, 回復1, 4, 8, 11, 14及び15日(電子天秤:PM2000, メトラー・トレド株式会社)]。

### 5.3. 摂餌量測定

#### 5.3.1. 雄

摂餌量は、交配開始前14日間及び交配期間終了後から1週間に2回測定した[残量測定日:投与2, 5, 9, 12, 30, 33, 37及び40日, 回復2, 5, 9及び12日(電子天秤:PM2000及びPG2002-S, メトラー・トレド株式会社)]。

#### 5.3.2. 試験群雌

摂餌量は、交配開始前14日間までは1週間に2回(残量測定日:投与2, 5, 9及び12日), 妊娠期間中は妊娠2, 9, 16及び20日に, 哺育期間中は哺育2日に測定した(電子天秤:PM2000, メトラー・トレド株式会社)]。

### 5.3.3. 回復群雌

摂餌量は、1週間に2回測定した[残量測定日:投与2, 5, 9, 12, 16, 19, 23, 26, 30, 33, 37及び40日, 回復2, 5, 9及び12日(電子天秤:PM2000及びPG2002-S, メトラー・トレド株式会社)].

## 5.4. 行動機能 (FOB) 観察

### 5.4.1. 雄

全例について、投与開始前、投与7, 14, 21, 28, 35及び41日に下記の1)～3)の項目を観察した。観察時刻は、投与後1時間とした。なお、観察者はほぼ固定し、Blindで実施した。

- 1) 姿勢、かみつき行動、眼瞼閉鎖状態及び痙攣はケージ内で観察した。
- 2) ケージからの出し易さ、扱い易さ、筋の緊張、毛の状態、流涙、流涎及び呼吸は手に持つて観察した。
- 3) 立ち上がり回数、毛づくろい回数、歩行状態、眼瞼閉鎖状態、覚醒度、行動異常及び正向反射はオープンフィールド内で観察した。

### 5.4.2. 試験群雌

全例について、投与開始前、投与8及び15日、妊娠1, 8及び15日並びに哺育3日に雄と同一項目を観察した。なお、不受胎雌の交尾後のデータは集計から除外した。

### 5.4.3. 回復群雌

全例について、投与開始前、投与8, 15, 22, 29, 36及び42日に雄と同一項目を観察した。

## 5.5. 感覚反応検査

### 5.5.1. 雄

投与期間終了時剖検例について、投与41日の行動機能 (FOB) 観察後に瞳孔反射、接近反射、触覚反射、聴覚反射及び痛覚反射を作業台の上で検査した。

### 5.5.2. 試験群雌

各群とも動物番号の若い順に各6例について、哺育3日の行動機能 (FOB) 観察後に雄と同一項目を検査した。

## 5.6. 握力測定

### 5.6.1. 雄

投与期間終了時剖検例について、投与41日の感覚反応検査終了後にCPUゲージ(アイコーベンジニアリング株式会社)を用いて、前肢及び後肢の握力を5回測定し、最高値と最低値を除いた中央の3測定値の平均値を採用した。

### 5.6.2. 試験群雌

各群とも動物番号の若い順に各6例について、哺育3日の感覚反応検査終了後にCPUゲージ(アイコーエンジニアリング株式会社)を用いて、雄と同様に測定した。

## 5.7. 自発運動量測定

### 5.7.1. 雄

投与期間終了時剖検例について、投与40日にActivity Monitor (MED Associates Inc.)を使用し、歩行量及び立ち上がり回数について投与後1時間まで10分間隔で測定した。

### 5.7.2. 試験群雌

各群とも動物番号の若い順に各6例について、哺育4日にActivity Monitor (MED Associates Inc.)を使用し、雄と同一項目を検査した。

## 5.8. 尿検査

### 5.8.1. 雄

投与期間終了前(投与37日)の投与検体投与前に投与期間終了時の剖検用動物、回復期間終了前(回復9日)に回復期間終了時の剖検用動物について、採尿ケージを用いて絶食・給水下で新鮮尿を採取した。その後、引き続いて給餌・給水下で24時間尿を採取した。採取した尿について、以下の検査を実施した。検査後の尿は廃棄した。

新鮮尿：色調は、外観判定とした。pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血及びウロビリノーゲンは、尿検査試験紙(栄研化学株式会社)に尿を滴下後に分光反射測光法により尿自動分析装置(US-2100、栄研化学株式会社)を用いて検査した。尿沈渣は、沈渣を尿沈渣染色液(新Sternheimer法、国際試薬株式会社)で染色後に顕微鏡下で観察した。

24時間尿：尿量(UV)は、尿比重と重量(電子天秤:PM2000、メトラー・トレド株式会社)から算出した。尿比重(S.G.)は、屈折率により屈折型尿比重計(ユリペット-II D、株式会社ニコン)を用いて測定した。

### 5.8.2. 試験群雌

各群とも動物番号の若い順に各6例について、哺育5日の投与検体投与前に採尿ケージを用いて絶食・給水下で新鮮尿を採取した。その後、引き続いて給餌・給水下で24時間尿を採取した。採取した尿について、雄の尿検査と同一項目(5.8.1.)の検査を同一機器を用いて実施した。ただし、尿重量の測定には電子天秤: PM2000(メトラー・トレド株式会社)を使用した。検査後の尿は廃棄した。

### 5.8.3. 回復群雌

回復期間終了前(回復9日)に採尿ケージを用いて絶食・給水下で新鮮尿を採取した。その後、引き続いて給餌・給水下で24時間尿を採取した。採取した尿について、雄の尿検査と同一項目(5.8.1.)の検査を同一機器を用いて実施した。ただし、尿重量の測定には電子天秤:PM2000(メト

ラー・トレド株式会社)を使用した。検査後の尿は廃棄した。

## 5.9. 血液学検査

### 5.9.1. 雄

最終投与の翌日及び回復期間終了後にペントバルビタールナトリウムの腹腔内投与(40 mg/kg)による麻酔下で腹大動脈からカニュレーションにより血液を採取し、以下の血液学検査を実施した。測定後の残余血液は廃棄した。

赤血球数(RBC), ヘモグロビン量(HGB), ヘマトクリット値(HCT), 血小板数(PLT)及び白血球数(WBC)は、EDTA-2K処理した血液について、多項目自動血球計数装置(Sysmex K-4500, シスメックス株式会社)を用いて測定した。さらに、平均赤血球容積(MCV), 平均赤血球血色素量(MCH)及び平均赤血球血色素濃度(MCHC)を算出した。

網状赤血球比率(RET)は、EDTA-2K処理した血液を Brecher 法により超生体染色してスライドガラスに塗抹後、Giemsa 染色標本を作製して顕微鏡下で赤血球 1000 個中の網状赤血球数を計数し、算出した。

白血球百分率は、EDTA-2K 処理した血液をスライドガラスに塗抹し、May-Giemsa 染色標本を作製して顕微鏡下で白血球 100 個を分類計数した。

プロトロンビン時間(PT), 活性化部分トロンボプラスチン時間(APTT)及びフィブリノーゲン濃度(Fbg)は、血液を 3.2%クエン酸ナトリウムで処理後、遠心分離[約 4 °C, 3000 rpm(約 1972 ×g), 15 分間, 遠心機:CF8DL, 日立工機株式会社]して得た血漿について、光散乱検出方式により全自动血液凝固測定装置(CA-530, シスメックス株式会社)を用いて測定した。

### 5.9.2. 試験群雌

各群とも動物番号の若い順に各 6 例について、最終投与の翌日(哺育 7 日)にペントバルビタールナトリウムの腹腔内投与(40 mg/kg)による麻酔下で腹大動脈からカニュレーションにより血液を採取し、雄の血液学検査と同一項目(5.9.1.)の検査を実施した。測定後の残余血液は廃棄した。

### 5.9.3. 回復群雌

回復期間終了後にペントバルビタールナトリウムの腹腔内投与(40 mg/kg)による麻酔下で腹大動脈からカニュレーションにより血液を採取し、雄の血液学検査と同一項目(5.9.1.)の検査を実施した。測定後の残余血液は廃棄した。

## 5.10. 血液生化学検査

### 5.10.1. 雄

血液学検査用の血液と同時期に腹大動脈から採取した血液から遠心分離[約 4 °C, 3000 rpm(約 1972 ×g), 15 分間, 遠心機:CF8DL, 日立工機株式会社]して得た血清について、以下の血液生化学検査を実施した。保存用血清は、最終報告書作成時まで冷凍庫(-80 °C 設定, 超低温フリーザー:ULT1786-9JD, Kendro Laboratory Products)内に保管した。

AST は MDH-UV 法, ALT は LDH-UV 法, ALP は p-ニトロフェニルリン酸基質法,  $\gamma$ -GTP は L- $\gamma$ -グルタミル-3-カルボキシ-4-ニトロアミニド基質法, 総蛋白(TP)は Biuret 法, 総ビリルビン(T-Bil)はジアゾ法, 尿素窒素(UN)はウレアーゼ・GIDH 法, クレアチニン(CRE)はクレアチニナーゼ・F-DAOS 法, ブドウ糖(Glu)はヘキソキナーゼ・G-6-PDH 法, 総コレステロール(T-Chol)は COD・HDAOS 法, トリグリセライド(TG)は GPO・HDAOS 法, Ca は o-CPC 法, 無機リン(IP)は PNP・XDH 法, Na, K 及び Cl はイオン選択電極法により, いずれも生化学自動分析装置(AU 400, オリンパス株式会社)を用いて測定した.

アルブミン(Alb)は総蛋白及び蛋白分画値[電気泳動法, 自動電気泳動装置(AES 310, オリンパス株式会社)]から, A/G(アルブミン/グロブリン)は蛋白分画値から算出した.

#### 5.10.2. 試験群雌

血液学検査用の血液と同時期に腹大動脈から採取した血液から遠心分離[約 4 °C, 3000 rpm(約 1972 × g), 15 分間, 遠心機:CF8DL, 日立工機株式会社]して得た血清について, 雄の血液生化学検査と同一項目(5.10.1.)の検査を実施した. 保存用血清は, 最終報告書作成時まで冷凍庫(-80 °C設定, 超低温フリーザー:ULT1786-9JD, Kendro Laboratory Products)内に保管した.

#### 5.10.3. 回復群雌

血液学検査用の血液と同時期に腹大動脈から採取した血液から遠心分離[約 4 °C, 3000 rpm(約 1972 × g), 15 分間, 遠心機:CF8DL, 日立工機株式会社]して得た血清について, 雄の血液生化学検査と同一項目(5.10.1.)の検査を実施した. 保存用血清は, 最終報告書作成時まで冷凍庫(-80 °C設定, 超低温フリーザー:ULT1786-9JD, Kendro Laboratory Products)内に保管した.

### 5.11. 剖検及び器官重量測定

#### 5.11.1. 雄

上記の 5.9.1. 及び 5.10.1. の項で採血した動物をさらに放血致死させた後に剖検した. 脳(大脳, 小脳, 延髄), 下垂体, 甲状腺, 胸腺, 心臓, 肝臓, 脾臓, 腎臓, 副腎, 精巢及び精巢上体は重量を測定した(電子天秤:AB204, メトラー・トレド株式会社). 各器官重量を最終体重で除して相対重量も算出した. 下垂体及び甲状腺は 20 vol%中性緩衝ホルマリンで 1 晩固定後, 測定した. これらの器官は, 肺, 気管, 膵臓, 唾液腺(舌下腺・顎下腺), 食道, 胃, 十二指腸, 空腸, 回腸, 盲腸, 結腸, 直腸, リンパ節(下頸・腸間膜), 膀胱, 精嚢, 前立腺, 上皮小体, 脊髄, 坐骨神経, 眼球, ハーダー腺, 胸骨及び大腿骨とともに 20 vol%中性緩衝ホルマリンで固定した. ただし, 精巢及び精巢上体はブアン液で 2~3 時間固定後, 90 vol%エタノールに再固定し, 眼球はグルタールアルデヒド・ホルマリンで 1 晩固定後, 20 vol%中性緩衝ホルマリンに再固定した.

#### 5.11.2. 試験群雌

上記の 5.9.2. 及び 5.10.2. の項で採血した動物をさらに放血致死させ, 妊娠黄体数及び着床数を算定後, 剖検した. また, 各群の尿検査, 血液体学検査及び血液生化学検査を実施しなかった動

物をペントバルビタールナトリウムの腹腔内投与(40 mg/kg)による麻酔下で腹大動脈から放血致死させ、妊娠黄体数及び着床数を算定後、剖検した。脳(大脳、小脳、延髄)、下垂体、甲状腺、胸腺、心臓、肝臓、脾臓、腎臓、副腎、卵巢及び子宮は重量を測定した(電子天秤:AB204、メトラー・トレド株式会社)。各器官重量を最終体重で除して相対重量も算出した。下垂体及び甲状腺は 20 vol%中性緩衝ホルマリンで 1 晩固定後、測定した。これらの器官は、肺、気管、脾臓、唾液腺(舌下腺・顎下腺)、食道、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、リンパ節(下頸・腸間膜)、膀胱、腔、上皮小体、脊髄、坐骨神経、眼球、ハーダー腺、胸骨、大腿骨及び乳腺とともに 20 vol%中性緩衝ホルマリンで固定した。ただし、眼球は、グルタールアルデヒド・ホルマリンで 1 晩固定後、20 vol%中性緩衝ホルマリンに再固定した。

妊娠 25 日の午前 10 時までに分娩しなかった雌動物は、ペントバルビタールナトリウムの腹腔内投与(40 mg/kg)による麻酔下で腹大動脈から放血致死させ後に剖検し、着床の有無により妊娠の成否を確認した。上記の器官・組織は、20 vol%中性緩衝ホルマリンで固定後、10 vol%中性緩衝ホルマリンに保存した。ただし、眼球は、グルタールアルデヒド・ホルマリンで 1 晩固定後、20 vol%中性緩衝ホルマリンに再固定した。

### 5.11.3. 回復群雌

上記の 5.9.3. 及び 5.10.3. の項で採血した動物をさらに放血致死させた後、剖検した。脳(大脳、小脳、延髄)、下垂体、甲状腺、胸腺、心臓、肝臓、脾臓、腎臓、副腎、卵巢及び子宮は重量を測定した(電子天秤:AB204、メトラー・トレド株式会社)。各器官重量を最終体重で除して相対重量も算出した。下垂体及び甲状腺は 20 vol%中性緩衝ホルマリンで 1 晩固定後、測定した。これらの器官は、肺、気管、脾臓、唾液腺(舌下腺・顎下腺)、食道、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、リンパ節(下頸・腸間膜)、膀胱、腔、上皮小体、脊髄、坐骨神経、眼球、ハーダー腺、胸骨、大腿骨及び乳腺とともに 20 vol%中性緩衝ホルマリンで固定した。ただし、眼球は、グルタールアルデヒド・ホルマリンで 1 晩固定後、20 vol%中性緩衝ホルマリンに再固定した。

## 5.12. 病理組織学検査

### 5.12.1. 雄

投与期間終了時剖検例について、心臓、肺、気管、肝臓、脾臓、唾液腺(舌下腺・顎下腺)、食道、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、胸腺、脾臓、リンパ節(下頸・腸間膜)、腎臓、膀胱、精巣、精巣上体、精嚢、前立腺、下垂体、副腎、甲状腺、上皮小体、脳(大脳・小脳・延髄)、脊髄、坐骨神経、眼球、ハーダー腺、骨髄(胸骨・大腿骨)及び骨(胸骨・大腿骨)のパラフィン包埋標本を作製した。切り出し後の器官・組織は、10 vol%中性緩衝ホルマリンで保存した。その後、対照群及び 1000 mg/kg 群について、HE 染色組織標本を作製し、病理組織学検査を実施した。なお、精巣については、PAS-ヘマトキシリソ染色組織標本も作製した。

### 5.12.2. 試験群雌

各群とも動物番号の若い順に各 6 例について、心臓、肺、気管、肝臓、脾臓、唾液腺(舌下腺・

頸下腺), 食道, 胃, 十二指腸, 空腸, 回腸, 盲腸, 結腸, 直腸, 胸腺, 脾臓, リンパ節(下頸・腸間膜), 腎臓, 膀胱, 卵巣, 子宮, 膝, 下垂体, 副腎, 甲状腺, 上皮小体, 脳(大脳・小脳・延髄), 脊髄, 坐骨神経, 眼球, ハーダー腺, 骨髓(胸骨・大腿骨), 骨(胸骨・大腿骨)及び乳腺のパラフィン包埋標本を作製した。切り出し後の器官・組織は, 10 vol%中性緩衝ホルマリンで保存した。その後, 対照群及び 1000 mg/kg 群の各 6 例について, HE 染色組織標本を作製し, 病理組織学検査を実施した。

#### 5.13. 性周期

試験群雌の性周期は, 投与開始日から交尾確認前日まで毎日 1 回観察した。なお, 発情期が連続 2 日間にわたって観察された場合は 1 回と計数した。

#### 5.14. 交配

14 日間投与した雄と試験群雌を同一群内で 1 対 1 に組み合わせて同居交配した。交配期間は 14 日を限度として, 交尾を確認するまでの連続同居交配とした。

交尾確認は毎朝ほぼ一定時刻を行い, 膨栓又は腔塞性内に精子を確認した雌を交尾成立動物として, その日を妊娠 0 日として起算した。

#### 5.15. 分娩状態の観察

交尾雌は自然分娩させ, 分娩状態の異常の有無, 分娩終了の確認を妊娠 21 日から妊娠 25 日の午前 10 時まで毎日行った。午前 10 時に分娩が終了していた場合, その日を哺育 0 日とした。

#### 5.16. 哺育状態の観察

母動物は, 哺育状態を哺育 0 日から 4 日まで毎日 1 回観察した。

#### 5.17. 児動物 ( $F_1$ )

##### 5.17.1. 出産時の観察

出産時に総出産児数と性, 死産児数, 新生児数及び外表異常の有無を観察した。死産児は, 剖検後, 20 vol%中性緩衝ホルマリンで固定し, 10 vol%中性緩衝ホルマリンに保存した。

##### 5.17.2. 児動物の観察

児動物は, 一般状態及び死亡の有無を毎日 1 回観察した。死亡児は, 剖検後, 20 vol%中性緩衝ホルマリンで固定し, 10 vol%中性緩衝ホルマリンに保存した。

##### 5.17.3. 体重測定

体重は, 哺育 0 日(出生日)及び 4 日に測定した(電子天秤:PM2000, メトラー・トレド株式会社)。

#### 5.17.4. 剖検

生存児は、哺育 4 日にジエチルエーテル麻酔下で腹大動脈から放血致死させた後に剖検した。

#### 6. 統計解析

有意差検定は下記に示したように、対照群と各投与群の間で行い、危険率を 5%とし、5%未満( $p<0.05$ )と 1%未満( $p<0.01$ )とに分けて表示した。不受胎雌の交尾後の一般状態、体重、摂餌量及び行動機能(FOB)は集計から除外した。児動物の体重は、一腹の平均を 1 単位とし、一腹の平均値と合計値を算出した。

##### 〈検定方法〉

体重(親動物、児動物)、摂餌量、行動機能(FOB)の毛づくろい及び立ち上がり回数、握力、自発運動量、尿量、尿比重、血液学検査成績、血液生化学検査成績、器官の絶対重量及び相対重量、発情回数、交尾所要日数、妊娠期間[分娩日(哺育 0 日)–交尾確認日]、妊娠黄体数、着床数、着床率[(着床数/妊娠黄体数)×100]、総出産児数(新生児数+死産児数)、新生児数、死産児数、分娩率[(総出産児数/着床数)×100]、児の産出率[(哺育 0 日の新生児数/着床数)×100]、出生率[(哺育 0 日の新生児数/総出産児数)×100]、哺育 4 日の生存児数、哺育 4 日の生存率[(哺育 4 日の生存児数/哺育 0 日の新生児数)×100]、外表異常の出現率[(外表異常児数/新生児数)×100]及び性比(雄/雌)は、各群で平均値及び標準偏差を算出した。その後、Bartlett 法による等分散性の検定を行い、等分散の場合には Dunnett 法により行った。一方、等分散と認められなかった場合は、順位を利用した Dunnett 型の検定法により行った。

行動機能(FOB)(但し、毛づくろい及び立ち上がり回数を除く)及び感覚反応は、各群で平均値及び範囲を算出した。その後、順位を利用した Dunnett 型の検定法により行った。

交尾率[(交尾成立動物数/同居動物数)×100]、受胎率[(受胎雌数/交尾成立動物数)×100]及び出産率[(新生児出産雌数/受胎雌数)×100]は、 $\chi^2$  検定により行った。

## 結果

### I. 反復投与毒性

#### 1. 一般状態

##### 1.1. 雄 (Table 1-1～1-5, Appendix 1-1～1-4)

死亡例及び瀕死例は、いずれの群にも認められなかった。

投与期間中及び回復期間中とも、一般状態の異常はいずれの群にもみられなかった。

##### 1.2. 試験群雌 (Table 2-1, 2-2, 3-1, 3-2 及び 4, Appendix 2-1～2-4, 3-1～3-4 及び 4-1～4-4)

死亡例及び瀕死例は、いずれの群にも認められなかった。

交配開始前、交配期間中、妊娠期間中及び哺育期間中とも、一般状態の異常はいずれの群にもみられなかった。

##### 1.3. 回復群雌 (Table 5-1～5-5, Appendix 5-1～5-3)

死亡例及び瀕死例は、いずれの群にも認められなかった。

投与期間中及び回復期間中とも、一般状態の異常はいずれの群にもみられなかった。

#### 2. 体重

##### 2.1. 雄 (Table 6, Fig.2, Appendix 6-1～6-4)

投与期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

回復期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

##### 2.2. 試験群雌 (Table 7～9, Fig.3, Appendix 7-1～7-4, 8-1～8-4 及び 9-1～9-4)

交配開始前及び交配期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

妊娠期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

哺育期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

##### 2.3. 回復群雌 (Table 10, Fig.4, Appendix 10-1～10-3)

投与期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

回復期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

#### 3. 摂餌量

##### 3.1. 雄 (Table 11, Fig.5, Appendix 11-1～11-4)

投与期間中には、各投与群とも対照群と比べて各測定日の摂餌量に有意差はみられなかった。

回復期間中には、1000 mg/kg 群では対照群と比べて各測定日の摂餌量に有意差はみられなかった。250 mg/kg 群では、対照群と比べて回復 5 日に摂餌量の有意な低値がみられたが、投与量に関連した変化ではないことから、投与による影響とは考えられない。

### 3.2. 試験群雌 (Table 12~14, Fig.6, Appendix 12-1~12-4, 13-1~13-4 及び 14-1~14-4)

交配開始前には、各投与群とも対照群と比べて各測定日の摂餌量に有意差はみられなかった。妊娠期間中には、各投与群とも対照群と比べて各測定日の摂餌量に有意差はみられなかった。哺育期間中には、各投与群とも対照群と比べて測定日の摂餌量に有意差はみられなかった。

### 3.3. 回復群雌 (Table 15, Fig.7, Appendix 15-1~15-3)

投与期間中には、各投与群とも対照群と比べて各測定日の摂餌量に有意差はみられなかった。回復期間中には、各投与群とも対照群と比べて各測定日の摂餌量に有意差はみられなかった。

## 4. 行動機能 (FOB)

### 4.1. 雄 (Table 16-1~16-6, Appendix 16-1~16-4)

各投与群とも、各検査日のいずれの項目にも異常はみられなかった。

### 4.2. 試験群雌 (Table 17-1~17-6, Appendix 17-1~17-4)

各投与群とも、各検査日のいずれの項目にも異常はみられなかった。

### 4.3. 回復群雌 (Table 18-1~18-6, Appendix 18-1~18-3)

1000 mg/kg 群では、対照群と比べて各検査日のいずれの項目にも異常はみられなかった。250 mg/kg 群では、対照群と比べて投与 36 日に立ち上がり回数の有意な高値がみられたが、投与量に関連した変化ではないことから、投与による影響とは考えられない。また、250 mg/kg 群では、投与前に立ち上がり回数の有意な高値がみられた。

## 5. 感覚反応

### 5.1. 雄 (Table 19, Appendix 19-1~19-4)

各投与群とも、いずれの項目にも異常はみられなかった。

### 5.2. 試験群雌 (Table 20, Appendix 20-1~20-4)

各投与群とも、いずれの項目にも異常はみられなかった。

## 6. 握力

### 6.1. 雄 (Table 21, Appendix 21-1~21-4)

各投与群とも、対照群と比べて前肢及び後肢の握力に有意差はみられなかった。

### 6.2. 試験群雌 (Table 22, Appendix 22-1~22-4)

各投与群とも、対照群と比べて前肢及び後肢の握力に有意差はみられなかった。

## 7. 自発運動量

### 7.1. 雄 (Table 23, Appendix 23-1～23-4)

1000 及び 62.5 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。250 mg/kg 群では、対照群と比べて投与後 60 分に歩行量及び立ち上がり回数の有意な低値がみられたが、投与量に関連した変化ではないことから、投与による影響とは考えられない。

### 7.2. 試験群雌 (Table 24, Appendix 24-1～24-4)

各投与群とも、対照群と比べて各測定項目に有意差はみられなかった。

## 8. 尿検査

### 8.1. 投与期間終了前

#### 8.1.1. 雄 (Table 25-1 及び 25-2, Appendix 25-1～25-4)

各投与群とも、対照群と比べて尿量及び尿比重に有意差はみられなかった。

各投与群とも、色調、pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血、ウロビリノーゲン及び沈渣は対照群とほぼ同程度であった。

#### 8.1.2. 試験群雌 (Table 26-1 及び 26-2, Appendix 26-1～26-4)

各投与群とも、対照群と比べて尿量及び尿比重に有意差はみられなかった。

各投与群とも、色調、pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血、ウロビリノーゲン及び沈渣は対照群とほぼ同程度であった。

### 8.2. 回復期間終了前

#### 8.2.1. 雄 (Table 27-1 及び 27-2, Appendix 27-1～27-4)

各投与群とも、対照群と比べて尿量及び尿比重に有意差はみられなかった。

各投与群とも、色調、pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血、ウロビリノーゲン及び沈渣は対照群とほぼ同程度であった。

#### 8.2.2. 回復群雌 (Table 28-1 及び 28-2, Appendix 28-1～28-3)

各投与群とも、対照群と比べて尿量及び尿比重に有意差はみられなかった。

各投与群とも、色調、pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血、ウロビリノーゲン及び沈渣は対照群とほぼ同程度であった。

## 9. 血液学検査

### 9.1. 投与期間終了時

#### 9.1.1. 雄 (Table 29, Appendix 29-1～29-4)

各投与群とも、対照群と比べて各測定項目に有意差はみられなかった。

### 9.1.2. 試験群雌 (Table 30, Appendix 30-1～30-4)

1000 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。250 及び 62.5 mg/kg 群では、対照群と比べて血小板数の有意な低値がみられたが、投与量に関連した変化ではないことから、投与による影響とは考えられない。

## 9.2. 回復期間終了時

### 9.2.1. 雄 (Table 31, Appendix 31-1～31-4)

各投与群とも、対照群と比べて各測定項目に有意差はみられなかった。

### 9.2.2. 回復群雌 (Table 32, Appendix 32-1～32-3)

1000 mg/kg 群では、対照群と比べてリンパ球率の有意な高値及び好中球率の有意な低値がみられたが、軽度な変化であること、投与期間終了時にそれらの傾向は認められなかつたことから、投与に基づくものではないと判断される。250 mg/kg 群では、対照群と比べて MCHC の有意な高値がみられたが、投与量に関連した変化ではないことから、投与による影響とは考えられない。

## 10. 血液生化学検査

### 10.1. 投与期間終了時

#### 10.1.1. 雄 (Table 33, Appendix 33-1～33-4)

1000 mg/kg 群では、対照群と比べて総ビリルビンの有意な低値がみられたが、軽度な変化であることから、毒性学的意義はないと考えられる。250 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。62.5 mg/kg 群では、対照群と比べて Cl の有意な高値、総蛋白及び総ビリルビンの有意な低値がみられたが、投与量に関連した変化ではないことから、投与による影響とは考えられない。

#### 10.1.2. 試験群雌 (Table 34, Appendix 34-1～34-4)

各投与群とも、対照群と比べて各測定項目に有意差はみられなかった。

### 10.2. 回復期間終了時

#### 10.2.1. 雄 (Table 35, Appendix 35-1～35-4)

各投与群とも、対照群と比べて各測定項目に有意差はみられなかった。

#### 10.2.2. 回復群雌 (Table 36, Appendix 36-1～36-3)

各投与群とも、対照群と比べて各測定項目に有意差はみられなかった。

## 11. 剖検

### 11.1. 投与期間終了時

#### 11.1.1. 雄 (Table 37, Appendix 37-1～37-4)

1000, 250 及び 62.5 mg/kg 群では、異常はみられなかった。対照群では、左精巢上体尾部に黄白色結節が 1 例にみられた。

#### 11.1.2. 試験群雌 (Table 38, Appendix 38-1～38-4)

いずれの群とも、異常はみられなかった。

### 11.2. 回復期間終了時

#### 11.2.1. 雄 (Table 39, Appendix 39-1～39-4)

いずれの群とも、異常はみられなかった。

#### 11.2.2. 回復群雌 (Table 40, Appendix 40-1～40-3)

いずれの群とも、異常はみられなかった。

## 12. 器官重量

### 12.1. 投与期間終了時

#### 12.1.1. 雄 (Table 41, Appendix 41-1～41-4)

剖検日の体重は、各投与群とも対照群と比べて有意差はみられなかった。

器官重量において、各投与群とも対照群と比べて各器官の絶対重量及び相対重量に有意差はみられなかった。

#### 12.1.2. 試験群雌 (Table 42, Appendix 42-1～42-4)

剖検日の体重は、各投与群とも対照群と比べて有意差はみられなかった。

器官重量において、1000 及び 250 mg/kg 群では対照群と比べて各器官の絶対重量及び相対重量に有意差はみられなかった。62.5 mg/kg 群では、対照群と比べて胸腺の相対重量の有意な高値がみられたが、投与量に関連した変化ではないことから、投与による影響とは考えられない。

### 12.2. 回復期間終了時

#### 12.2.1. 雄 (Table 43, Appendix 43-1～43-4)

剖検日の体重は、各投与群とも対照群と比べて有意差はみられなかった。

器官重量において、各投与群とも対照群と比べて各器官の絶対重量及び相対重量に有意差はみられなかった。

#### 12.2.2. 回復群雌 (Table 44, Appendix 44-1～44-3)

剖検日の体重は、各投与群とも対照群と比べて有意差はみられなかった。

器官重量において、1000 mg/kg 群では対照群と比べて各器官の絶対重量及び相対重量に有意

差はみられなかった。250 mg/kg 群では、対照群と比べて卵巢の絶対重量及び相対重量の有意な低値がみられたが、投与量に関連した変化ではないことから、投与による影響とは考えられない。

### 13. 病理組織学検査

#### 13.1. 投与期間終了時

##### 13.1.1. 雄 (Table 45, Appendix 45-1~45-2)

肺：泡沫細胞集簇が 1000 mg/kg 群で 1 例と対照群で 2 例にみられた。

空腸：パイエル氏板の鉱質沈着が 1000 mg/kg 群で 1 例にみられた。

精巣上体：リンパ細胞浸潤及び片側性精子肉芽腫が対照群で 1 例にみられた。

前立腺：リンパ細胞浸潤が 1000 mg/kg 群で 1 例にみられた。

なお、これらの変化は対照群でも通常観察される変化であること、それらの程度はいずれもごく軽度であること、1000 mg/kg 群のそれらの出現頻度は対照群と比べて差がないことから、偶発的変化と判断される。

その他には、1000 mg/kg 群及び対照群では、心臓、気管、肝臓、脾臓、舌下腺、顎下腺、食道、胃、十二指腸、回腸、盲腸、結腸、直腸、胸腺、脾臓、下頸リンパ節、腸間膜リンパ節、腎臓、膀胱、精巣、精嚢、下垂体、副腎、甲状腺、上皮小体、大脳、小脳、延髄、脊髄、坐骨神経、眼球、ハーダー腺、骨髓(胸骨・大腿骨)及び骨(胸骨・大腿骨)に異常はみられなかった。

##### 13.1.2. 試験群雌 (Table 46, Appendix 46-1~46-2)

空腸：パイエル氏板の鉱質沈着が 1000 mg/kg 群で 1 例にみられた。

脾臓：髓外造血が 1000 mg/kg 群で 1 例と対照群で 3 例にみられた。

眼球：右網膜異形成が 1000 mg/kg 群で 1 例にみられた。

なお、これらの変化は対照群でも通常観察される変化であること、それらの程度はいずれもごく軽度であること、1000 mg/kg 群のそれらの出現頻度は対照群と比べて差がないことから、偶発的変化と判断される。

その他には、1000 mg/kg 群及び対照群では、心臓、肺、気管、肝臓、脾臓、舌下腺、顎下腺、食道、胃、十二指腸、回腸、盲腸、結腸、直腸、胸腺、下頸リンパ節、腸間膜リンパ節、腎臓、膀胱、卵巣、子宮、腔、下垂体、副腎、甲状腺、上皮小体、大脳、小脳、延髄、脊髄、坐骨神経、ハーダー腺、骨髓(胸骨・大腿骨)、骨(胸骨・大腿骨)及び乳腺に異常はみられなかった。

## II. 生殖発生毒性

### 1. 親動物の生殖発生

#### 1.1. 発情回数 (Table 47, Appendix 47-1~47-4)

交配開始前の投与期間(14 日間)の発情回数は、各投与群とも対照群と比べて有意差はみられなかった。

### 1.2. 交尾所要日数, 交尾率, 受胎雌数及び受胎率 (Table 47, Appendix 47-1~47-4)

いずれの群とも全例が交尾した。交尾率は、いずれの群とも 100.0% であった。交尾所要日数は、各投与群とも対照群との間に有意差はみられなかった。

不受胎雌は、対照群及び 1000 mg/kg 群で各 1 例にみられた。受胎率は、各投与群とも対照群との間に有意差はみられなかった。

### 1.3. 妊娠期間 (Table 48, Appendix 48-1~48-4)

妊娠期間は、各投与群とも対照群と比べて有意差はみられなかった。

### 1.4. 妊娠黄体数, 着床数及び着床率 (Table 48, Appendix 48-1~48-4)

1000 及び 250 mg/kg 群では、対照群と比べて妊娠黄体数、着床数及び着床率に有意差はみられなかった。62.5 mg/kg 群では、対照群と比べて着床率の有意な高値がみられたが、投与量に関連したものではないことから、投与による影響とは考えられない。

### 1.5. 出産率, 分娩状態及び哺育状態 (Table 48 及び 49, Appendix 48-1~48-4 及び 49-1~49-4)

出産率は、いずれの群とも 100.0% であった。

分娩状態及び哺育状態において、いずれの群とも異常はみられなかった。

## 2. 児動物 ( $F_1$ )

### 2.1. 総出産児数, 死産児数, 哺育 0 日の新生児数, 哺育 0 日の性比, 分娩率, 児の産出率及び出生率 (Table 48, Appendix 48-1~48-4)

1000 及び 62.5 mg/kg 群では、対照群と比べて総出産児数、死産児数、哺育 0 日の新生児数、哺育 0 日の性比、分娩率、児の産出率及び出生率に有意差はみられなかった。250 mg/kg 群では、対照群と比べて分娩率及び児の産出率の有意な低値がみられたが、投与量に関連したものではないことから、投与による影響とは考えられない。

### 2.2. 児動物の一般状態, 哺育 4 日の生存児数, 哺育 4 日の性比, 哺育 4 日の生存率及び外表異常 (Table 48 及び 50, Appendix 48-1~48-4 及び 50-1~50-4)

各投与群とも、対照群と比べて哺育 4 日の生存児数、哺育 4 日の性比及び哺育 4 日の生存率に有意差はみられなかった。

新生児の外表異常としては、1000 mg/kg 群で無尾が 1 例にみられたが、対照群との間に有意差は認められず、自然発生例と考えられる。

児動物の一般状態において、いずれの群とも異常はみられなかった。

### 2.3. 児動物の体重 (Table 51, Appendix 51-1~51-4)

各投与群とも、対照群と比べて哺育 0 及び 4 日の雌雄別平均体重、哺育 0 及び 4 日の一腹平均体重、哺育 0 及び 4 日の一腹合計体重に有意差はみられなかった。

#### 2.4. 死亡児の剖検 (Table 52, Appendix 52-1～52-4)

1000 及び 62.5 mg/kg 群並びに対照群では、異常はみられなかった。250 mg/kg 群では、腹腔内器官の欠損が 1 例にみられたが、投与量に関連したものではないことから、投与による影響とは考えられない。

#### 2.5. 生存児の剖検 (Table 53, Appendix 53-1～53-4)

いずれの群とも、異常はみられなかった。

### 考察

ブメトリゾールのラットを用いる経口投与による反復投与毒性・生殖発生毒性併合試験を行い、雌雄動物に対する一般毒性学的影響を検討するとともに、性腺機能、交尾行動、受胎及び分娩などの生殖行動に及ぼす影響について検討した。投与量は、1000 mg/kg を高用量とし、以下 250 及び 62.5 mg/kg とした。

反復投与による毒性については、死亡例及び瀕死例は雌雄ともいずれの群にも認められなかった。一般状態の異常は、雌雄ともいずれの群にもみられなかった。体重及び摂餌量では、雌雄とも投与に起因する変化はみられなかった。行動機能(FOB)、感覚反応、握力及び自発運動量では、雌雄とも投与に起因する変化はみられなかった。尿検査、血液学検査、血液生化学検査、剖検、器官重量及び病理組織学検査において、雌雄とも投与に起因する変化はみられなかった。

親動物の生殖発生毒性については、交配開始前の投与期間(14 日間)の発情回数、交尾率、交尾所要日数、受胎雌数、受胎率、妊娠期間、出産率、分娩状態、哺育状態、妊娠黄体数、着床数及び着床率に投与に起因する変化はみられなかった。

児動物( $F_1$ )については、総出産児数、死産児数、哺育 0 日の新生児数、哺育 0 日の性比、分娩率、児の産出率、出生率、一般状態、哺育 4 日の生存児数、哺育 4 日の性比、哺育 4 日の生存率、外表、体重及び剖検において、投与に起因する変化はみられなかった。

以上のように、ブメトリゾールの無影響量は、雌雄とも 1000 mg/kg 投与でいずれの項目にも影響が認められなかつたことから 1000 mg/kg/day を越えると考えられる。また、生殖発生毒性学的な無影響量は、雌雄とも 1000 mg/kg 投与でいずれの項目にも影響が認められなかつたことから 1000 mg/kg/day を越えると考えられる。児動物への無影響量は、1000 mg/kg 投与で生存性及び体重などに影響が認められなかつたことから 1000 mg/kg/day を越えると考えられる。

## 文献

- 1) [REDACTED]: ブメトリゾール調製液の安定性確認試験(試験番号 : 402024P)(株式会社日本バイオリサーチセンター 羽島研究所)
- 2) [REDACTED]: ブメトリゾールのラットを用いる経口投与による反復投与毒性・生殖発生毒性併合試験の予備試験(試験番号 : 100624P)(株式会社日本バイオリサーチセンター 羽島研究所)

### Analysis of bumetizole (Study No. 402024P)

Test articles: bumetizole (Lot No. 01721IW4)  
Method: HPLC  
Date of analysis: February 16, 2005  
Study period: Initial  
Testing facility: Hashima Laboratory, Nihon Bioresearch Inc.

Analytical items	Results
Content	99.5%

**Deviation from the protocol:**

This analysis was conducted according to the protocol and there were no deviations from the protocol during the analysis.

**GLP:**

This study was conducted in compliance with the OECD Guidelines for Safety Studies on Chemicals (OECD GLP Standards) and the Law Concerning the Examination and Regulation of Manufacture etc. of Chemical Substances.

## Analysis of bumetizole

Test articles: bumetizole (Lot No. 01721IW4)  
Method: HPLC  
Date of analysis: July 28, 2005  
Study period Final  
Testing facility: Hashima Laboratory, Nihon Bioresearch Inc.

Analytical items	Results
Content	100.6%

### Deviation from the protocol:

This analysis was conducted according to the protocol and there were no deviations from the protocol during the analysis.

### GLP:

This study was conducted in compliance with the OECD Guidelines for Safety Studies on Chemicals (OECD GLP Standards) and the Law Concerning the Examination and Regulation of Manufacture etc. of Chemical Substances.

## Stability and homogeneity of bumetizole in test preparations (Study No. 402024P)

**Test article:** bumetizole (Lot No. 01721IW4)  
**Vehicle:** 0.5% Methylcellulose solution  
**Date of preparation:** February 21, 2005  
**Method:** HPLC  
**Date of analysis:** February 21, 2005, February 22, 2005, February 28, 2005  
**Storage condition:**  
 1) Stored at refrigeration (set at 4°C) and light-shielded conditions for 1 day  
 2) Stored at room temperature (set at 23°C) and light-shielded conditions for 6 hours after being stored under refrigeration (set at 4°C) and light-shielded conditions for 7 days  
**Testing facility:** Hashima Laboratory, Nihon Bioresearch Inc.

### Results

Concentration of bumetizole (mg/mL)	Storage period	Measured concentration (mg/mL)				Recovery rate (%)	Residual rate to the value immediately after preparation (%)	CV (%)
		1st	2nd	3rd	Mean			
2	Immediately after preparation	1.974	2.000	1.981	1.985	99.3	-	0.7
	At 1 day after preparation <sup>1)</sup>	2.057	2.046	2.063	2.055	102.8	103.5	0.4
	At 7 days after preparation <sup>2)</sup>	2.021	2.011	2.026	2.019	101.0	101.7	0.4
20	Immediately after preparation	19.98	20.22	20.10	20.10	100.5	-	0.6
	At 1 day after preparation <sup>1)</sup>	20.65	20.50	20.88	20.68	103.4	102.9	0.9
	At 7 days after preparation <sup>2)</sup>	20.74	20.67	20.68	20.70	103.5	103.0	0.2
200	Immediately after preparation	197.1	198.3	198.3	197.9	99.0	-	0.3
	At 1 day after preparation <sup>1)</sup>	200.4	207.8	197.0	201.7	100.9	101.9	2.7
	At 7 days after preparation <sup>2)</sup>	192.6	195.6	196.5	194.9	97.5	98.5	1.0

The concentration of each preparation was within the acceptable range (100±10%).

The stability of each preparation was in conformity with the regulation [Residual rate (%) to the value immediately after preparation was 90% or higher].  
 The homogeneity of each preparation was within the acceptable range (CV≤5%).

### Deviation from the protocol:

This analysis was conducted according to the protocol and there were no deviations from the protocol during the analysis.

### GLP:

This study was conducted in compliance with the OECD Guidelines for Safety Studies on Chemicals (OECD GLP Standards) and the Law Concerning the Examination and Regulation of Manufacture etc. of Chemical Substances.

**Concentrations of bumetizole in dosing preparations  
at the start of administration**

**Test article:** bumetizole (Lot No. 01721IW4)  
**Vehicle:** 0.5 w/v% Methylcellulose solution  
**Date of preparation:** May 31, 2005  
**Method:** HPLC  
**Date of analysis:** May 31, 2005  
**Testing facility:** Hashima Laboratory, Nihon Bioresearch Inc.

**Results**

Concentration of bumetizole (w/v%)	Measured concentrations (w/v%)				Recovery rate (%)	CV (%)
	1st	2nd	3rd	Mean		
1.25	1.275	1.258	1.275	1.269	101.5	0.8
5	5.194	5.097	5.121	5.137	102.7	1.0
20	20.56	20.72	20.08	20.45	102.3	1.6

The concentration of each preparation was within the acceptable range ( $100\pm10\%$ ).

The homogeneity of each preparation was within the acceptable range ( $CV \leq 5\%$ ).

**Deviation from the protocol:**

This analysis was conducted according to the protocol and there were no deviations from the protocol during the analysis.

**GLP:**

This study was conducted in compliance with the OECD Guidelines for Safety Studies on Chemicals (OECD GLP Standards) and Law Concerning the Examination and Regulation of Manufacture etc. of Chemical Substances.

**Concentrations of bumetizole in dosing preparations  
at the end of administration**

**Test article:** bumetizole (Lot No. 01721IW4)  
**Vehicle:** 0.5 w/v% Methylcellulose solution  
**Date of preparation:** July 5, 2005  
**Method:** HPLC  
**Date of analysis:** July 6, 2005  
**Testing facility:** Hashima Laboratory, Nihon Bioresearch Inc.

**Results**

Concentration of bumetizole (w/v%)	Measured concentrations (w/v%)				Recovery rate (%)	CV (%)
	1st	2nd	3rd	Mean		
1.25	1.284	1.275	1.277	1.279	102.3	0.4
5	5.130	5.100	5.071	5.100	102.0	0.6
20	20.38	20.31	20.32	20.34	101.7	0.2

The concentration of each preparation was within the acceptable range ( $100\pm10\%$ ).

The homogeneity of each preparation was within the acceptable range ( $CV \leq 5\%$ ).

**Deviation from the protocol:**

This analysis was conducted according to the protocol and there were no deviations from the protocol during the analysis.

**GLP:**

This study was conducted in compliance with the OECD Guidelines for Safety Studies on Chemicals (OECD GLP Standards) and Law Concerning the Examination and Regulation of Manufacture etc. of Chemical Substances.

Table 1-1 General signs of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of males and general signs	Days of administration																									
			1		2		3		4		5		6		7		8		9		10		11		12		13	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
Control	0	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
bumetizole	62.5	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	250	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	1000	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.

Table 1-2 General signs of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of males and general signs	Days of administration																									
			14		15		16		17		18		19		20		21		22		23		24		25		26	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control	0	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
bumetizole	62.5	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	250	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	1000	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.

Table 1-3 General signs of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of males and general signs	Days of administration																									
			27		28		29		30		31		32		33		34		35		36		37		38		39	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control	0	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
bumetizole	62.5	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	250	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	1000	Number of males Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		

Pre: Before administration, Post: after administration.

Table 1-4 General signs of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of males and general signs	Days of administration					
			40		41		42	
			Pre	Post	Pre	Post	Pre	Post
Control	0	Number of males Normal	12	12	12	12	12	6
bumetizole	62.5	Number of males Normal	12	12	12	12	12	6
	250	Number of males Normal	12	12	12	12	12	6
	1000	Number of males Normal	12	12	12	12	12	6

Pre: Before administration, Post: after administration.

Table 1-5 General signs of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of males and general signs	Days of recovery													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
Control	0	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6
bumetizole	62.5	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	250	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	1000	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Table 2-1 General signs of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of females and general signs	Days of administration																			
			1		2		3		4		5		6		7		8		9		10	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control	0	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
bumetizole	62.5	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	250	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	1000	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

Table 2-2 General signs of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of females and general signs	Days of administration																									
			15*		16		17		18		19		20		21		22		23		24		25		26		27	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control	0	Number of females	12	12	10	10	7	7	6	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Normal	12	12	10	10	7	7	6	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
bumetizole	62.5	Number of females	12	12	7	7	3	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Normal	12	12	7	7	3	3	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	250	Number of females	12	12	9	9	8	8	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Normal	12	12	9	9	8	8	4	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	1000	Number of females	12	12	8	8	4	4	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
		Normal	12	12	8	8	4	4	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		

Pre: Before administration, Post: after administration.

\*: Start of pairing.

Table 3-1 General signs of dams during pregnancy in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of dams and general signs	Days of pregnancy																													
			0		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control	0	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11		
		Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11		
bumetizole	62.5	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	250	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	1000	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11		
		Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11		

Pre: Before administration, Post: after administration.

Table 3-2 General signs of dams during pregnancy in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of dams and general signs	Days of pregnancy																						
			15		16		17		18		19		20		21		22		23		24		25		
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Control	0	Number of dams Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	3	0	0	0	0	0	0
bumetizole	62.5	Number of dams Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	0	0	0	0	0	0
	250	Number of dams Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	-	-	-	-	-	-
	1000	Number of dams Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	3	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Table 4 General signs of dams during lactation in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of dams and general signs	Days of lactation													
			0		1		2		3		4		5		6	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control	0	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11
		Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11
bumetizole	62.5	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	250	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	1000	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11
		Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11

Pre: Before administration, Post: after administration.

Table 5-1 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of females and general signs	Days of administration																									
			1		2		3		4		5		6		7		8		9		10		11		12		13	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
Control	0	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
bumetizole	250	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
	1000	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			

Pre: Before administration, Post: after administration.

Table 5-2 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of females and general signs	Days of administration																									
			14		15		16		17		18		19		20		21		22		23		24		25		26	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control	0	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
bumetizole	250	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
	1000	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

Table 5-3 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of females and general signs	Days of administration																									
			27		28		29		30		31		32		33		34		35		36		37		38		39	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control	0	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
bumetizole	250	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
	1000	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		

Pre: Before administration, Post: after administration.

Table 5-4 General signs of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	mg/kg	Number of females and general signs	Days of administration					
			40		41		42	
			Pre	Post	Pre	Post	Pre	Post
Control	0	Number of females	6	6	6	6	6	6
		Normal	6	6	6	6	6	6
bumetizole	250	Number of females	6	6	6	6	6	6
		Normal	6	6	6	6	6	6
	1000	Number of females	6	6	6	6	6	6
		Normal	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

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

Group	mg/kg	Number of females and general signs	Days of recovery														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control	0	Number of females Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
bumetizole	250	Number of females Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	1000	Number of females Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Table 6 Body weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of males	12	12	12	12	
Days of administration					
1	381 ± 12	380 ± 11	381 ± 12	380 ± 13	
4	395 ± 14	392 ± 12	389 ± 13	389 ± 12	
8	409 ± 20	404 ± 14	401 ± 14	404 ± 13	
11	419 ± 20	415 ± 18	410 ± 15	415 ± 15	
15	429 ± 22	425 ± 17	420 ± 18	422 ± 16	
18	434 ± 23	434 ± 22	427 ± 19	429 ± 18	
22	446 ± 23	446 ± 22	442 ± 20	442 ± 18	
25	456 ± 25	457 ± 23	452 ± 23	454 ± 21	
29	469 ± 26	468 ± 24	465 ± 23	463 ± 24	
32	477 ± 28	477 ± 23	473 ± 23	472 ± 24	
36	488 ± 30	488 ± 24	484 ± 26	481 ± 24	
39	495 ± 31	493 ± 25	489 ± 26	490 ± 24	
42	496 ± 32	497 ± 26	487 ± 26	490 ± 22	
Number of males	6	6	6	6	
Days of recovery					
1	507 ± 30	504 ± 26	494 ± 35	493 ± 30	
4	514 ± 32	512 ± 30	499 ± 36	499 ± 28	
8	523 ± 30	522 ± 27	508 ± 38	507 ± 30	
11	526 ± 31	529 ± 28	513 ± 39	509 ± 32	
14	535 ± 31	540 ± 29	521 ± 38	519 ± 32	

Each value shows mean (g) ± S.D.

Table 7 Body weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of females	12	12	12	12	
Days of administration					
1	250 ± 7	250 ± 7	251 ± 6	249 ± 8	
4	259 ± 13	256 ± 9	257 ± 6	256 ± 10	
8	269 ± 15	266 ± 10	266 ± 7	264 ± 9	
11	272 ± 19	269 ± 8	266 ± 9	265 ± 10	
15	281 ± 21	277 ± 9	273 ± 10	272 ± 11	
18	280 ± 10 (6)	307 (1)	284 ± 12 (4)	279 ± 13 (4)	
22	-	-	-	323 (1)	
25	-	-	-	335 (1)	

Each value shows mean (g) ± S.D.

**Table 8** Body weights of dams during pregnancy in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of dams	11	12	12	11	
Days of pregnancy					
0	285 ± 18	278 ± 13	278 ± 13	278 ± 20	
7	324 ± 18	319 ± 16	316 ± 20	316 ± 20	
14	359 ± 21	354 ± 19	351 ± 29	351 ± 24	
21	444 ± 27	444 ± 27	443 ± 37	443 ± 33	

Each value shows mean (g) ± S.D.

**Table 9** Body weights of dams during lactation in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of dams	11		12		11
Days of lactation					
0	334 ± 25	325 ± 24	330 ± 35	322 ± 29	
4	351 ± 27	347 ± 19	343 ± 26	349 ± 30	
6	335 ± 19	332 ± 22	334 ± 31	327 ± 31	

Each value shows mean (g) ± S.D.

Table 10 Body weights of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole	
	0		250	1000
Number of females	6		6	6
Days of administration				
1	257 ± 7		258 ± 6	257 ± 7
4	259 ± 13		267 ± 11	263 ± 11
8	268 ± 11		277 ± 15	273 ± 17
11	270 ± 10		279 ± 17	276 ± 15
15	278 ± 12		288 ± 17	279 ± 16
18	286 ± 13		298 ± 17	285 ± 13
22	293 ± 15		305 ± 22	293 ± 12
25	299 ± 16		311 ± 20	296 ± 11
29	307 ± 19		316 ± 22	303 ± 12
32	304 ± 17		317 ± 25	301 ± 9
36	310 ± 20		324 ± 24	304 ± 9
39	319 ± 19		325 ± 25	310 ± 14
42	322 ± 20		328 ± 27	315 ± 15
Number of females	6		6	6
Days of recovery				
1	319 ± 22		327 ± 25	309 ± 13
4	326 ± 24		333 ± 26	319 ± 13
8	333 ± 25		338 ± 25	321 ± 12
11	334 ± 23		344 ± 21	322 ± 9
14	337 ± 27		348 ± 22	325 ± 8

Each value shows mean (g) ± S.D.

Table 11 Food consumption of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of males	12	12	12	12	
Days of administration					
2	25 ± 3	26 ± 3	24 ± 3	26 ± 3	
5	25 ± 3	25 ± 2	25 ± 2	25 ± 3	
9	24 ± 2	25 ± 2	24 ± 2	25 ± 3	
12	25 ± 2	26 ± 2	25 ± 3	26 ± 4	
30	26 ± 2	26 ± 2	25 ± 3	26 ± 3	
33	25 ± 2	26 ± 3	26 ± 3	25 ± 2	
37	26 ± 2	26 ± 2	26 ± 2	27 ± 2	
40	25 ± 2	26 ± 3	24 ± 2	26 ± 2	
Number of males	6	6	6	6	
Days of recovery					
2	24 ± 2	24 ± 2	23 ± 2	23 ± 2	
5	24 ± 2	23 ± 1	22 ± 1 *	22 ± 1	
9	26 ± 3	26 ± 2	26 ± 3	25 ± 2	
12	27 ± 3	27 ± 1	27 ± 2	27 ± 3	

Each value shows mean (g/day) ± S.D.

Significantly different from control group (\*: P&lt;0.05).

Table 12 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	Control		bumetizole		
	mg/kg	0	62.5	250	1000
Number of females	12	12	12	12	
Days of administration					
2	19 ± 2	19 ± 3	18 ± 4	19 ± 2	
5	20 ± 2	20 ± 3	20 ± 3	19 ± 4	
9	19 ± 3	19 ± 3	18 ± 3	18 ± 4	
12	20 ± 3	19 ± 3	19 ± 3	18 ± 3	

Each value shows mean (g/day) ± S.D.

Table 13 Food consumption of dams during pregnancy in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of dams	11	12	12	11	
Days of pregnancy					
2	22 ± 3	22 ± 2	21 ± 3	22 ± 2	
9	23 ± 3	25 ± 4	30 ± 22	24 ± 3	
16	24 ± 3	25 ± 4	25 ± 4	24 ± 3	
20	22 ± 3	23 ± 3	22 ± 3	23 ± 4	

Each value shows mean (g/day) ± S.D.

Table 14 Food consumption of dams during lactation in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group	Control	bumetizole		
		62.5	250	1000
mg/kg	0	62.5	250	1000
Number of dams	11	12	12	11
Days of lactation	2	30 ± 6	30 ± 3	27 ± 5
				33 ± 5

Each value shows mean (g/day) ± S.D.

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

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

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of males	12	12	12	12	
<b>Observation of animals in cages</b>					
Posture	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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 bumetizole by oral administration

Group mg/kg	Control		bumetizole	
	0	62.5	250	1000
Number of males	12	12	12	12
<b>Observation of animals in cages</b>				
Tonic convulsions	Pre	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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)
	Day 41	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 16-3 FOB of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole	
	0	62.5	250	1000
Number of males	12	12	12	12
<b>Observation of animals on observer's palm</b>				
Ease of removal from cage	Pre	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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)
	Day 41	2.0 (2)	2.0 (2)	2.0 (2)
Ease of handling	Pre	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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)
	Day 41	2.0 (2)	2.0 (2)	2.0 (2)
Muscle tone	Pre	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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)
	Day 41	2.0 (2)	2.0 (2)	2.0 (2)
Fur conditions	Pre	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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)
	Day 41	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.

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 bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of males	12	12	12	12	
<b>Observation of animals on observer's palm</b>					
Lacration	Pre	1.0 (1)	1.0 (1)	1.0 (1)	
Mean (range)	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)	
	Day 41	1.0 (1)	1.0 (1)	1.0 (1)	
Salivation	Pre	1.0 (1)	1.0 (1)	1.0 (1)	
Mean (range)	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)	
	Day 41	1.0 (1)	1.0 (1)	1.0 (1)	
Respiration	Pre	1.0 (1)	1.0 (1)	1.0 (1)	
Mean (range)	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)	
	Day 41	1.0 (1)	1.0 (1)	1.0 (1)	

Findings were graded as follows

- Lacration                    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 bumetizole by oral administration

Group mg/kg	Control		bumetizole			
	0	62.5	250	250	1000	
Number of males	12	12	12	12	12	
<b>Open-field test</b>						
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

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

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of males	12	12	12	12	
<b>Open-field test</b>					
Consciousness	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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)
Behavioral abnormalities	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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)
Righting reflex	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	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

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 bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of females	12	12	12	12	
<b>Observation of animals in cages</b>					
Posture	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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	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]
Biting behavior	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]
Clonic convulsions	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.

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 bumetizole by oral administration**

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of females	12	12	12	12	
<b>Observation of animals in cages</b>					
Tonic convulsions	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.

Findings were graded as follows

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

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

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
	12	12	12	12	
<b>Observation of animals on observer's palm</b>					
Ease of removal from cage	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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]
Ease of handling	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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]
Muscle tone	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	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]
Fur conditions	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.

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 bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of females	12	12	12	12	
<b>Observation of animals on observer's palm</b>					
Lacration	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)
Mean (range)	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]
Mean (range)	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]
Salivation	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)
Mean (range)	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]
Mean (range)	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]
Respiration	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)
Mean (range)	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]
Mean (range)	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

Lacration 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 bumetizole by oral administration

Group mg/kg	Control				bumetizole			
	0	12	62.5	12	250	12	1000	12
Number of females								
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.	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 bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of females	12	12	12	12	
<b>Open-field test</b>					
Consciousness Mean (range)	Pre Day 8 Day 15 Day 1 of pregnancy Day 8 of pregnancy Day 15 of pregnancy Day 3 of lactation	2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2) [11] 2.0 (2) [11] 2.0 (2) [11] 2.0 (2) [11]	2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2)	2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2)	2.0 (2) 2.0 (2) 2.0 (2) 2.0 (2) [11] 2.0 (2) [11] 2.0 (2) [11] 2.0 (2) [11]
Behavioral abnormalities Mean (range)	Pre Day 8 Day 15 Day 1 of pregnancy Day 8 of pregnancy Day 15 of pregnancy Day 3 of lactation	1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) [11] 1.0 (1) [11] 1.0 (1) [11] 1.0 (1) [11]	1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1)	1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1)	1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) [11] 1.0 (1) [11] 1.0 (1) [11] 1.0 (1) [11]
Righting reflex Mean (range)	Pre Day 8 Day 15 Day 1 of pregnancy Day 8 of pregnancy Day 15 of pregnancy Day 3 of lactation	1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) [11] 1.0 (1) [11] 1.0 (1) [11] 1.0 (1) [11]	1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1)	1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1)	1.0 (1) 1.0 (1) 1.0 (1) 1.0 (1) [11] 1.0 (1) [11] 1.0 (1) [11] 1.0 (1) [11]

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 bumetizole by oral administration

Group mg/kg	Control	bumetizole	
		250	1000
Number of females	6	6	6
<b>Observation of animals in cages</b>			
Posture	Pre	2.0 (2)	2.0 (2)
Mean (range)	Day 8	2.0 (2)	2.0 (2)
	Day 15	2.0 (2)	2.0 (2)
	Day 22	2.0 (2)	2.0 (2)
	Day 29	2.0 (2)	2.0 (2)
	Day 36	2.0 (2)	2.0 (2)
	Day 42	2.0 (2)	2.0 (2)
Palpebral closure	Pre	1.0 (1)	1.0 (1)
Mean (range)	Day 8	1.0 (1)	1.0 (1)
	Day 15	1.0 (1)	1.0 (1)
	Day 22	1.0 (1)	1.0 (1)
	Day 29	1.0 (1)	1.0 (1)
	Day 36	1.0 (1)	1.0 (1)
	Day 42	1.0 (1)	1.0 (1)
Biting behavior	Pre	1.0 (1)	1.0 (1)
Mean (range)	Day 8	1.0 (1)	1.0 (1)
	Day 15	1.0 (1)	1.0 (1)
	Day 22	1.0 (1)	1.0 (1)
	Day 29	1.0 (1)	1.0 (1)
	Day 36	1.0 (1)	1.0 (1)
	Day 42	1.0 (1)	1.0 (1)
Clonic convulsions	Pre	1.0 (1)	1.0 (1)
Mean (range)	Day 8	1.0 (1)	1.0 (1)
	Day 15	1.0 (1)	1.0 (1)
	Day 22	1.0 (1)	1.0 (1)
	Day 29	1.0 (1)	1.0 (1)
	Day 36	1.0 (1)	1.0 (1)
	Day 42	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 bumetizole by oral administration

Group mg/kg	Control			bumetizole		
	0	250	1000	6	6	6
<b>Observation of animals in cages</b>						
Tonic convulsions Mean (range)	Pre	1.0 (1)	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)	1.0 (1)
	Day 15	1.0 (1)	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)	1.0 (1)
	Day 29	1.0 (1)	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)	1.0 (1)
	Day 42	1.0 (1)	1.0 (1)	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 bumetizole by oral administration

Group mg/kg	Control			bumetizole		
	0	250	1000	6	6	6
<b>Observation of animals on observer's palm</b>						
Ease of removal from cage	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 8	2.0 (2)	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)	2.0 (2)
	Day 22	2.0 (2)	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)	2.0 (2)
	Day 36	2.0 (2)	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)	2.0 (2)
Ease of handling	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 8	2.0 (2)	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)	2.0 (2)
	Day 22	2.0 (2)	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)	2.0 (2)
	Day 36	2.0 (2)	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)	2.0 (2)
Muscle tone	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 8	2.0 (2)	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)	2.0 (2)
	Day 22	2.0 (2)	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)	2.0 (2)
	Day 36	2.0 (2)	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)	2.0 (2)
Fur conditions	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 22	1.0 (1)	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)	1.0 (1)
	Day 36	1.0 (1)	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)	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.

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 bumetizole by oral administration

Group mg/kg	Control			bumetizole		
	0	250	1000	6	6	6
Number of females						
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 bumetizole by oral administration

Group mg/kg	Control		bumetizole			
			250		1000	
	6		6		6	
<b>Open-field test</b>						
Frequency of rearing Mean ± S.D.	Pre	5.5 ± 2.9	10.7 ± 2.9 *	6.2 ± 3.3		
	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 Mean ± S.D.	Pre	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		
	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 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)		
Palpebral closure 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)		

Significantly different from control group (\*: P&lt;0.05, \*\*: P&lt;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 bumetizole by oral administration

Group mg/kg	Control			bumetizole		
	0	250	1000	0	250	1000
Number of females	6	6	6			
Open-field test						
Consciousness	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)
Behavioral abnormalities	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)
Righting reflex	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

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 bumetizole by oral administration

Group	Control		bumetizole			
	mg/kg	0	62.5	250	1000	
Number of males	6	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.

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 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 bumetizole by oral administration

Group	Control	bumetizole		
		62.5	250	1000
mg/kg	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 bumetizole by oral administration

Group	Control		bumetizole		
	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 bumetizole by oral administration

Group	Control	bumetizole		
		250	1000	
mg/kg	0	62.5		
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 bumetizole by oral administration

Group mg/kg	Control		bumetizole			
	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 bumetizole by oral administration

Group mg/kg	Control		bumetizole			
	0	62.5	250	1000		
Number of females	6	6	6	6		
<b>Ambulatory counts</b>						
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		
<b>Vertical counts</b>						
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 bumetizole by oral administration

Group	Control		bumetizole		
	mg/kg	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 bumetizole by oral administration**

Group	Control	bumetizole		
		62.5	250	1000
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 bumetizole by oral administration

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

Table 26-2 Urinary examination of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control	bumetizole		
		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 bumetizole by oral administration

Group	Control		bumetizole		
	mg/kg	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 bumetizole by oral administration**

Group	Control	bumetizole		
		62.5	250	1000
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	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 bumetizole by oral administration

Group mg/kg	Control		bumetizole	
	0	250	1000	6
Number of females	6	6	6	
Volume (mL): Mean $\pm$ S.D.	12.4 $\pm$ 4.1	13.3 $\pm$ 3.1	10.0 $\pm$ 3.4	
Specific gravity: Mean $\pm$ S.D.	1.050 $\pm$ 0.013	1.046 $\pm$ 0.005	1.058 $\pm$ 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 bumetizole by oral administration

Group mg/kg	Control	bumetizole	
		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

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

Group mg/kg	Control		bumetizole			
	0	62.5	250	1000		
Number of males	6	6	6	6		
RBC	(10 <sup>4</sup> /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 <sup>4</sup> /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 <sup>2</sup> /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 bumetizole by oral administration

Group mg/kg	Control		bumetizole			
	0	62.5	250	1000		
Number of females	6	6	6	6		
RBC	(10 <sup>6</sup> /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 <sup>3</sup> /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 <sup>3</sup> /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 bumetizole by oral administration

Group mg/kg	Control		bumetizole			
	0	62.5	250	1000		
Number of males	6	6	6	6		
RBC (10 <sup>6</sup> /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 <sup>3</sup> /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 <sup>3</sup> /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 bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0		250	1000	
Number of females	6		6	6	
RBC ( $10^4/\mu\text{L}$ )	761 ± 19		743 ± 38	760 ± 25	
HGB (g/dL)	15.0 ± 0.5		14.6 ± 0.7	14.8 ± 0.5	
HCT (%)	43.3 ± 1.2		41.2 ± 1.9	42.7 ± 1.5	
MCV (fL)	56.9 ± 1.4		55.4 ± 1.4	56.3 ± 0.7	
MCH (pg)	19.7 ± 0.5		19.7 ± 0.7	19.5 ± 0.3	
MCHC (g/dL)	34.6 ± 0.4		35.5 ± 0.3 **	34.7 ± 0.3	
PLT ( $10^4/\mu\text{L}$ )	94.5 ± 19.0		94.8 ± 3.8	92.9 ± 9.7	
RET (%)	27 ± 6		27 ± 5	26 ± 4	
PT (sec.)	15.2 ± 1.1		15.1 ± 0.4	15.2 ± 0.3	
APTT (sec.)	17.9 ± 1.2		17.3 ± 1.2	17.0 ± 1.0	
Fbg (mg/dL)	159.3 ± 8.6		162.8 ± 5.7	163.9 ± 5.8	
WBC ( $10^2/\mu\text{L}$ )	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 bumetizole by oral administration

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

Each value shows mean ± S.D.

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

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

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

Each value shows mean ± S.D.

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

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of males	6	6	6	6	
AST (IU/L)	82.4 ± 12.3	78.2 ± 8.4	79.5 ± 4.1	83.5 ± 9.3	
ALT (IU/L)	32.2 ± 3.8	31.4 ± 3.9	32.4 ± 3.4	33.9 ± 4.8	
ALP (IU/L)	287.5 ± 41.7	275.2 ± 37.1	313.2 ± 36.2	311.2 ± 40.9	
γ-GTP (IU/L)	0.46 ± 0.18	0.33 ± 0.15	0.39 ± 0.08	0.37 ± 0.11	
TP (g/dL)	5.45 ± 0.19	5.45 ± 0.30	5.41 ± 0.26	5.34 ± 0.20	
Alb (g/dL)	2.72 ± 0.14	2.67 ± 0.13	2.71 ± 0.03	2.68 ± 0.17	
A/G	1.00 ± 0.08	0.96 ± 0.07	1.01 ± 0.11	1.01 ± 0.10	
T-Bil (mg/dL)	0.11 ± 0.01	0.11 ± 0.02	0.12 ± 0.01	0.11 ± 0.01	
UN (mg/dL)	18.7 ± 2.9	17.5 ± 1.4	19.0 ± 2.2	18.6 ± 2.0	
CRE (mg/dL)	0.31 ± 0.02	0.30 ± 0.02	0.32 ± 0.02	0.31 ± 0.03	
Glu (mg/dL)	124.4 ± 12.7	116.8 ± 7.9	119.9 ± 18.8	119.4 ± 14.3	
T-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 bumetizole by oral administration

Group mg/kg	Control		bumetizole	
	0	250	1000	
Number of females	6	6	6	
AST (IU/L)	71.2 ± 11.5	76.9 ± 13.4	75.5 ± 7.0	
ALT (IU/L)	26.8 ± 4.5	27.2 ± 10.4	27.8 ± 5.6	
ALP (IU/L)	147.9 ± 31.8	142.1 ± 24.4	122.4 ± 15.7	
γ-GTP (IU/L)	0.58 ± 0.31	0.58 ± 0.11	0.52 ± 0.18	
TP (g/dL)	6.37 ± 0.39	6.26 ± 0.49	6.25 ± 0.38	
Alb (g/dL)	3.58 ± 0.29	3.45 ± 0.36	3.56 ± 0.29	
A/G	1.29 ± 0.11	1.23 ± 0.11	1.33 ± 0.12	
T-Bil (mg/dL)	0.14 ± 0.02	0.13 ± 0.02	0.14 ± 0.02	
UN (mg/dL)	17.7 ± 2.8	20.1 ± 2.9	19.2 ± 4.3	
CRE (mg/dL)	0.39 ± 0.08	0.38 ± 0.02	0.39 ± 0.03	
Glu (mg/dL)	125.0 ± 14.0	123.9 ± 6.1	115.4 ± 8.1	
T-Chol (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 bumetizole by oral administration**

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

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

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

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

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

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

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

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

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

Each value shows mean ± S.D.

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

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

Each value shows mean ± S.D.

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

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

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

Each value shows mean ± S.D.

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

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

Each value shows mean ± S.D.

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

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

Group mg/kg	Control						bumetizole					
	0						1000					
	N <sup>a)</sup>	A <sup>b)</sup>	±	+	2+	3+	N <sup>a)</sup>	A <sup>b)</sup>	±	+	2+	3+
Findings												
Heart	[6] <sup>c)</sup>						[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 bumetizole by oral administration**

Group mg/kg	Control						bumetizole					
	0						1000					
	N <sup>a)</sup>	A <sup>b)</sup>	±	+	2+	3+	N <sup>a)</sup>	A <sup>b)</sup>	±	+	2+	3+
Findings												
Heart	[6] <sup>c)</sup>											
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 bumetizole by oral administration

Group	Control	bumetizole		
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 (%) <sup>a)</sup>	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 (%) <sup>b)</sup>	91.7	100.0	100.0	91.7

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

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

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

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

Each value shows mean ± S.D. per dam.

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

a): (Number of implantation scars/number of corpora lutea)×100.

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 bumetizole 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 Normal	11 11	11	11	11	11	11
bumetizole	62.5	Number of dams Normal	12 12	12	12	12	12	12
	250	Number of dams Normal	12 12	12	12	12	12	12
	1000	Number of dams Normal	11 11	11	11	11	11	11

Table 50 General signs of pups ( $F_1$ ) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole 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
bumetizole	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 ( $F_1$ ) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole		
	0	62.5	250	1000	
Number of dams	11	12	12	11	
Male weight					
Days of lactation					
0	6.9 ± 0.5	7.2 ± 0.7	7.0 ± 0.6	6.8 ± 0.4	
4	10.9 ± 0.8	11.2 ± 0.8	11.4 ± 1.4	10.8 ± 0.7	
Female weight					
Days of lactation					
0	6.4 ± 0.6	6.8 ± 0.6	6.6 ± 0.7	6.4 ± 0.7	
4	10.4 ± 0.8	10.6 ± 0.9	10.8 ± 1.5	10.3 ± 0.9	
Mean pups weight					
Days of lactation					
0	6.7 ± 0.5	7.0 ± 0.7	6.9 ± 0.6	6.6 ± 0.6	
4	10.6 ± 0.8	10.9 ± 0.9	11.1 ± 1.4	10.6 ± 0.7	
Litter weight					
Days of lactation					
0	90.5 ± 9.3	93.8 ± 16.4	91.3 ± 14.0	94.8 ± 10.9	
4	143.8 ± 15.1	142.0 ± 19.4	145.5 ± 20.6	149.6 ± 13.3	

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

**Table 52** Necropsy findings of dead pups ( $F_1$ ) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control		bumetizole	
	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 ( $F_1$ ) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

Group mg/kg	Control	bumetizole		
		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

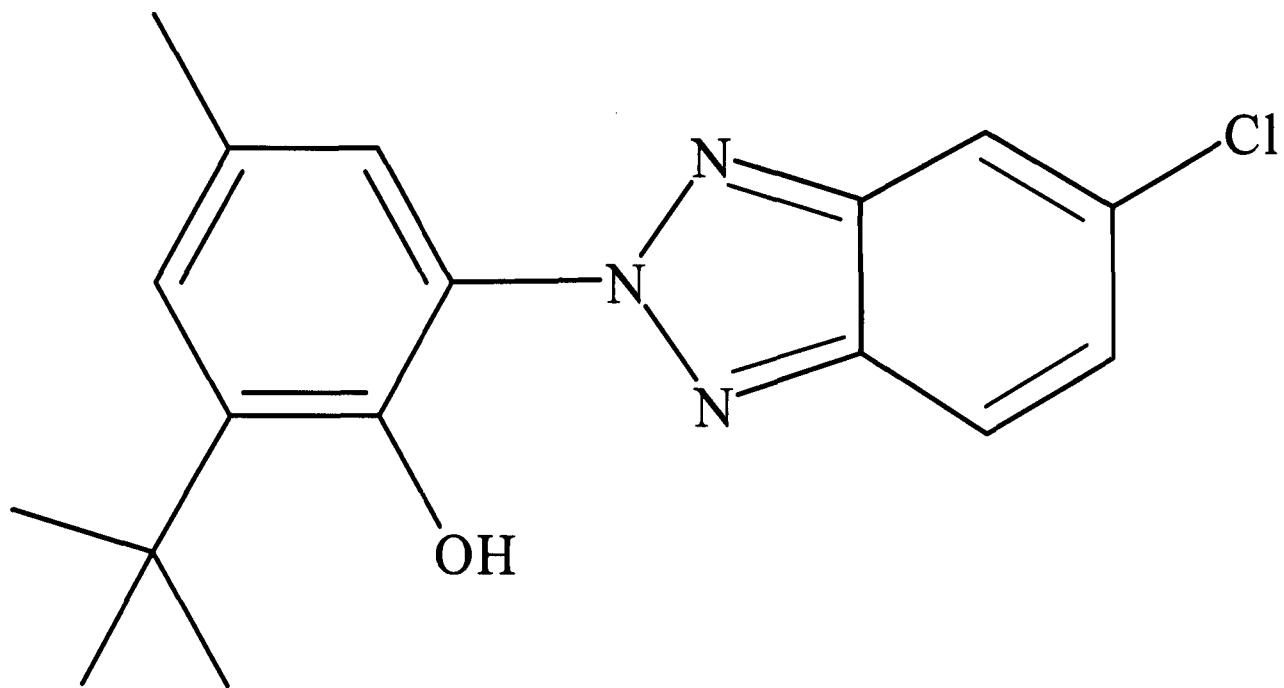


Fig. 1 Chemical structure of bumetizole

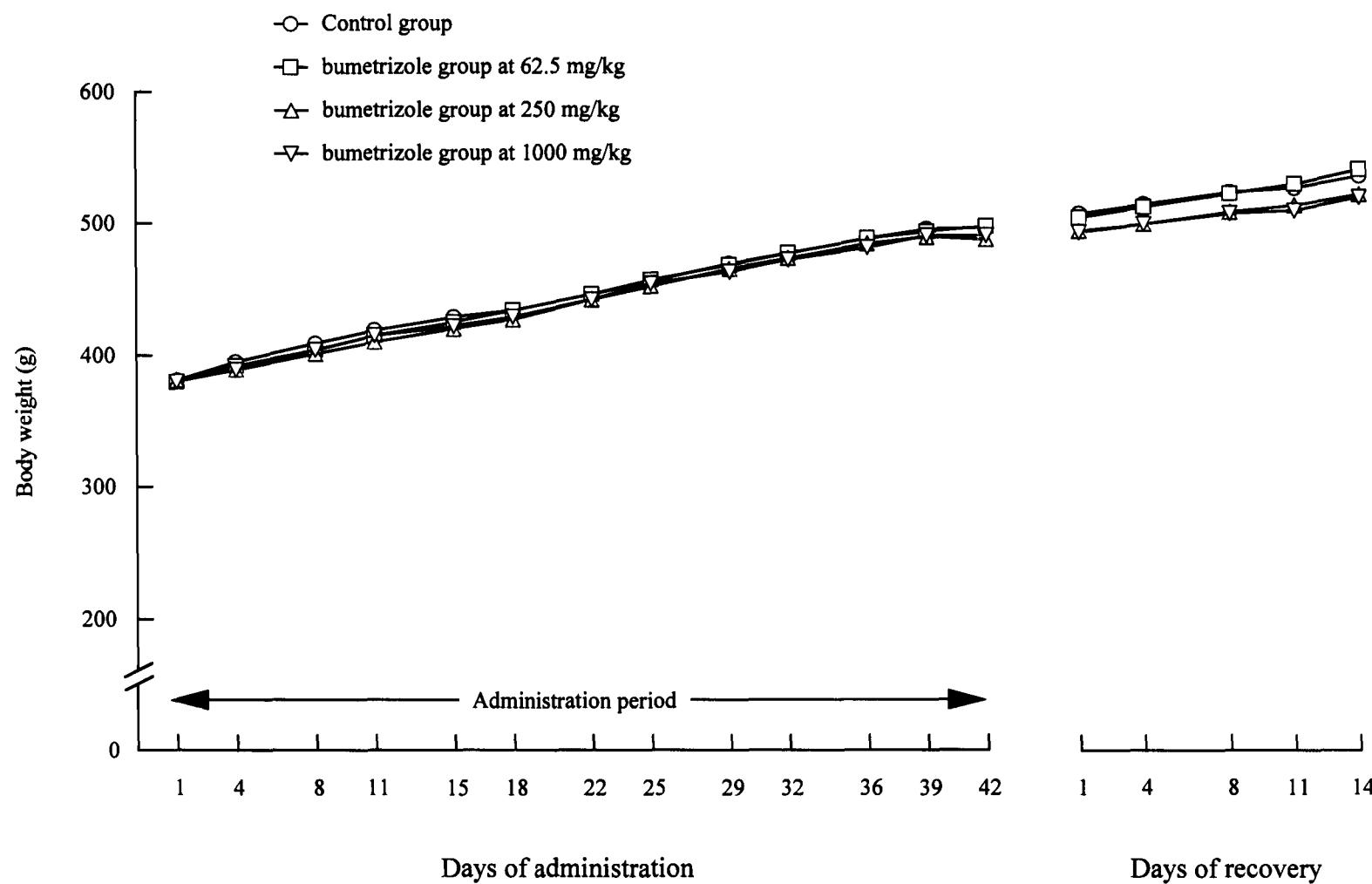


Fig. 2 Body weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

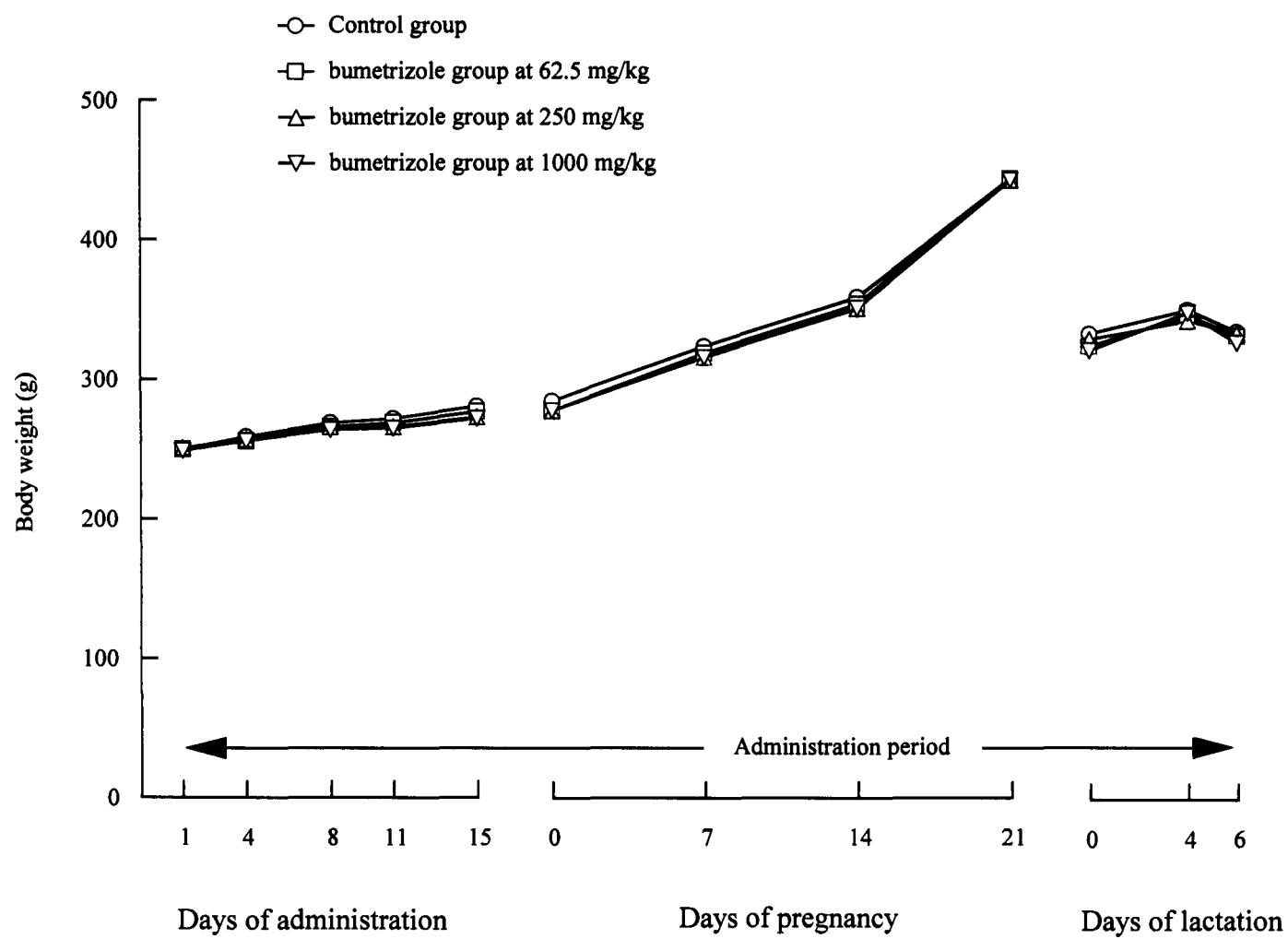


Fig. 3 Body weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

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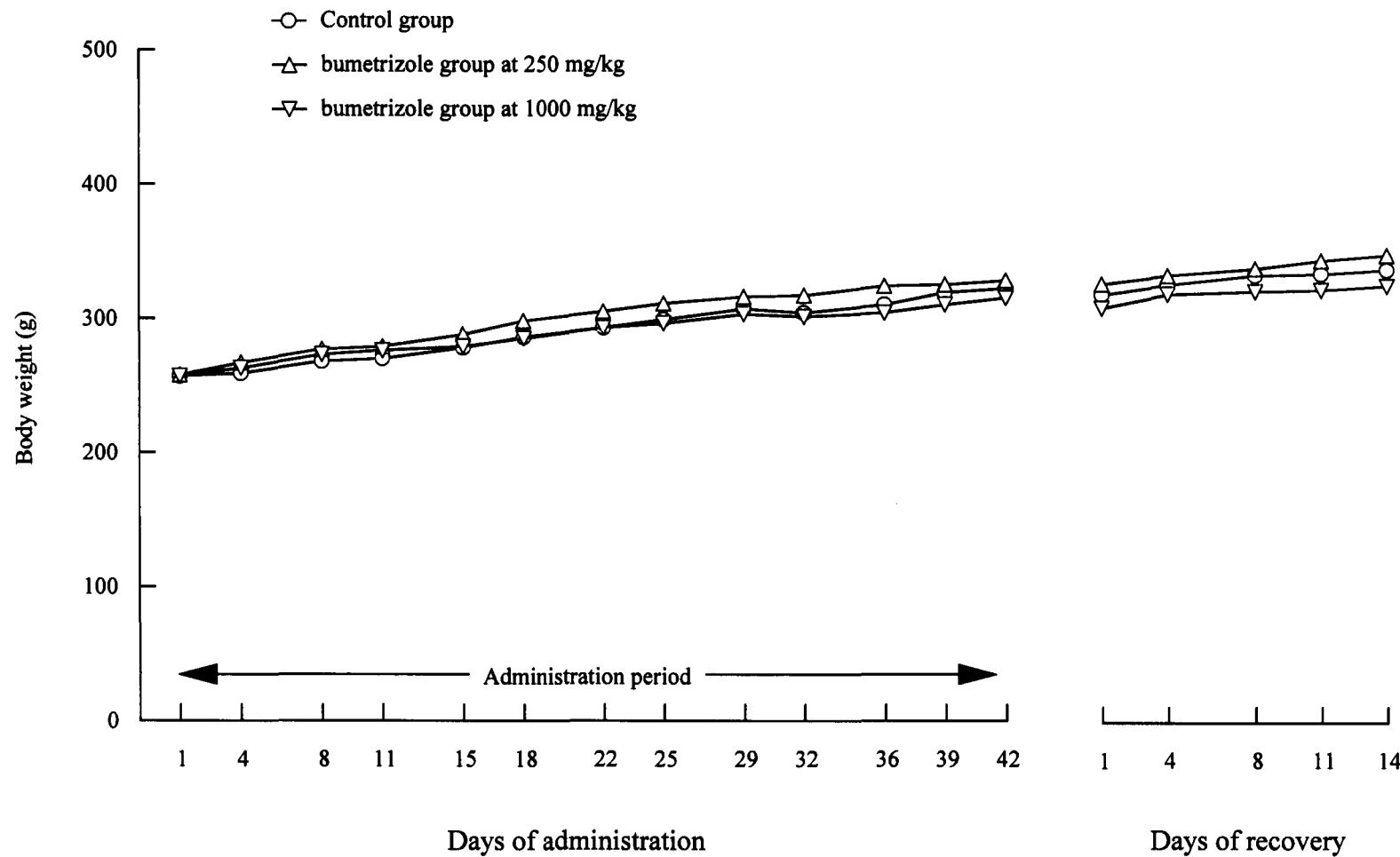


Fig. 4 Body weights of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

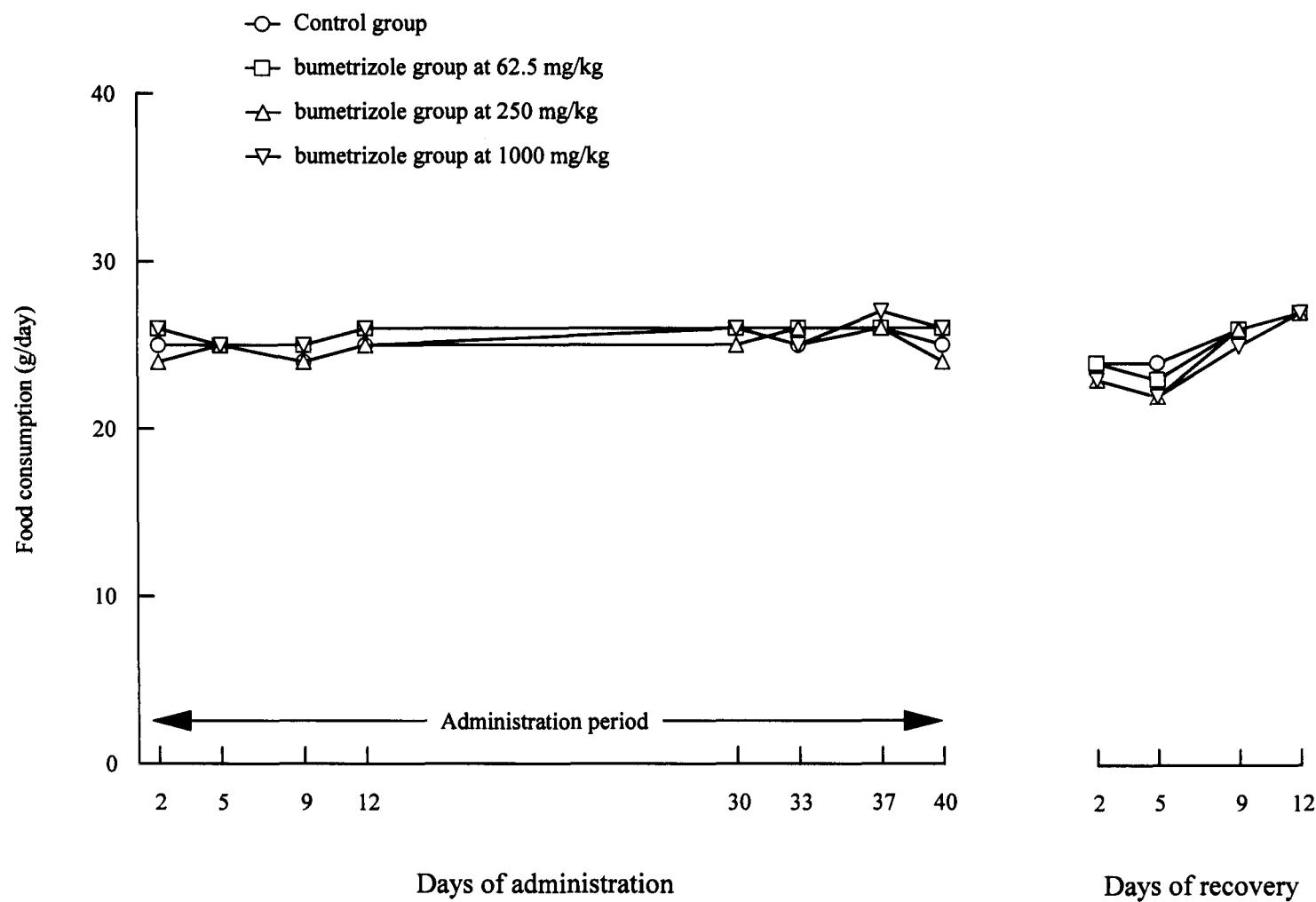


Fig. 5 Food consumption of male rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

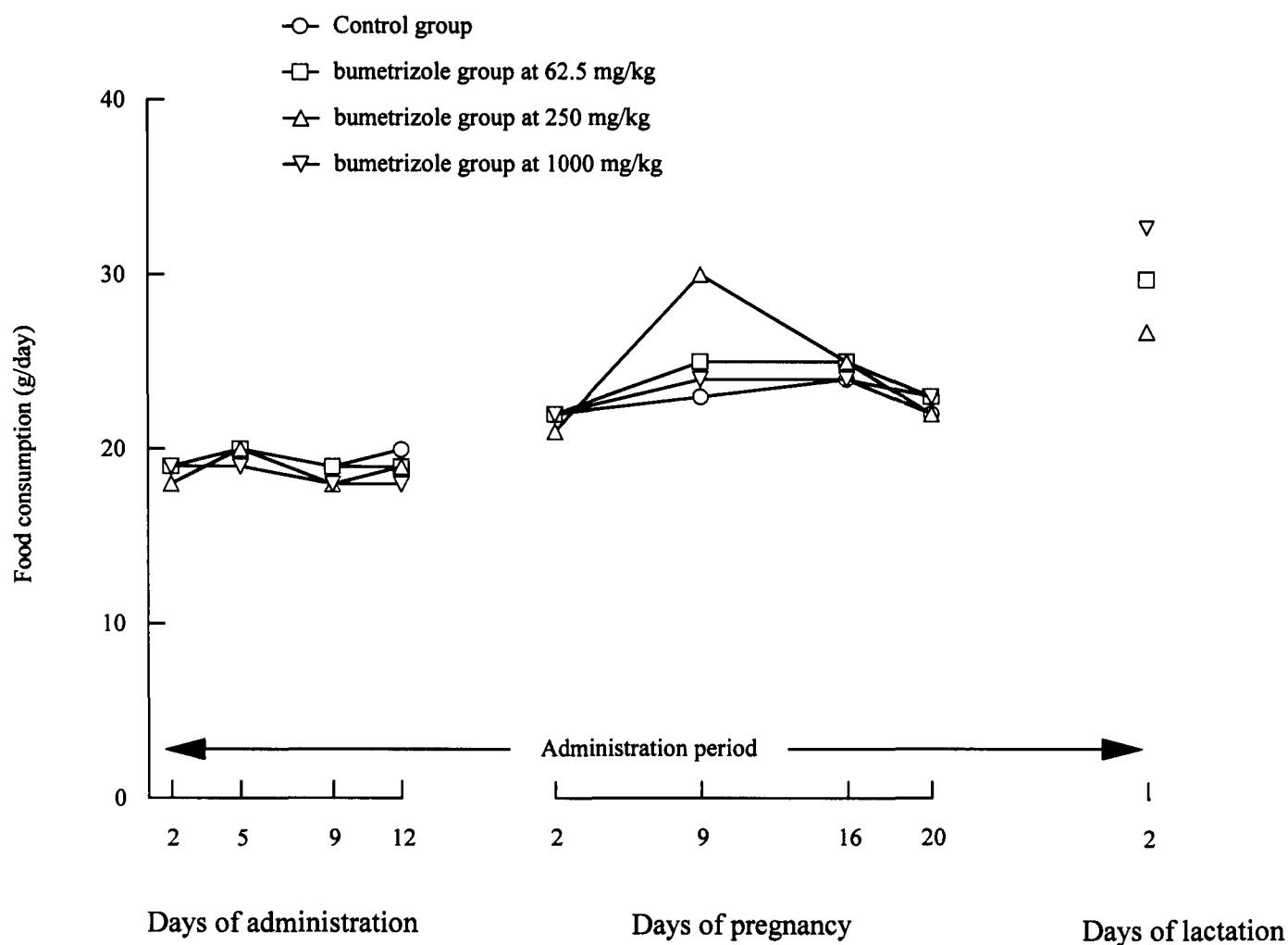


Fig. 6 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

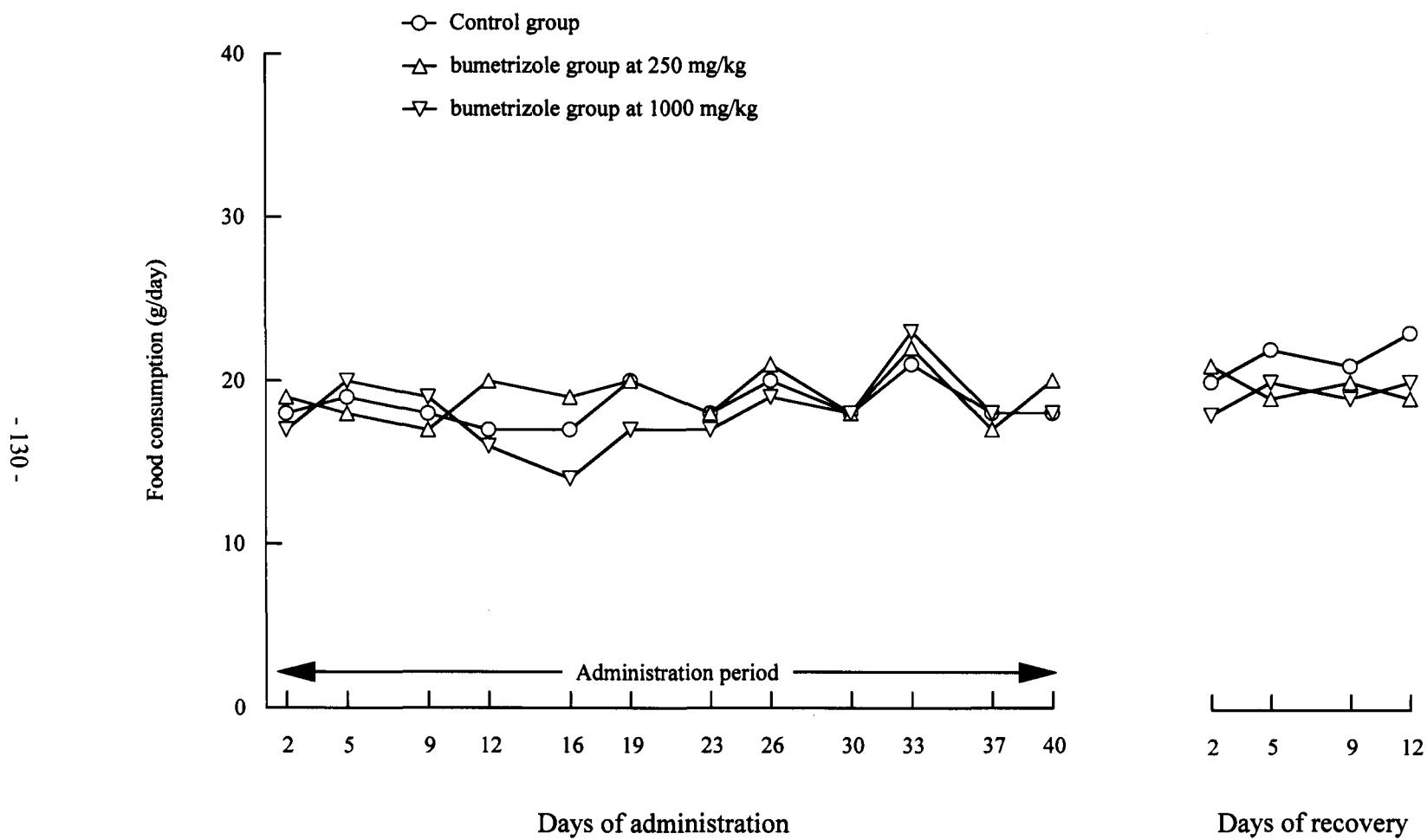


Fig. 7 Food consumption of female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of bumetizole by oral administration

## Appendix 1-1 Individual general signs of male rats

Male No.	Days of administration																								
	1		2		3		4		5		6		7		8		9		10		11		12		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
M01101	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01102	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01103	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01104	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01105	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01106	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01107	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01108	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01109	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01110	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01111	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01112	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
131	Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	N		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 1-1 (Continued) Individual general signs of male rats

Male No.	Days of administration																										
	14		15		16		17		18		19		20		21		22		23		24		25		26		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
M01101	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01102	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01103	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01104	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01105	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01106	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01107	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01108	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01109	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01110	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01111	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01112	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

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Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 1-1 (Continued) Individual general signs of male rats

(Control group)

Male No.	Days of administration																									
	27		28		29		30		31		32		33		34		35		36		37		38		39	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M01101	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01102	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01103	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01104	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01105	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01106	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01107	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01108	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01109	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01110	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01111	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M01112	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

(Continued)

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 1-1 (Continued) Individual general signs of male rats

Male No.	(Control group)						
	Days of administration						
	40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	
M01101	N	N	N	N	N	N	N
M01102	N	N	N	N	N	N	N
M01103	N	N	N	N	N	N	N
M01104	N	N	N	N	N	N	N
M01105	N	N	N	N	N	N	N
M01106	N	N	N	N	N	N	N
M01107	N	N	N	N	N	N	
M01108	N	N	N	N	N	N	
M01109	N	N	N	N	N	N	
M01110	N	N	N	N	N	N	
M01111	N	N	N	N	N	N	
M01112	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	6
N	12	12	12	12	12	12	6

- 134 - Pre: Before administration, Post: after administration.  
N: Normal.

(Continued)

## Appendix 1-1 (Continued) Individual general signs of male rats

(Control group)		Days of recovery														
Male No.		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M01107	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01108	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01109	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01110	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01111	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M01112	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

N: Normal.

## Appendix 1-2 Individual general signs of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Days of administration																									
	1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M02201	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02202	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02203	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02204	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02205	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02206	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02207	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02208	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02209	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02210	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02211	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M02212	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

(Continued)

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 1-2 (Continued) Individual general signs of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Days of administration																							
	14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M02201	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02202	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02203	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02204	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02205	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02206	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02207	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02208	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02209	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02210	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02211	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02212	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 1-2 (Continued) Individual general signs of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Days of administration																									
	27		28		29		30		31		32		33		34		35		36		37		38		39	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M02201	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02202	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02203	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02204	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02205	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02206	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02207	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02208	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02209	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02210	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02211	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02212	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 1-2 (Continued) Individual general signs of male rats

Male No.	Days of administration						
	40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	
M02201	N	N	N	N	N	N	N
M02202	N	N	N	N	N	N	N
M02203	N	N	N	N	N	N	N
M02204	N	N	N	N	N	N	N
M02205	N	N	N	N	N	N	N
M02206	N	N	N	N	N	N	N
M02207	N	N	N	N	N	N	
M02208	N	N	N	N	N	N	
M02209	N	N	N	N	N	N	
M02210	N	N	N	N	N	N	
M02211	N	N	N	N	N	N	
M02212	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	6
N	12	12	12	12	12	12	6

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 1-2 (Continued) Individual general signs of male rats

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M02207	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02208	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02209	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02210	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02211	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M02212	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

N: Normal.

## Appendix 1-3 Individual general signs of male rats

(bumetizole group at 250 mg/kg)

Male No.	Days of administration																									
	1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M03301	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03302	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03303	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03304	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03305	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03306	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03307	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03308	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03309	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03310	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03311	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03312	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 1-3 (Continued) Individual general signs of male rats

Male No.	Days of administration																							
	14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M03301	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03302	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03303	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03304	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03305	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03306	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03307	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03308	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03309	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03310	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03311	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03312	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 1-3 (Continued) Individual general signs of male rats

(bumetizole group at 250 mg/kg)

Male No.	Days of administration																									
	27		28		29		30		31		32		33		34		35		36		37		38		39	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M03301	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03302	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03303	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03304	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03305	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03306	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03307	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03308	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03309	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03310	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03311	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M03312	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 1-3 (Continued) Individual general signs of male rats

(bumetizole group at 250 mg/kg)

Male No.	Days of administration					
	40		41		42	
	Pre	Post	Pre	Post	Pre	Post
M03301	N	N	N	N	N	N
M03302	N	N	N	N	N	N
M03303	N	N	N	N	N	N
M03304	N	N	N	N	N	N
M03305	N	N	N	N	N	N
M03306	N	N	N	N	N	N
M03307	N	N	N	N	N	N
M03308	N	N	N	N	N	N
M03309	N	N	N	N	N	N
M03310	N	N	N	N	N	N
M03311	N	N	N	N	N	N
M03312	N	N	N	N	N	N
Number of males	12	12	12	12	12	6
N	12	12	12	12	12	6

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 1-3 (Continued) Individual general signs of male rats

(bumetizole group at 250 mg/kg)

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M03307	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03308	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03309	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03310	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03311	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M03312	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

N: Normal.

## Appendix 1-4 Individual general signs of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Days of administration																									
	1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M04401	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04402	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04403	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04404	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04405	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04406	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04407	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04408	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04409	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04410	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04411	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04412	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.  
N: Normal.

(Continued)

## Appendix 1-4 (Continued) Individual general signs of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Days of administration																							
	14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M04401	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04402	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04403	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04404	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04405	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04406	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04407	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04408	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04409	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04410	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04411	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04412	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 1-4 (Continued) Individual general signs of male rats

Male No.	Days of administration																									
	27		28		29		30		31		32		33		34		35		36		37		38		39	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M04401	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04402	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04403	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04404	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04405	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04406	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04407	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04408	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04409	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04410	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04411	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
M04412	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.  
N: Normal.

(Continued)

## Appendix 1-4 (Continued) Individual general signs of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Days of administration						
	40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	
M04401	N	N	N	N	N	N	N
M04402	N	N	N	N	N	N	N
M04403	N	N	N	N	N	N	N
M04404	N	N	N	N	N	N	N
M04405	N	N	N	N	N	N	N
M04406	N	N	N	N	N	N	N
M04407	N	N	N	N	N	N	
M04408	N	N	N	N	N	N	
M04409	N	N	N	N	N	N	
M04410	N	N	N	N	N	N	
M04411	N	N	N	N	N	N	
M04412	N	N	N	N	N	N	
Number of males	12	12	12	12	12	12	6
N	12	12	12	12	12	12	6

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 1-4 (Continued) Individual general signs of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M04407	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04408	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04409	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04410	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04411	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
M04412	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

N: Normal.

## Appendix 2-1 Individual general signs of female rats

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01151	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01152	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01153	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01154	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01155	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01156	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01157	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01158	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01159	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01160	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01161	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01162	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

151 Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 2-1 (Continued) Individual general signs of female rats

Female No.	Days of administration																											
	15*		16		17		18		19		20		21		22		23		24		25		26		27			
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F01151	N	N																										
F01152	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F01153	N	N	N	N																								
F01154	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F01155	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F01156	N	N	N	N																								
F01157	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F01158	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F01159	N	N	N	N																								
F01160	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F01161	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F01162	N	N																										
Number of females	12	12	10	10	7	7	6	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	N	12	12	10	10	7	7	6	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			

Pre: Before administration, Post: after administration.

\*: Start of pairing.

N: Normal.

## Appendix 2-2 Individual general signs of female rats

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F02251	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
F02252	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02253	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02254	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02255	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02256	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02257	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02258	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02259	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02260	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02261	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
F02262	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N			
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		

(Continued)

Pre: Before administration, Post: after administration.  
 N: Normal.

## Appendix 2-2 (Continued) Individual general signs of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Days of administration																								
	15*		16		17		18		19		20		21		22		23		24		25		26		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F02251	N	N	N	N																					
F02252	N	N	N	N	N	N																			
F02253	N	N	N	N																					
F02254	N	N	N	N	N	N																			
F02255	N	N																							
F02256	N	N																							
F02257	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02258	N	N																							
F02259	N	N	N	N																					
F02260	N	N	N	N																					
F02261	N	N																							
F02262	N	N																							
Number of females	12	12	7	7	3	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	12	12	7	7	3	3	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

Pre: Before administration, Post: after administration.

\*: Start of pairing.

N: Normal.

## Appendix 2-3 Individual general signs of female rats

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03351	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03352	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03353	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03354	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03355	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03356	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03357	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03358	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03359	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03360	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03361	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03362	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

(Continued)

Pre: Before administration, Post: after administration.  
N: Normal.

## Appendix 2-3 (Continued) Individual general signs of female rats

(bumetizole group at 250 mg/kg)

Female No.	Days of administration																									
	15*		16		17		18		19		20		21		22		23		24		25		26		27	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03351	N	N																								
F03352	N	N	N	N	N	N																				
F03353	N	N	N	N	N	N																				
F03354	N	N	N	N	N	N																				
F03355	N	N																								
F03356	N	N	N	N																						
F03357	N	N	N	N	N	N																				
F03358	N	N	N	N	N	N																				
F03359	N	N	N	N	N	N																				
F03360	N	N																								
F03361	N	N	N	N	N	N																				
F03362	N	N	N	N	N	N																				
Number of females	12	12	9	9	8	8	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	N	N	12	12	9	9	8	8	4	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

Pre: Before administration, Post: after administration.

\*: Start of pairing.

N: Normal.

## Appendix 2-4 Individual general signs of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04451	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04452	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04453	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04454	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04455	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04456	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04457	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04458	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04459	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04460	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04461	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04462	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 2-4 (Continued) Individual general signs of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Days of administration																													
	15*		16		17		18		19		20		21		22		23		24		25		26		27					
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F04451	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
F04452	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
F04453	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
F04454	N	N																												
F04455	N	N																												
F04456	N	N	N	N																										
F04457	N	N	N	N																										
F04458	N	N	N	N																										
F04459	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
F04460	N	N																												
F04461	N	N	N	N																										
F04462	N	N																												
Number of females	12	12	8	8	4	4	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
N	12	12	8	8	4	4	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	

Pre: Before administration, Post: after administration.

\*: Start of pairing.

N: Normal.

## Appendix 3-1 Individual general signs of dams during pregnancy

(Control group)

Dam No.

Dam No.	Days of pregnancy																													
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01151	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01152	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01153	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01154	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01155	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01156	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01157	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01158	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01159	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N
F01160	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01161	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01162	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
N	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	

Pre: Before administration, Post: after administration.

&gt;: Excluded from analysis of data because of non-pregnancy.

N: Normal.

(Continued)

## Appendix 3-1 (Continued) Individual general signs of dams during pregnancy

(Control group)

Dam No.	Days of pregnancy																				
	15		16		17		18		19		20		21		22		23		24		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F01151	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01152	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01153	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01154	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01155	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01156	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01157	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01158	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01159	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	>	N	
F01160	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01161	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01162	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	3	0	0	0	0
	N	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	3	-	-	-	-

Pre: Before administration, Post: after administration.

&gt;: Excluded from analysis of data because of non-pregnancy.

N: Normal.

## Appendix 3-2 Individual general signs of dams during pregnancy

(bumetizole group at 62.5 mg/kg)

Dam No.	Days of pregnancy																													
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02251	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02252	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02253	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02254	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02255	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02256	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02257	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02258	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02259	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02260	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02261	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02262	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 3-2 (Continued) Individual general signs of dams during pregnancy

(bumetizole group at 62.5 mg/kg)

Dam No.	Days of pregnancy																				
	15		16		17		18		19		20		21		22		23		24		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F02251	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02252	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02253	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02254	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02255	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02256	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02257	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02258	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02259	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02260	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02261	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F02262	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	0	0	0
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	-	-	-

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 3-3 Individual general signs of dams during pregnancy

(bumetizole group at 250 mg/kg)

Dam No.	Days of pregnancy																													
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03351	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03352	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03353	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03354	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03355	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03356	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03357	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03358	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03359	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03360	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03361	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03362	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

(Continued)

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 3-3 (Continued) Individual general signs of dams during pregnancy

(bumetizole group at 250 mg/kg)

Dam No.	Days of pregnancy																				
	15		16		17		18		19		20		21		22		23		24		25
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F03351	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03352	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03353	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03354	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03355	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03356	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03357	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03358	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03359	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03360	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03361	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03362	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4	0	0	0	0
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4	-	-	-	-

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 3-4 Individual general signs of dams during pregnancy

(bumetizole group at 1000 mg/kg)

Dam No.	Days of pregnancy																														
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F04451	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04452	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04453	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04454	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04455	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04456	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04457	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04458	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04459	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04460	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04461	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04462	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N		
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
N	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

(Continued)

Pre: Before administration, Post: after administration.

&gt;: Excluded from analysis of data because of non-pregnancy.

N: Normal.

## Appendix 3-4 (Continued) Individual general signs of dams during pregnancy

(bumetizole group at 1000 mg/kg)

Dam No.	Days of pregnancy																			
	15		16		17		18		19		20		21		22		23		24	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04451	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04452	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04453	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04454	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04455	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04456	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04457	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04458	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04459	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04460	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04461	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04462	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N	> N
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	3	0	0
N	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	3	-	-

Pre: Before administration, Post: after administration.

&gt;: Excluded from analysis of data because of non-pregnancy.

N: Normal.

## Appendix 4-1 Individual general signs of dams during lactation

Dam No.	Days of lactation														
	0		1		2		3		4		5		6		7
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F01151	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01152	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01153	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01154	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01155	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01156	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01157	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01158	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01159	Non-pregnancy														
F01160	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01161	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01162	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
N	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 4-2 Individual general signs of dams during lactation

Dam No.	Days of lactation													
	0		1		2		3		4		5		6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02251	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02252	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02253	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02254	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02255	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02256	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02257	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02258	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02259	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02260	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02261	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F02262	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 4-3 Individual general signs of dams during lactation

Dam No.	Days of lactation													
	0		1		2		3		4		5		6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03351	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03352	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03353	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03354	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03355	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03356	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03357	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03358	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03359	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03360	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03361	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03362	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 4-4 Individual general signs of dams during lactation

Dam No.	Days of lactation														
	0		1		2		3		4		5		6		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F04451	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04452	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04453	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04454	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04455	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04456	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04457	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04458	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04459	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04460	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04461	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04462	Non-pregnancy														
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
N	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

Pre: Before administration, Post: after administration.

N: Normal.

## Appendix 5-1 Individual general signs of female rats (recovery group)

Female No.	Days of administration																									
	1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01171	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01172	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01173	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01174	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01175	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01176	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-1 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of administration																							
	14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01171	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01172	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01173	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01174	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01175	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01176	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-1 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of administration																									
	27		28		29		30		31		32		33		34		35		36		37		38		39	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01171	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01172	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01173	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01174	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01175	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F01176	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-1 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of administration					
	40		41		42	
	Pre	Post	Pre	Post	Pre	Post
F01171	N	N	N	N	N	N
F01172	N	N	N	N	N	N
F01173	N	N	N	N	N	N
F01174	N	N	N	N	N	N
F01175	N	N	N	N	N	N
F01176	N	N	N	N	N	N
Number of females	6	6	6	6	6	6
N	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 5-1 (Continued) Individual general signs of female rats (recovery group)

(Control group)		Days of recovery														
Female No.		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F01171		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01172		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01173		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01174		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01175		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F01176		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

N: Normal.

## Appendix 5-2 Individual general signs of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Days of administration																									
	1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03371	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03372	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03373	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03374	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03375	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F03376	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-2 (Continued) Individual general signs of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Days of administration																							
	14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03371	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03372	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03373	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03374	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03375	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03376	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-2 (Continued) Individual general signs of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Days of administration																								
	27		28		29		30		31		32		33		34		35		36		37		38		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F03371	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03372	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03373	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03374	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03375	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03376	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-2 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of administration					
	40		41		42	
	Pre	Post	Pre	Post	Pre	Post
F03371	N	N	N	N	N	N
F03372	N	N	N	N	N	N
F03373	N	N	N	N	N	N
F03374	N	N	N	N	N	N
F03375	N	N	N	N	N	N
F03376	N	N	N	N	N	N
Number of females	6	6	6	6	6	6
N	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 5-2 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F03371	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03372	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03373	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03374	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03375	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F03376	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

N: Normal.

## Appendix 5-3 Individual general signs of female rats (recovery group)

Female No.	Days of administration																							
	1		2		3		4		5		6		7		8		9		10		11		12	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04471	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04472	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04473	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04474	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04475	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04476	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-3 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of administration																							
	14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04471	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04472	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04473	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04474	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04475	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04476	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-3 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of administration																									
	27		28		29		30		31		32		33		34		35		36		37		38		39	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04471	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04472	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04473	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04474	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04475	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
F04476	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

## Appendix 5-3 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of administration					
	40		41		42	
	Pre	Post	Pre	Post	Pre	Post
F04471	N	N	N	N	N	N
F04472	N	N	N	N	N	N
F04473	N	N	N	N	N	N
F04474	N	N	N	N	N	N
F04475	N	N	N	N	N	N
F04476	N	N	N	N	N	N
Number of females	6	6	6	6	6	6
N	6	6	6	6	6	6

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group)

Female No.	Blind No.	Observation of animals in cages														
		Biting behavior							Clonic convulsions							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F01171	F00087	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01172	F00096	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01173	F00074	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01174	F00092	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01175	F00083	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01176	F00090	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

Biting behavior      1: Not observed, 2: observed.

Clonic convulsions    1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 5-3 (Continued) Individual general signs of female rats (recovery group)

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F04471	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04472	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04473	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04474	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04475	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
F04476	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

N: Normal.

## Appendix 6-1 Individual body weights (g) of male rats

Male No.	Days of administration												Days of recovery					
	1	4	8	11	15	18	22	25	29	32	36	39	42	1	4	8	11	14
M01101	387	406	420	437	447	455	469	481	494	500	510	517	521					
M01102	367	377	384	392	397	397	407	419	421	426	438	437	438					
M01103	365	380	402	407	420	422	436	437	452	458	467	476	471					
M01104	385	399	416	424	429	425	444	449	464	473	476	487	481					
M01105	379	390	392	413	419	427	436	448	464	467	480	492	485					
M01106	405	417	441	443	458	457	477	486	503	515	521	524	527					
M01107	381	394	412	422	436	434	452	461	474	486	496	509	516	514	515	522	533	540
M01108	375	386	400	405	413	424	442	451	476	477	494	501	503	504	508	514	508	518
M01109	384	404	421	439	451	461	473	491	504	520	537	544	548	551	559	564	566	571
M01110	393	412	432	443	456	460	466	476	479	493	507	514	518	519	532	540	546	558
M01111	364	371	373	380	389	396	407	414	431	436	443	448	455	459	463	475	477	485
M01112	382	400	409	419	437	444	446	464	470	475	488	494	493	497	507	520	527	540
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	6	6	6
Mean	381	395	409	419	429	434	446	456	469	477	488	495	496	507	514	523	526	535
S.D.	12	14	20	20	22	23	23	25	26	28	30	31	32	30	32	30	31	31

## Appendix 6-2 Individual body weights (g) of male rats

Male No.	Days of administration												Days of recovery					
	1	4	8	11	15	18	22	25	29	32	36	39	42	1	4	8	11	14
M02201	367	374	386	397	412	418	431	438	455	467	474	474	477					
M02202	374	383	401	411	417	427	433	444	459	460	472	479	479					
M02203	394	402	423	431	443	464	476	489	496	497	505	508	497					
M02204	390	396	411	422	427	436	447	453	463	469	479	488	495					
M02205	387	411	429	445	455	466	477	494	509	516	528	531	540					
M02206	371	378	388	397	407	410	419	433	443	453	455	461	467					
M02207	366	376	394	399	410	399	416	426	441	451	467	462	470	473	475	489	495	503
M02208	373	392	393	389	401	415	429	439	439	448	459	469	472	480	485	493	501	512
M02209	377	385	391	410	417	432	448	455	464	478	491	497	504	495	507	524	527	535
M02210	375	394	405	416	427	427	443	457	470	483	502	501	503	507	515	525	535	547
M02211	384	402	419	436	451	463	475	487	501	506	520	529	530	534	545	549	561	568
M02212	399	405	412	426	429	448	458	473	480	501	506	518	531	534	547	551	557	573
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	6	6	6
Mean	380	392	404	415	425	434	446	457	468	477	488	493	497	504	512	522	529	540
S.D.	11	12	14	18	17	22	22	23	24	23	24	25	26	26	30	27	28	29
Significance																		
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 6-3 Individual body weights (g) of male rats

Male No.	Days of administration												Days of recovery					
	1	4	8	11	15	18	22	25	29	32	36	39	42	1	4	8	11	14
M03301	392	400	408	415	430	435	448	460	472	478	487	482	482					
M03302	377	379	397	406	418	421	442	452	465	468	490	494	493					
M03303	378	385	403	410	427	424	444	457	474	479	492	499	489					
M03304	382	392	401	413	419	427	444	449	461	467	480	489	489					
M03305	396	405	410	420	432	442	455	470	482	488	503	505	502					
M03306	358	367	377	390	396	402	410	417	436	442	452	456	454					
M03307	361	366	373	381	388	392	406	411	419	430	437	441	444	444	447	456	463	468
M03308	373	382	394	401	409	417	426	434	442	454	463	469	466	476	485	490	490	499
M03309	394	397	407	411	417	426	446	459	466	475	482	495	483	487	490	496	503	516
M03310	390	400	415	425	436	450	459	473	487	493	499	512	512	513	518	537	541	554
M03311	390	404	423	438	454	463	480	492	504	516	538	540	542	547	554	564	573	573
M03312	381	390	401	414	413	427	439	454	466	480	481	490	489	494	499	504	507	517
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	6	6	6
Mean	381	389	401	410	420	427	442	452	465	473	484	489	487	494	499	508	513	521
S.D.	12	13	14	15	18	19	20	23	23	23	26	26	26	35	36	38	39	38
Significance																		
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 6-4 Individual body weights (g) of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Days of administration												Days of recovery					
	1	4	8	11	15	18	22	25	29	32	36	39	42	1	4	8	11	14
M04401	378	381	397	410	408	420	434	445	449	462	471	483	484					
M04402	384	396	408	415	420	423	438	442	444	450	461	468	473					
M04403	393	402	419	427	439	452	463	481	497	501	510	521	516					
M04404	388	401	413	426	436	440	462	479	486	499	510	517	505					
M04405	374	384	399	408	417	425	434	447	450	453	462	469	473					
M04406	360	375	399	413	421	432	441	461	469	482	495	498	497					
M04407	403	411	433	452	456	470	478	492	513	521	524	530	532	539	537	546	551	559
M04408	372	384	398	405	416	417	435	441	453	466	473	483	493	496	499	506	518	525
M04409	361	371	384	394	400	404	411	419	430	440	448	453	456	459	468	476	473	478
M04410	374	380	391	401	402	416	423	434	449	450	458	467	462	459	465	469	468	482
M04411	390	398	405	417	421	422	441	451	458	470	478	493	496	501	512	523	523	535
M04412	381	390	401	416	424	430	441	454	463	472	483	492	492	502	511	523	523	537
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	6	6	6
Mean	380	389	404	415	422	429	442	454	463	472	481	490	490	493	499	507	509	519
S.D.	13	12	13	15	16	18	18	21	24	24	24	22	30	28	30	32	32	
Significance																		
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	

DU: Analysis by Dunnett's test.

## Appendix 7-1 Individual body weights (g) of female rats

(Control group) Female No.	Days of administration							
	1	4	8	11	15	18	22	25
F01151	240	243	248	263	274			
F01152	243	243	255	253	264	277		
F01153	259	278	303	317	335			
F01154	259	273	277	281	291			
F01155	243	248	256	254	257	268		
F01156	254	276	287	291	299			
F01157	257	267	271	267	276	295		
F01158	252	260	269	273	277	288		
F01159	255	262	271	280	287			
F01160	241	247	254	254	263	277		
F01161	245	254	262	257	269	277		
F01162	253	258	269	274	285			
Number of females	12	12	12	12	12	6		
Mean	250	259	269	272	281	280		
S.D.	7	13	15	19	21	10		

## Appendix 7-2 Individual body weights (g) of female rats

Female No.	Days of administration						
	1	4	8	11	15	18	22
F02251	240	255	260	261	274		
F02252	258	267	276	271	286		
F02253	255	272	286	286	295		
F02254	247	249	259	264	270		
F02255	252	256	260	268	271		
F02256	247	255	268	267	277		
F02257	259	264	277	280	286	307	
F02258	255	256	266	272	279		
F02259	236	248	256	259	265		
F02260	249	259	265	269	273		
F02261	244	245	251	261	265		
F02262	253	245	266	273	278		
Number of females	12	12	12	12	12	1	
Mean	250	256	266	269	277	307	
S.D.	7	9	10	8	9		
Significance							
Statistical method	DU	DU	DU	DT	DT	NA	NA

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

NA: Not analyzed.

## Appendix 7-3 Individual body weights (g) of female rats

Female No.	Days of administration							
	1	4	8	11	15	18	22	25
F03351	261	259	275	281	288			
F03352	253	265	276	275	288			
F03353	242	251	257	258	264			
F03354	249	254	257	252	260	269		
F03355	253	257	269	275	284			
F03356	247	250	262	265	271			
F03357	248	260	261	253	269	279		
F03358	254	260	268	267	277	295		
F03359	241	248	259	258	262			
F03360	246	248	261	264	266			
F03361	260	267	273	273	277	291		
F03362	252	261	270	268	274			
Number of females	12	12	12	12	12	4		
Mean	251	257	266	266	273	284		
S.D.	6	6	7	9	10	12		
Significance								
Statistical method	DU	DU	DU	DT	DT	DU	NA	NA

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

NA: Not analyzed.

## Appendix 7-4 Individual body weights (g) of female rats

Female No.	Days of administration							
	1	4	8	11	15	18	22	25
F04451	250	257	265	264	270	298	323	335
F04452	253	256	265	261	268	277		
F04453	247	248	259	252	258	269		
F04454	262	263	270	278	283			
F04455	236	235	244	251	260			
F04456	250	258	266	266	273			
F04457	255	271	277	278	286			
F04458	249	266	274	277	284			
F04459	246	245	258	255	258	270		
F04460	238	246	254	261	263			
F04461	246	257	264	267	274			
F04462	259	265	274	275	284			
Number of females	12	12	12	12	12	4	1	1
Mean	249	256	264	265	272	279	323	335
S.D.	8	10	9	10	11	13		
Significance								
Statistical method	DU	DU	DU	DT	DT	DU	NA	NA

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

NA: Not analyzed.

## Appendix 8-1 Individual body weights (g) of dams during pregnancy

Dam No.	Days of pregnancy			
	0	7	14	21
F01151	274	316	351	444
F01152	277	322	355	445
F01153	329	353	391	482
F01154	286	338	378	479
F01155	269	297	326	407
F01156	299	344	377	446
F01157	294	340	379	474
F01158	281	313	348	437
F01159	>	284	> 321	> 334
F01160	283	327	368	452
F01161	272	311	347	417
F01162	269	306	333	402
Number of dams	11	11	11	11
Mean	285	324	359	444
S.D.	18	18	21	27

>: Excluded from analysis of data because of non-pregnancy.

## Appendix 8-2 Individual body weights (g) of dams during pregnancy

Dam No.	Days of pregnancy			
	0	7	14	21
F02251	270	308	342	431
F02252	295	322	350	430
F02253	289	330	364	446
F02254	272	327	365	469
F02255	269	307	343	432
F02256	279	314	356	440
F02257	308	352	390	489
F02258	272	318	354	440
F02259	265	296	329	412
F02260	276	308	333	421
F02261	267	303	336	420
F02262	276	341	381	495
Number of dams	12	12	12	12
Mean	278	319	354	444
S.D.	13	16	19	27
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 8-3 Individual body weights (g) of dams during pregnancy

Dam No.	Days of pregnancy			
	0	7	14	21
F03351	287	345	387	493
F03352	289	329	364	462
F03353	268	305	329	414
F03354	277	313	340	418
F03355	277	311	343	430
F03356	269	300	335	432
F03357	280	307	342	420
F03358	300	350	402	508
F03359	263	290	321	408
F03360	264	304	332	426
F03361	299	342	397	496
F03362	264	296	325	408
Number of dams	12	12	12	12
Mean	278	316	351	443
S.D.	13	20	29	37
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 8-4 Individual body weights (g) of dams during pregnancy

Dam No.	Days of pregnancy			
	0	7	14	21
F04451	330	362	404	503
F04452	280	327	368	470
F04453	267	300	329	417
F04454	287	317	347	413
F04455	251	295	333	414
F04456	272	312	350	440
F04457	290	336	378	490
F04458	274	314	346	423
F04459	268	316	351	460
F04460	265	297	329	418
F04461	272	300	327	423
F04462	> 280	> 324	> 326	> 330
Number of dams	11	11	11	11
Mean	278	316	351	443
S.D.	20	20	24	33
Significance				
Statistical method	DU	DU	DU	DU

&gt;: Excluded from analysis of data because of non-pregnancy.

DU: Analysis by Dunnett's test.

## Appendix 9-1 Individual body weights (g) of dams during lactation

Dam No.	Days of lactation		
	0	4	6
F01151	322	312	322
F01152	345	353	336
F01153	381	397	373
F01154	357	377	345
F01155	299	323	311
F01156	345	359	346
F01157	350	371	344
F01158	326	346	329
F01159	Non-pregnancy		
F01160	341	364	346
F01161	309	349	330
F01162	303	315	306
Number of dams	11	11	11
Mean	334	351	335
S.D.	25	27	19

## Appendix 9-2 Individual body weights (g) of dams during lactation

Dam No.	Days of lactation		
	0	4	6
F02251	324	338	322
F02252	343	358	333
F02253	322	344	335
F02254	336	368	345
F02255	328	339	325
F02256	298	328	310
F02257	325	360	346
F02258	321	351	338
F02259	303	336	316
F02260	302	327	326
F02261	313	327	299
F02262	386	388	384
Number of dams	12	12	12
Mean	325	347	332
S.D.	24	19	22
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 9-3 Individual body weights (g) of dams during lactation

Dam No.	Days of lactation		
	0	4	6
F03351	352	384	350
F03352	371	340	365
F03353	280	316	322
F03354	349	335	329
F03355	307	322	312
F03356	281	319	283
F03357	306	327	319
F03358	387	393	386
F03359	313	332	313
F03360	330	325	320
F03361	365	374	384
F03362	321	343	329
Number of dams	12	12	12
Mean	330	343	334
S.D.	35	26	31
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 9-4 Individual body weights (g) of dams during lactation

Dam No.	Days of lactation		
	0	4	6
F04451	394	423	399
F04452	322	367	342
F04453	287	315	302
F04454	316	343	312
F04455	310	322	300
F04456	303	339	289
F04457	355	374	357
F04458	320	331	316
F04459	310	353	334
F04460	310	335	316
F04461	311	342	325
F04462	Non-pregnancy		
Number of dams	11	11	11
Mean	322	349	327
S.D.	29	30	31
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 10-1 Individual body weights (g) of female rats (recovery group)

Female No.	Days of administration												Days of recovery					
	1	4	8	11	15	18	22	25	29	32	36	39	42	1	4	8	11	14
F01171	247	242	259	260	262	268	270	280	286	291	299	301	299	298	300	303	311	316
F01172	267	281	289	287	294	299	305	319	335	328	336	341	340	346	352	360	358	371
F01173	261	259	267	269	281	292	304	305	315	312	323	338	343	343	354	362	359	363
F01174	261	261	265	267	272	286	293	302	309	303	305	310	317	307	317	321	333	331
F01175	256	262	268	276	289	298	304	306	310	310	319	328	335	323	335	340	339	342
F01176	252	248	258	260	268	275	280	279	284	281	279	296	300	295	300	310	305	300
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	257	259	268	270	278	286	293	299	307	304	310	319	322	319	326	333	334	337
S.D.	7	13	11	10	12	13	15	16	19	17	20	19	20	22	24	25	23	27

## Appendix 10-2 Individual body weights (g) of female rats (recovery group)

Female No.	Days of administration												Days of recovery					
	1	4	8	11	15	18	22	25	29	32	36	39	42	1	4	8	11	14
F03371	267	282	301	307	316	321	326	330	340	347	353	364	356	360	367	369	366	370
F03372	259	256	260	262	271	284	291	295	299	294	296	301	308	300	312	319	323	320
F03373	255	267	280	276	287	309	328	336	342	341	342	341	355	343	354	362	368	368
F03374	250	258	266	267	275	276	273	287	291	290	297	300	291	299	299	305	319	325
F03375	254	262	269	269	280	292	299	299	304	304	319	312	317	318	326	329	339	342
F03376	264	278	288	290	296	306	315	318	318	327	335	333	340	341	342	342	351	360
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	258	267	277	279	288	298	305	311	316	317	324	325	328	327	333	338	344	348
S.D.	6	11	15	17	17	17	22	20	22	25	24	25	27	25	26	25	21	22
Significance																		
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	

DU: Analysis by Dunnett's test.

## Appendix 10-3 Individual body weights (g) of female rats (recovery group)

Female No.	Days of administration												Days of recovery					
	1	4	8	11	15	18	22	25	29	32	36	39	42	1	4	8	11	14
F04471	257	256	268	273	278	281	294	291	304	300	305	317	325	313	325	324	323	326
F04472	249	249	257	264	272	277	290	285	293	293	298	303	309	310	313	318	315	318
F04473	251	258	265	265	261	287	294	300	304	300	306	307	319	306	320	321	327	323
F04474	260	278	301	294	285	289	293	299	302	298	299	301	311	301	314	318	321	323
F04475	259	259	262	263	270	269	276	287	291	295	297	296	291	294	300	305	311	320
F04476	267	275	284	294	307	307	313	315	326	318	321	335	336	332	339	342	337	340
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	257	263	273	276	279	285	293	296	303	301	304	310	315	309	319	321	322	325
S.D.	7	11	17	15	16	13	12	11	12	9	9	14	15	13	13	12	9	8
Significance																		
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	

DU: Analysis by Dunnett's test.

## Appendix 11-1 Individual food consumption (g/day) of male rats

(Control group)

Male No.	Days of administration								Days of recovery			
	2	5	9	12	30	33	37	40	2	5	9	12
M01101	26	25	27	26	25	27	30	29				
M01102	21	20	24	20	20	23	23	23				
M01103	26	26	23	25	26	26	28	25				
M01104	25	26	24	25	25	27	26	24				
M01105	26	24	26	26	25	24	24	25				
M01106	29	24	22	23	26	20	26	23				
M01107	25	28	26	27	27	29	27	26	24	26	23	26
M01108	25	23	22	21	25	26	29	25	26	21	21	26
M01109	25	30	25	27	30	26	28	29	24	26	27	30
M01110	23	25	26	28	26	25	25	24	23	23	27	30
M01111	21	21	21	25	25	24	22	25	21	24	25	22
M01112	33	27	25	24	27	28	25	23	25	25	30	27
Number of males	12	12	12	12	12	12	12	12	6	6	6	6
Mean	25	25	24	25	26	25	26	25	24	24	26	27
S.D.	3	3	2	2	2	2	2	2	2	2	3	3

## Appendix 11-2 Individual food consumption (g/day) of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Days of administration								Days of recovery			
	2	5	9	12	30	33	37	40	2	5	9	12
M02201	24	24	23	24	27	24	25	26				
M02202	23	22	27	24	25	25	29	26				
M02203	26	27	26	29	25	25	23	21				
M02204	32	30	25	25	26	27	27	30				
M02205	28	25	28	28	29	34	29	28				
M02206	24	22	22	24	24	24	25	24				
M02207	24	22	23	24	25	24	26	21	23	23	23	27
M02208	26	26	22	25	23	23	28	26	22	21	24	26
M02209	25	24	26	27	26	26	25	26	26	24	25	25
M02210	24	23	24	26	27	26	26	27	22	24	28	28
M02211	28	25	28	28	26	26	26	29	27	24	28	27
M02212	23	24	26	23	28	27	28	28	24	21	27	26
Number of males	12	12	12	12	12	12	12	12	6	6	6	6
Mean	26	25	25	26	26	26	26	26	24	23	26	27
S.D.	3	2	2	2	2	3	2	3	2	1	2	1
Significance												
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 11-3 Individual food consumption (g/day) of male rats

Male No.	Days of administration								Days of recovery			
	2	5	9	12	30	33	37	40	2	5	9	12
M03301	27	25	25	26	25	23	24	24				
M03302	26	24	24	23	26	28	28	24				
M03303	22	26	24	24	24	27	24	24				
M03304	27	24	25	23	24	28	27	27				
M03305	26	26	26	23	25	29	25	23				
M03306	20	22	22	21	20	25	22	24				
M03307	22	23	19	21	22	22	22	21	24	21	23	24
M03308	25	26	23	24	26	24	26	25	24	22	27	27
M03309	19	24	22	25	24	25	26	19	20	21	23	25
M03310	24	25	25	24	23	28	26	23	22	21	27	25
M03311	22	30	28	32	30	32	29	26	26	22	31	29
M03312	22	28	26	29	28	26	28	24	23	22	25	30
Number of males	12	12	12	12	12	12	12	12	6	6	6	6
Mean	24	25	24	25	25	26	26	24	23	22	26	27
S.D.	3	2	2	3	3	3	2	2	2	1	3	2
Significance									*			
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

Significantly different from control group (\*: P&lt;0.05).

DU: Analysis by Dunnett's test.

## Appendix 11-4 Individual food consumption (g/day) of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Days of administration								Days of recovery			
	2	5	9	12	30	33	37	40	2	5	9	12
M04401	25	20	22	21	29	25	28	26				
M04402	29	25	25	25	19	22	28	26				
M04403	27	23	27	31	23	28	27	23				
M04404	27	25	22	24	29	25	28	24				
M04405	27	29	26	24	26	23	27	26				
M04406	26	25	23	24	25	24	22	24				
M04407	29	30	31	34	30	27	28	29	25	23	23	28
M04408	27	24	25	24	27	24	28	26	22	20	27	26
M04409	20	25	24	23	23	21	24	26	23	23	24	24
M04410	21	24	26	26	24	26	26	23	20	23	23	22
M04411	28	24	24	23	26	26	26	26	26	21	25	30
M04412	26	26	28	27	28	26	30	27	24	23	29	30
Number of males	12	12	12	12	12	12	12	12	6	6	6	6
Mean	26	25	25	26	26	25	27	26	23	22	25	27
S.D.	3	3	3	4	3	2	2	2	1	2	2	3
Significance												
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 12-1 Individual food consumption (g/day) of female rats

(Control group)

Female No.	Days of administration			
	2	5	9	12
F01151	18	21	23	15
F01152	17	19	17	20
F01153	18	23	25	25
F01154	15	20	20	21
F01155	18	17	15	16
F01156	20	18	15	23
F01157	23	21	21	22
F01158	20	23	20	21
F01159	20	18	17	22
F01160	17	18	19	18
F01161	20	20	15	17
F01162	23	22	18	19
Number of females	12	12	12	12
Mean	19	20	19	20
S.D.	2	2	3	3

## Appendix 12-2 Individual food consumption (g/day) of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Days of administration			
	2	5	9	12
F02251	19	15	16	21
F02252	14	23	17	24
F02253	21	19	17	18
F02254	16	20	20	22
F02255	21	21	21	14
F02256	20	20	20	16
F02257	20	23	22	24
F02258	23	25	23	14
F02259	17	15	13	20
F02260	16	16	15	19
F02261	22	20	19	17
F02262	15	20	19	17
Number of females	12	12	12	12
Mean	19	20	19	19
S.D.	3	3	3	3
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 12-3 Individual food consumption (g/day) of female rats

(bumetizole group at 250 mg/kg)

Female No.	Days of administration			
	2	5	9	12
F03351	21	23	22	17
F03352	16	22	20	21
F03353	10	18	16	19
F03354	21	23	22	21
F03355	20	20	18	16
F03356	15	15	14	21
F03357	17	15	20	19
F03358	20	24	23	23
F03359	16	20	14	16
F03360	19	19	16	16
F03361	23	22	20	22
F03362	16	20	15	21
Number of females	12	12	12	12
Mean	18	20	18	19
S.D.	4	3	3	3
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 12-4 Individual food consumption (g/day) of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Days of administration			
	2	5	9	12
F04451	18	22	22	21
F04452	19	20	23	20
F04453	17	20	15	20
F04454	19	24	21	15
F04455	19	20	19	16
F04456	20	14	13	21
F04457	18	16	13	20
F04458	18	14	14	22
F04459	17	20	21	19
F04460	22	21	16	14
F04461	17	14	16	16
F04462	21	23	21	17
Number of females	12	12	12	12
Mean	19	19	18	18
S.D.	2	4	4	3
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 13-1 Individual food consumption (g/day) of dams during pregnancy

(Control group) Dam No.	Days of pregnancy			
	2	9	16	20
F01151	23	23	26	24
F01152	21	22	21	24
F01153	23	23	22	25
F01154	19	27	27	24
F01155	17	17	19	19
F01156	27	27	28	19
F01157	25	26	27	27
F01158	21	23	27	25
F01159	>	24	>	20
			>	14
F01160	25	24	26	25
F01161	21	20	22	18
F01162	19	19	20	17
Number of dams	11	11	11	11
Mean	22	23	24	22
S.D.	3	3	3	3

&gt;: Excluded from analysis of data because of non-pregnancy.

## Appendix 13-2 Individual food consumption (g/day) of dams during pregnancy

Dam No.	Days of pregnancy			
	2	9	16	20
F02251	20	23	24	24
F02252	26	25	27	20
F02253	23	24	25	24
F02254	25	28	28	24
F02255	22	22	24	23
F02256	21	21	21	23
F02257	23	29	29	23
F02258	23	29	23	22
F02259	21	21	23	22
F02260	18	27	21	23
F02261	20	20	24	18
F02262	25	30	33	31
Number of dams	12	12	12	12
Mean	22	25	25	23
S.D.	2	4	4	3
Significance				
Statistical method	DU	DT	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 13-3 Individual food consumption (g/day) of dams during pregnancy

Dam No.	Days of pregnancy			
	2	9	16	20
F03351	27	27	28	19
F03352	21	24	30	22
F03353	18	21	24	21
F03354	22	20	24	24
F03355	19	22	23	25
F03356	20	22	20	20
F03357	21	22	23	23
F03358	26	30	30	28
F03359	19	23	22	17
F03360	19	99	23	21
F03361	26	27	29	27
F03362	19	22	20	21
Number of dams	12	12	12	12
Mean	21	30	25	22
S.D.	3	22	4	3
Significance				
Statistical method	DU	DT	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 13-4 Individual food consumption (g/day) of dams during pregnancy

Dam No.	Days of pregnancy				
	2	9	16	20	
F04451	22	30	26	29	
F04452	24	22	28	22	
F04453	20	23	22	20	
F04454	20	23	24	20	
F04455	23	22	23	22	
F04456	22	19	22	21	
F04457	24	28	29	29	
F04458	22	23	22	21	
F04459	24	27	26	26	
F04460	19	19	18	18	
F04461	18	23	23	23	
F04462	>	21	> 26	> 17	> 16
Number of dams	11	11	11	11	
Mean	22	24	24	23	
S.D.	2	3	3	4	
Significance					
Statistical method	DU	DT	DU	DU	

&gt;: Excluded from analysis of data because of non-pregnancy.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 14-1 Individual food consumption (g/day) of dams during lactation

(Control group)	
Dam No.	Days of lactation
	2
F01151	30
F01152	30
F01153	27
F01154	33
F01155	24
F01156	21
F01157	32
F01158	30
F01159	Non-pregnancy
F01160	39
F01161	36
F01162	23
Number of dams	11
Mean	30
S.D.	6

## Appendix 14-2 Individual food consumption (g/day) of dams during lactation

(bumetizole group at 62.5 mg/kg)	
Dam No.	Days of lactation
	2
F02251	32
F02252	27
F02253	31
F02254	36
F02255	30
F02256	30
F02257	27
F02258	33
F02259	34
F02260	28
F02261	28
F02262	29
Number of dams	12
Mean	30
S.D.	3
Significance	
Statistical method	DU

DU: Analysis by Dunnett's test.

## Appendix 14-3 Individual food consumption (g/day) of dams during lactation

<u>(bumetizole group at 250 mg/kg)</u>	
Dam No.	Days of lactation
	2
F03351	29
F03352	19
F03353	29
F03354	16
F03355	25
F03356	34
F03357	24
F03358	29
F03359	25
F03360	31
F03361	27
F03362	34
Number of dams	12
Mean	27
S.D.	5
Significance	
Statistical method	DU

DU: Analysis by Dunnett's test.

## Appendix 14-4 Individual food consumption (g/day) of dams during lactation

(bumetizole group at 1000 mg/kg)	
Dam No.	Days of lactation
	2
F04451	28
F04452	33
F04453	24
F04454	43
F04455	34
F04456	31
F04457	34
F04458	31
F04459	33
F04460	31
F04461	38
F04462	Non-pregnancy
Number of dams	11
Mean	33
S.D.	5
Significance	
Statistical method	DU

DU: Analysis by Dunnett's test.

## Appendix 15-1 Individual food consumption (g/day) of female rats (recovery group)

(Control group)		Days of administration										Days of recovery					
Female No.		2	5	9	12	16	19	23	26	30	33	37	40	2	5	9	12
F01171		15	19	21	18	21	16	16	16	14	23	18	19	19	17	17	15
F01172		19	21	17	23	19	19	18	16	12	22	19	22	24	22	20	18
F01173		17	18	19	14	16	23	22	21	20	19	22	19	22	28	25	30
F01174		15	20	18	19	17	19	17	24	21	22	18	18	19	19	18	23
F01175		20	20	17	16	13	22	16	22	21	21	17	17	18	21	25	27
F01176		21	17	17	14	13	18	17	21	21	20	15	12	16	22	18	22
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		18	19	18	17	17	20	18	20	18	21	18	18	20	22	21	23
S.D.		3	1	2	3	3	3	2	3	4	1	2	3	3	4	4	6

## Appendix 15-2 Individual food consumption (g/day) of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Days of administration												Days of recovery			
	2	5	9	12	16	19	23	26	30	33	37	40	2	5	9	12
F03371	24	20	17	23	22	25	22	24	20	20	16	23	24	24	25	22
F03372	19	18	21	17	17	14	13	19	18	23	19	16	17	14	13	20
F03373	19	21	20	21	21	22	20	25	22	24	18	22	25	18	21	23
F03374	16	12	10	17	16	17	16	13	12	20	17	17	21	18	22	13
F03375	18	18	20	20	17	20	15	21	15	24	15	21	18	16	18	16
F03376	20	19	16	22	21	23	21	22	21	21	17	23	23	23	21	20
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	19	18	17	20	19	20	18	21	18	22	17	20	21	19	20	19
S.D.	3	3	4	3	3	4	4	4	4	2	1	3	3	4	4	4
Significance																
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 15-3 Individual food consumption (g/day) of female rats (recovery group)

(bumetizole group at 1000 mg/kg)

Female No.	Days of administration												Days of recovery			
	2	5	9	12	16	19	23	26	30	33	37	40	2	5	9	12
F04471	17	19	17	13	11	19	20	23	19	21	18	15	15	21	21	21
F04472	16	16	14	14	12	19	16	19	16	18	16	17	16	20	19	19
F04473	15	15	20	19	16	14	14	19	18	25	18	20	18	15	14	17
F04474	22	26	23	19	13	13	15	21	18	24	18	18	19	20	17	23
F04475	13	19	20	18	18	18	17	15	14	22	17	22	21	21	20	15
F04476	20	22	22	14	15	21	18	18	20	25	21	15	18	20	20	25
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	17	20	19	16	14	17	17	19	18	23	18	18	18	20	19	20
S.D.	3	4	3	3	3	3	2	3	2	3	2	3	2	2	3	4
Significance																
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 16-1 Individual FOB of male rats

(Control group)

Male No.	Blind No.	Observation of animals in cages													
		Posture						Palpebral closure							
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01102	M00055	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01103	M00037	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01104	M00070	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01105	M00010	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01106	M00039	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01107	M00062	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01108	M00026	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01109	M00040	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01110	M00009	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01111	M00013	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01112	M00033	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

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.

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)

Male No.	Blind No.	Observation of animals in cages													
		Biting behavior							Clonic convulsions						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01102	M00055	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01103	M00037	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01104	M00070	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01105	M00010	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01106	M00039	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01107	M00062	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01108	M00026	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01109	M00040	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01110	M00009	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01111	M00013	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01112	M00033	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

Biting behavior      1: Not observed, 2: observed.

Clonic convulsions      1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)		Observation of animals in cages						
Male No.	Blind No.	Tonic convulsions						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	1	1	1	1	1	1	1
M01102	M00055	1	1	1	1	1	1	1
M01103	M00037	1	1	1	1	1	1	1
M01104	M00070	1	1	1	1	1	1	1
M01105	M00010	1	1	1	1	1	1	1
M01106	M00039	1	1	1	1	1	1	1
M01107	M00062	1	1	1	1	1	1	1
M01108	M00026	1	1	1	1	1	1	1
M01109	M00040	1	1	1	1	1	1	1
M01110	M00009	1	1	1	1	1	1	1
M01111	M00013	1	1	1	1	1	1	1
M01112	M00033	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

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

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)

Male No.	Blind No.	Observation of animals on observer's palm													
		Ease of removal from cage							Ease of handling						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01102	M00055	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01103	M00037	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01104	M00070	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01105	M00010	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01106	M00039	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01107	M00062	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01108	M00026	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01109	M00040	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01110	M00009	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01111	M00013	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01112	M00033	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2

Findings were graded as follows

(Continued)

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.

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)

Male No.	Blind No.	Observation of animals on observer's palm													
		Muscle tone						Fur conditions							
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01102	M00055	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01103	M00037	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01104	M00070	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01105	M00010	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01106	M00039	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01107	M00062	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01108	M00026	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01109	M00040	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01110	M00009	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01111	M00013	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01112	M00033	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

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

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

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)

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Male No.	Blind No.	Observation of animals on observer's palm													
		Lacrimation							Salivation						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01102	M00055	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01103	M00037	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01104	M00070	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01105	M00010	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01106	M00039	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01107	M00062	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01108	M00026	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01109	M00040	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01110	M00009	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01111	M00013	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M01112	M00033	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

Lacrimation            1: None, 2: mild, 3: marked.  
 Salivation            1: None, 2: mild, 3: marked.

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)		Observation of animals on observer's palm						
Male No.	Blind No.	Respiration						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	1	1	1	1	1	1	1
M01102	M00055	1	1	1	1	1	1	1
M01103	M00037	1	1	1	1	1	1	1
M01104	M00070	1	1	1	1	1	1	1
M01105	M00010	1	1	1	1	1	1	1
M01106	M00039	1	1	1	1	1	1	1
M01107	M00062	1	1	1	1	1	1	1
M01108	M00026	1	1	1	1	1	1	1
M01109	M00040	1	1	1	1	1	1	1
M01110	M00009	1	1	1	1	1	1	1
M01111	M00013	1	1	1	1	1	1	1
M01112	M00033	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

Findings were graded as follows

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

(Continued)

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)		Open-field test													
Male No.	Blind No.	Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	9	3	2	0	2	2	3	0	0	0	0	0	0	0
M01102	M00055	4	7	2	2	9	2	11	0	0	0	0	0	0	0
M01103	M00037	8	2	0	0	1	0	4	0	0	0	0	0	0	0
M01104	M00070	4	6	0	2	4	1	1	0	0	0	0	0	0	0
M01105	M00010	6	0	0	0	5	4	4	0	0	0	0	0	0	0
M01106	M00039	10	2	1	5	4	6	3	0	0	0	0	0	0	0
M01107	M00062	6	0	0	0	1	0	2	0	0	0	0	0	0	0
M01108	M00026	6	1	3	3	0	2	0	0	0	0	0	0	0	0
M01109	M00040	12	7	2	2	0	2	3	0	0	0	0	0	0	0
M01110	M00009	18	8	7	4	8	9	10	0	0	0	0	0	0	0
M01111	M00013	6	0	1	1	2	2	6	0	0	1	0	0	0	0
M01112	M00033	16	3	6	8	3	11	14	0	0	0	0	0	0	0
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		8.8	3.3	2.0	2.3	3.3	3.4	5.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0
S.D.		4.5	3.0	2.3	2.5	2.9	3.5	4.3	0.0	0.0	0.3	0.0	0.0	0.0	0.0

(Continued)

## Appendix 16-1 (Continued) Individual FOB of male rats

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(Control group)		Male No.	Blind No.	Open-field test													
				Gait				Palpebral closure									
				Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01102	M00055	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01103	M00037	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01104	M00070	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01105	M00010	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01106	M00039	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01107	M00062	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01108	M00026	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01109	M00040	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01110	M00009	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01111	M00013	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M01112	M00033	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	

Findings were graded as follows

(Continued)

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.

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)

Male No.	Blind No.	Open-field test							Behavioral abnormalities						
		Consciousness							Behavioral abnormalities						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01102	M00055	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01103	M00037	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01104	M00070	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01105	M00010	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01106	M00039	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01107	M00062	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01108	M00026	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01109	M00040	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01110	M00009	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01111	M00013	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M01112	M00033	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

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.

## Appendix 16-1 (Continued) Individual FOB of male rats

(Control group)		Open-field test						
Male No.	Blind No.	Righting reflex						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M01101	M00059	1	1	1	1	1	1	1
M01102	M00055	1	1	1	1	1	1	1
M01103	M00037	1	1	1	1	1	1	1
M01104	M00070	1	1	1	1	1	1	1
M01105	M00010	1	1	1	1	1	1	1
M01106	M00039	1	1	1	1	1	1	1
M01107	M00062	1	1	1	1	1	1	1
M01108	M00026	1	1	1	1	1	1	1
M01109	M00040	1	1	1	1	1	1	1
M01110	M00009	1	1	1	1	1	1	1
M01111	M00013	1	1	1	1	1	1	1
M01112	M00033	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

Findings were graded as follows

Righting reflex

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

## Appendix 16-2 Individual FOB of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Blind No.	Observation of animals in cages													
		Posture							Palpebral closure						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02202	M00029	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02203	M00020	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02204	M00060	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02205	M00035	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02206	M00046	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02207	M00003	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02208	M00065	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02209	M00027	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02210	M00031	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02211	M00042	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02212	M00041	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-2 (Continued) Individual FOB of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Blind No.	Observation of animals in cages														
		Biting behavior							Clonic convulsions							
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02202	M00029	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02203	M00020	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02204	M00060	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02205	M00035	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02206	M00046	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02207	M00003	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02208	M00065	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02209	M00027	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02210	M00031	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02211	M00042	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02212	M00041	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 16-2 (Continued) Individual FOB of male rats

		Observation of animals in cages						
		Tonic convulsions						
Male No.	Blind No.	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	1	1	1	1	1	1	1
M02202	M00029	1	1	1	1	1	1	1
M02203	M00020	1	1	1	1	1	1	1
M02204	M00060	1	1	1	1	1	1	1
M02205	M00035	1	1	1	1	1	1	1
M02206	M00046	1	1	1	1	1	1	1
M02207	M00003	1	1	1	1	1	1	1
M02208	M00065	1	1	1	1	1	1	1
M02209	M00027	1	1	1	1	1	1	1
M02210	M00031	1	1	1	1	1	1	1
M02211	M00042	1	1	1	1	1	1	1
M02212	M00041	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

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

## Appendix 16-2 (Continued) Individual FOB of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm													
		Ease of removal from cage							Ease of handling						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02202	M00029	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02203	M00020	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02204	M00060	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02205	M00035	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02206	M00046	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02207	M00003	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02208	M00065	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02209	M00027	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02210	M00031	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02211	M00042	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02212	M00041	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-2 (Continued) Individual FOB of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm													
		Muscle tone							Fur conditions						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02202	M00029	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02203	M00020	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02204	M00060	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02205	M00035	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02206	M00046	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02207	M00003	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02208	M00065	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02209	M00027	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02210	M00031	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02211	M00042	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02212	M00041	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

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

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

## Appendix 16-2 (Continued) Individual FOB of male rats

(bumetizole group at 62.5 mg/kg)

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Male No.	Blind No.	Observation of animals on observer's palm														
		Lacrimation						Salivation								
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02202	M00029	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02203	M00020	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02204	M00060	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02205	M00035	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02206	M00046	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02207	M00003	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02208	M00065	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02209	M00027	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02210	M00031	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02211	M00042	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M02212	M00041	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

## Appendix 16-2 (Continued) Individual FOB of male rats

		(bumetizole group at 62.5 mg/kg)						
Male No.	Blind No.	Observation of animals on observer's palm						
		Respiration						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	1	1	1	1	1	1	1
M02202	M00029	1	1	1	1	1	1	1
M02203	M00020	1	1	1	1	1	1	1
M02204	M00060	1	1	1	1	1	1	1
M02205	M00035	1	1	1	1	1	1	1
M02206	M00046	1	1	1	1	1	1	1
M02207	M00003	1	1	1	1	1	1	1
M02208	M00065	1	1	1	1	1	1	1
M02209	M00027	1	1	1	1	1	1	1
M02210	M00031	1	1	1	1	1	1	1
M02211	M00042	1	1	1	1	1	1	1
M02212	M00041	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Respiration                    1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 16-2 (Continued) Individual FOB of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Blind No.	Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	7	1	2	1	2	5	1	0	0	0	0	0	0	0
M02202	M00029	8	1	7	2	17	11	4	0	0	0	0	0	0	0
M02203	M00020	5	1	2	3	6	2	4	0	0	0	0	0	0	0
M02204	M00060	3	1	0	1	0	1	0	0	0	0	0	0	0	0
M02205	M00035	3	3	2	3	6	1	1	0	0	0	0	0	0	0
M02206	M00046	12	7	11	7	4	4	4	0	0	0	0	0	0	0
M02207	M00003	15	3	4	4	0	0	0	0	0	0	0	0	0	0
M02208	M00065	7	4	1	2	3	4	4	0	0	0	0	0	0	0
M02209	M00027	3	0	1	7	0	3	13	0	0	0	0	0	0	0
M02210	M00031	5	0	5	0	2	1	0	0	0	0	0	0	0	0
M02211	M00042	12	0	0	0	0	1	0	0	0	0	0	0	0	0
M02212	M00041	4	0	0	0	0	0	1	0	0	0	0	0	0	0
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		7.0	1.8	2.9	2.5	3.3	2.8	2.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S.D.		4.0	2.1	3.3	2.5	4.9	3.1	3.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Significance															
Statistical method		DU	DU	DU	DU	DU	DU	DU	UA	UA	DU	UA	UA	UA	UA

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

## Appendix 16-2 (Continued) Individual FOB of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Blind No.	Open-field test													
		Gait							Palpebral closure						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02202	M00029	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02203	M00020	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02204	M00060	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02205	M00035	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02206	M00046	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02207	M00003	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02208	M00065	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02209	M00027	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02210	M00031	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02211	M00042	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M02212	M00041	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-2 (Continued) Individual FOB of male rats

(bumetizole group at 62.5 mg/kg)

Male No.	Blind No.	Open-field test													
		Consciousness							Behavioral abnormalities						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M02201	M00023	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02202	M00029	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02203	M00020	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02204	M00060	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02205	M00035	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02206	M00046	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02207	M00003	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02208	M00065	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02209	M00027	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02210	M00031	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02211	M00042	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M02212	M00041	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-2 (Continued) Individual FOB of male rats

		(bumetizole group at 62.5 mg/kg)					
Male No.	Blind No.	Open-field test					
		Righting reflex					
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35
M02201	M00023	1	1	1	1	1	1
M02202	M00029	1	1	1	1	1	1
M02203	M00020	1	1	1	1	1	1
M02204	M00060	1	1	1	1	1	1
M02205	M00035	1	1	1	1	1	1
M02206	M00046	1	1	1	1	1	1
M02207	M00003	1	1	1	1	1	1
M02208	M00065	1	1	1	1	1	1
M02209	M00027	1	1	1	1	1	1
M02210	M00031	1	1	1	1	1	1
M02211	M00042	1	1	1	1	1	1
M02212	M00041	1	1	1	1	1	1
Number of males		12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1
Significance							
Statistical method		UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Righting reflex

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

## Appendix 16-3 Individual FOB of male rats

(bumetizole group at 250 mg/kg)

Male No.	Blind No.	Observation of animals in cages													
		Posture							Palpebral closure						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03302	M00044	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03303	M00047	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03304	M00012	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03305	M00017	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03306	M00073	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03307	M00057	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03308	M00015	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03309	M00071	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03310	M00016	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03311	M00051	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03312	M00025	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

Male No.	Blind No.	Observation of animals in cages							Clonic convulsions						
		Biting behavior							Clonic convulsions						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03302	M00044	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03303	M00047	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03304	M00012	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03305	M00017	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03306	M00073	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03307	M00057	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03308	M00015	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03309	M00071	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03310	M00016	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03311	M00051	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03312	M00025	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

Male No.	Blind No.	Observation of animals in cages						
		Tonic convulsions						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	1	1	1	1	1	1	1
M03302	M00044	1	1	1	1	1	1	1
M03303	M00047	1	1	1	1	1	1	1
M03304	M00012	1	1	1	1	1	1	1
M03305	M00017	1	1	1	1	1	1	1
M03306	M00073	1	1	1	1	1	1	1
M03307	M00057	1	1	1	1	1	1	1
M03308	M00015	1	1	1	1	1	1	1
M03309	M00071	1	1	1	1	1	1	1
M03310	M00016	1	1	1	1	1	1	1
M03311	M00051	1	1	1	1	1	1	1
M03312	M00025	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

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

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm													
		Ease of removal from cage							Ease of handling						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03302	M00044	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03303	M00047	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03304	M00012	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03305	M00017	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03306	M00073	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03307	M00057	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03308	M00015	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03309	M00071	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03310	M00016	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03311	M00051	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03312	M00025	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Significance															
Statistical method	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

- 250 -

Male No.	Blind No.	Observation of animals on observer's palm														
		Muscle tone							Fur conditions							
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03302	M00044	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03303	M00047	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03304	M00012	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03305	M00017	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03306	M00073	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03307	M00057	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03308	M00015	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03309	M00071	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03310	M00016	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03311	M00051	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
M03312	M00025	2	2	2	2	2	2	2	1	1	1	1	1	1	1	
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1	
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

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

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

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm														
		Lacrimation						Salivation								
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03302	M00044	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03303	M00047	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03304	M00012	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03305	M00017	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03306	M00073	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03307	M00057	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03308	M00015	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03309	M00071	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03310	M00016	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03311	M00051	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
M03312	M00025	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA		

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm						
		Respiration						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	1	1	1	1	1	1	1
M03302	M00044	1	1	1	1	1	1	1
M03303	M00047	1	1	1	1	1	1	1
M03304	M00012	1	1	1	1	1	1	1
M03305	M00017	1	1	1	1	1	1	1
M03306	M00073	1	1	1	1	1	1	1
M03307	M00057	1	1	1	1	1	1	1
M03308	M00015	1	1	1	1	1	1	1
M03309	M00071	1	1	1	1	1	1	1
M03310	M00016	1	1	1	1	1	1	1
M03311	M00051	1	1	1	1	1	1	1
M03312	M00025	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

Male No.	Blind No.	Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	18	10	4	10	14	7	11	0	0	0	0	0	0	0
M03302	M00044	8	0	0	0	2	5	6	0	0	0	0	0	0	0
M03303	M00047	5	0	0	0	0	0	0	0	0	0	0	0	0	0
M03304	M00012	12	6	4	1	2	1	2	0	0	0	0	0	0	0
M03305	M00017	6	5	0	0	1	1	1	0	0	0	0	0	0	0
M03306	M00073	3	2	0	1	4	5	1	0	0	0	0	0	0	0
M03307	M00057	4	0	0	1	0	0	2	0	0	0	0	0	0	0
M03308	M00015	11	1	1	0	5	3	5	0	0	0	0	0	0	0
M03309	M00071	12	3	3	3	3	8	3	0	0	0	0	0	0	0
M03310	M00016	1	0	0	0	5	2	3	0	0	0	0	0	0	0
M03311	M00051	2	4	0	2	2	2	4	0	0	0	0	0	0	0
M03312	M00025	5	1	0	7	11	4	10	0	0	0	0	0	0	0
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		7.3	2.7	1.0	2.1	4.1	3.2	4.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S.D.		5.1	3.1	1.7	3.2	4.3	2.7	3.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Significance															
Statistical method		DU	DU	DU	DU	DU	DU	DU	UA	UA	DU	UA	UA	UA	UA

DU: Analysis by Dunnett's test.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

254

Male No.	Blind No.	Open-field test													
		Gait				Palpebral closure									
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03302	M00044	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03303	M00047	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03304	M00012	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03305	M00017	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03306	M00073	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03307	M00057	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03308	M00015	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03309	M00071	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03310	M00016	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03311	M00051	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M03312	M00025	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

255

Male No.	Blind No.	Open-field test							Behavioral abnormalities						
		Consciousness							Behavioral abnormalities						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03302	M00044	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03303	M00047	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03304	M00012	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03305	M00017	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03306	M00073	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03307	M00057	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03308	M00015	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03309	M00071	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03310	M00016	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03311	M00051	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M03312	M00025	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-3 (Continued) Individual FOB of male rats

(bumetizole group at 250 mg/kg)

Male No.	Blind No.	Open-field test						
		Righting reflex						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M03301	M00011	1	1	1	1	1	1	1
M03302	M00044	1	1	1	1	1	1	1
M03303	M00047	1	1	1	1	1	1	1
M03304	M00012	1	1	1	1	1	1	1
M03305	M00017	1	1	1	1	1	1	1
M03306	M00073	1	1	1	1	1	1	1
M03307	M00057	1	1	1	1	1	1	1
M03308	M00015	1	1	1	1	1	1	1
M03309	M00071	1	1	1	1	1	1	1
M03310	M00016	1	1	1	1	1	1	1
M03311	M00051	1	1	1	1	1	1	1
M03312	M00025	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Righting reflex

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

## Appendix 16-4 Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Observation of animals in cages													
		Posture							Palpebral closure						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04402	M00028	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04403	M00032	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04404	M00019	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04405	M00045	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04406	M00034	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04407	M00064	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04408	M00068	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04409	M00005	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04410	M00002	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04411	M00061	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04412	M00058	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-4 (Continued) Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Observation of animals in cages														
		Biting behavior							Clonic convulsions							
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04402	M00028	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04403	M00032	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04404	M00019	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04405	M00045	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04406	M00034	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04407	M00064	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04408	M00068	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04409	M00005	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04410	M00002	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04411	M00061	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04412	M00058	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 16-4 (Continued) Individual FOB of male rats

		(bumetizole group at 1000 mg/kg)						
Male No.	Blind No.	Observation of animals in cages						
		Tonic convulsions						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	1	1	1	1	1	1	1
M04402	M00028	1	1	1	1	1	1	1
M04403	M00032	1	1	1	1	1	1	1
M04404	M00019	1	1	1	1	1	1	1
M04405	M00045	1	1	1	1	1	1	1
M04406	M00034	1	1	1	1	1	1	1
M04407	M00064	1	1	1	1	1	1	1
M04408	M00068	1	1	1	1	1	1	1
M04409	M00005	1	1	1	1	1	1	1
M04410	M00002	1	1	1	1	1	1	1
M04411	M00061	1	1	1	1	1	1	1
M04412	M00058	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

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

## Appendix 16-4 (Continued) Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm													
		Ease of removal from cage							Ease of handling						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04402	M00028	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04403	M00032	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04404	M00019	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04405	M00045	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04406	M00034	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04407	M00064	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04408	M00068	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04409	M00005	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04410	M00002	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04411	M00061	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04412	M00058	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-4 (Continued) Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm													
		Muscle tone							Fur conditions						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04402	M00028	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04403	M00032	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04404	M00019	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04405	M00045	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04406	M00034	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04407	M00064	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04408	M00068	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04409	M00005	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04410	M00002	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04411	M00061	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04412	M00058	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

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

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

## Appendix 16-4 (Continued) Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm														
		Lacrimation							Salivation							
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04402	M00028	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04403	M00032	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04404	M00019	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04405	M00045	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04406	M00034	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04407	M00064	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04408	M00068	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04409	M00005	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04410	M00002	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04411	M00061	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04412	M00058	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Lacrimation	1: None, 2: mild, 3: marked.
Salivation	1: None, 2: mild, 3: marked.

## Appendix 16-4 (Continued) Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Observation of animals on observer's palm						
		Respiration						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	1	1	1	1	1	1	1
M04402	M00028	1	1	1	1	1	1	1
M04403	M00032	1	1	1	1	1	1	1
M04404	M00019	1	1	1	1	1	1	1
M04405	M00045	1	1	1	1	1	1	1
M04406	M00034	1	1	1	1	1	1	1
M04407	M00064	1	1	1	1	1	1	1
M04408	M00068	1	1	1	1	1	1	1
M04409	M00005	1	1	1	1	1	1	1
M04410	M00002	1	1	1	1	1	1	1
M04411	M00061	1	1	1	1	1	1	1
M04412	M00058	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 16-4 (Continued) Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	0	1	1	0	3	3	4	0	0	0	0	0	0	0
M04402	M00028	14	14	11	6	7	2	6	0	0	0	0	0	0	0
M04403	M00032	10	2	1	0	3	1	0	0	0	0	0	0	0	0
M04404	M00019	1	2	0	1	0	2	4	0	0	0	0	0	0	0
M04405	M00045	6	3	8	1	3	0	1	0	0	0	0	0	0	0
M04406	M00034	5	0	0	0	2	1	6	0	0	0	0	0	0	0
M04407	M00064	5	14	6	8	9	9	9	0	0	0	0	0	0	0
M04408	M00068	6	2	2	3	2	3	12	0	0	0	0	0	0	0
M04409	M00005	6	2	4	2	2	1	6	0	0	0	0	0	0	0
M04410	M00002	2	1	8	2	5	4	9	0	0	0	0	0	0	0
M04411	M00061	0	0	1	2	1	0	1	0	0	0	0	0	0	0
M04412	M00058	4	3	4	4	2	4	2	0	0	0	0	0	0	0
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		4.9	3.7	3.8	2.4	3.3	2.5	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S.D.		4.1	4.9	3.7	2.5	2.6	2.5	3.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Significance															
Statistical method		DU	DU	DU	DU	DU	DU	DU	UA	UA	DU	UA	UA	UA	UA

DU: Analysis by Dunnett's test.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 16-4 (Continued) Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Open-field test													
		Gait							Palpebral closure						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04402	M00028	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04403	M00032	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04404	M00019	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04405	M00045	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04406	M00034	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04407	M00064	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04408	M00068	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04409	M00005	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04410	M00002	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04411	M00061	1	1	1	1	1	1	1	1	1	1	1	1	1	1
M04412	M00058	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-4 (Continued) Individual FOB of male rats

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Open-field test							Behavioral abnormalities						
		Consciousness							Behavioral abnormalities						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04402	M00028	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04403	M00032	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04404	M00019	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04405	M00045	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04406	M00034	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04407	M00064	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04408	M00068	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04409	M00005	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04410	M00002	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04411	M00061	2	2	2	2	2	2	2	1	1	1	1	1	1	1
M04412	M00058	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 16-4 (Continued) Individual FOB of male rats

		(bumetizole group at 1000 mg/kg)						
Male No.	Blind No.	Open-field test						
		Righting reflex						
		Pre	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41
M04401	M00004	1	1	1	1	1	1	1
M04402	M00028	1	1	1	1	1	1	1
M04403	M00032	1	1	1	1	1	1	1
M04404	M00019	1	1	1	1	1	1	1
M04405	M00045	1	1	1	1	1	1	1
M04406	M00034	1	1	1	1	1	1	1
M04407	M00064	1	1	1	1	1	1	1
M04408	M00068	1	1	1	1	1	1	1
M04409	M00005	1	1	1	1	1	1	1
M04410	M00002	1	1	1	1	1	1	1
M04411	M00061	1	1	1	1	1	1	1
M04412	M00058	1	1	1	1	1	1	1
Number of males		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Righting reflex

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

## Appendix 17-1 Individual FOB of female rats

(Control group)		Observation of animals in cages													
Female No.	Blind No.	Posture							Palpebral closure						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01152	F00006	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01153	F00039	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01154	F00041	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01155	F00034	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01156	F00043	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01157	F00026	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01158	F00065	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01159	F00025	2	2	2	Non-pregnancy				1	1	1	Non-pregnancy			
F01160	F00033	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01161	F00024	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01162	F00044	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

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.

(Continued)

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)		Observation of animals in cages													
Female No.	Blind No.	Biting behavior							Clonic convulsions						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01152	F00006	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01153	F00039	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01154	F00041	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01155	F00034	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01156	F00043	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01157	F00026	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01158	F00065	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01159	F00025	1	1	1	Non-pregnancy			1	1	1	1	Non-pregnancy			
F01160	F00033	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01161	F00024	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01162	F00044	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

Findings were graded as follows

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

(Continued)

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)		Observation of animals in cages						
Female No.	Blind No.	Tonic convulsions						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	1	1	1	1	1	1	1
F01152	F00006	1	1	1	1	1	1	1
F01153	F00039	1	1	1	1	1	1	1
F01154	F00041	1	1	1	1	1	1	1
F01155	F00034	1	1	1	1	1	1	1
F01156	F00043	1	1	1	1	1	1	1
F01157	F00026	1	1	1	1	1	1	1
F01158	F00065	1	1	1	1	1	1	1
F01159	F00025	1	1	1	Non-pregnancy			
F01160	F00033	1	1	1	1	1	1	1
F01161	F00024	1	1	1	1	1	1	1
F01162	F00044	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

(Continued)

Findings were graded as follows

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

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)		Observation of animals on observer's palm													
Female No.	Blind No.	Ease of removal from cage							Ease of handling						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01152	F00006	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01153	F00039	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01154	F00041	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01155	F00034	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01156	F00043	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01157	F00026	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01158	F00065	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01159	F00025	2	2	2	Non-pregnancy			2	2	2	2	Non-pregnancy			
F01160	F00033	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01161	F00024	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01162	F00044	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2

P: Pregnancy, L: lactation.

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.

(Continued)

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)		Observation of animals on observer's palm													
Female No.	Blind No.	Muscle tone							Fur conditions						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01152	F00006	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01153	F00039	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01154	F00041	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01155	F00034	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01156	F00043	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01157	F00026	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01158	F00065	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01159	F00025	2	2	2	Non-pregnancy				1	1	1	Non-pregnancy			
F01160	F00033	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01161	F00024	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01162	F00044	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	11	12	12	12	12	11	11	11
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

Findings were graded as follows

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

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

(Continued)

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)

Female No.	Blind No.	Observation of animals on observer's palm											
		Lacrimation					Salivation						
Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	1	1	1	1	1	1	1	1	1	1	1	1
F01152	F00006	1	1	1	1	1	1	1	1	1	1	1	1
F01153	F00039	1	1	1	1	1	1	1	1	1	1	1	1
F01154	F00041	1	1	1	1	1	1	1	1	1	1	1	1
F01155	F00034	1	1	1	1	1	1	1	1	1	1	1	1
F01156	F00043	1	1	1	1	1	1	1	1	1	1	1	1
F01157	F00026	1	1	1	1	1	1	1	1	1	1	1	1
F01158	F00065	1	1	1	1	1	1	1	1	1	1	1	1
F01159	F00025	1	1	1	Non-pregnancy			1	1	1	Non-pregnancy		
F01160	F00033	1	1	1	1	1	1	1	1	1	1	1	1
F01161	F00024	1	1	1	1	1	1	1	1	1	1	1	1
F01162	F00044	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	12	12	12	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

(Continued)

Findings were graded as follows

Lacrimation      1: None, 2: mild, 3: marked.  
 Salivation      1: None, 2: mild, 3: marked.

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)		Observation of animals on observer's palm						
Female No.	Blind No.	Respiration						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	1	1	1	1	1	1	1
F01152	F00006	1	1	1	1	1	1	1
F01153	F00039	1	1	1	1	1	1	1
F01154	F00041	1	1	1	1	1	1	1
F01155	F00034	1	1	1	1	1	1	1
F01156	F00043	1	1	1	1	1	1	1
F01157	F00026	1	1	1	1	1	1	1
F01158	F00065	1	1	1	1	1	1	1
F01159	F00025	1	1	1	Non-pregnancy			
F01160	F00033	1	1	1	1	1	1	1
F01161	F00024	1	1	1	1	1	1	1
F01162	F00044	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

Findings were graded as follows

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

(Continued)

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)

Female No.	Blind No.	Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	14	13	10	5	8	2	4	0	0	0	0	0	0	1
F01152	F00006	10	11	17	10	12	18	10	0	0	0	0	0	0	0
F01153	F00039	4	11	5	4	9	10	7	0	0	0	0	0	0	1
F01154	F00041	16	3	8	2	10	1	5	0	0	0	0	0	0	0
F01155	F00034	9	2	0	3	8	4	9	0	0	0	0	0	0	3
F01156	F00043	17	8	3	2	1	1	2	0	0	0	0	0	0	0
F01157	F00026	9	7	10	2	2	5	7	0	0	0	0	0	0	0
F01158	F00065	2	6	1	4	11	8	16	0	0	0	0	0	0	0
F01159	F00025	10	11	6	Non-pregnancy			0	0	0	0	Non-pregnancy			
F01160	F00033	3	10	3	3	8	6	4	0	0	0	0	0	0	0
F01161	F00024	8	6	2	6	16	14	1	0	0	0	0	0	0	0
F01162	F00044	9	2	3	0	1	0	0	0	0	0	0	0	0	0
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		9.3	7.5	5.7	3.7	7.8	6.3	5.9	0.0	0.0	0.0	0.0	0.0	0.0	0.5
S.D.		4.8	3.8	4.9	2.6	4.8	5.8	4.6	0.0	0.0	0.0	0.0	0.0	0.0	0.9

P: Pregnancy, L: lactation.

(Continued)

## Appendix 17-1 (Continued) Individual FOB of female rats

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(Control group)		Female No.	Blind No.	Open-field test											
				Gait						Palpebral closure					
Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		
F01151	F00052	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01152	F00006	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01153	F00039	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01154	F00041	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01155	F00034	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01156	F00043	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01157	F00026	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01158	F00065	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01159	F00025	1	1	1	Non-pregnancy			1	1	1	Non-pregnancy				
F01160	F00033	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01161	F00024	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01162	F00044	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

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.

(Continued)

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)

Female No.	Blind No.	Open-field test							Behavioral abnormalities						
		Consciousness													
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01152	F00006	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01153	F00039	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01154	F00041	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01155	F00034	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01156	F00043	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01157	F00026	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01158	F00065	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01159	F00025	2	2	2	Non-pregnancy				1	1	1	Non-pregnancy			
F01160	F00033	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01161	F00024	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F01162	F00044	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

(Continued)

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.

## Appendix 17-1 (Continued) Individual FOB of female rats

(Control group)		Open-field test						
		Righting reflex						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F01151	F00052	1	1	1	1	1	1	1
F01152	F00006	1	1	1	1	1	1	1
F01153	F00039	1	1	1	1	1	1	1
F01154	F00041	1	1	1	1	1	1	1
F01155	F00034	1	1	1	1	1	1	1
F01156	F00043	1	1	1	1	1	1	1
F01157	F00026	1	1	1	1	1	1	1
F01158	F00065	1	1	1	1	1	1	1
F01159	F00025	1	1	1	Non-pregnancy			
F01160	F00033	1	1	1	1	1	1	1
F01161	F00024	1	1	1	1	1	1	1
F01162	F00044	1	1	1	1	1	1	1
Number of females		12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

P: Pregnancy, L: lactation.

Findings were graded as follows

Righting reflex

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

## Appendix 17-2 Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Observation of animals in cages													
		Posture							Palpebral closure						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02252	F00067	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02253	F00059	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02254	F00047	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02255	F00020	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02256	F00061	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02257	F00005	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02258	F00048	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02259	F00071	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02260	F00019	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02261	F00050	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02262	F00015	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-2 (Continued) Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Observation of animals in cages													
		Biting behavior							Clonic convulsions						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02252	F00067	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02253	F00059	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02254	F00047	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02255	F00020	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02256	F00061	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02257	F00005	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02258	F00048	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02259	F00071	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02260	F00019	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02261	F00050	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02262	F00015	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Biting behavior      1: Not observed, 2: observed.

Clonic convulsions    1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 17-2 (Continued) Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Observation of animals in cages						
		Tonic convulsions						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	1	1	1	1	1	1	1
F02252	F00067	1	1	1	1	1	1	1
F02253	F00059	1	1	1	1	1	1	1
F02254	F00047	1	1	1	1	1	1	1
F02255	F00020	1	1	1	1	1	1	1
F02256	F00061	1	1	1	1	1	1	1
F02257	F00005	1	1	1	1	1	1	1
F02258	F00048	1	1	1	1	1	1	1
F02259	F00071	1	1	1	1	1	1	1
F02260	F00019	1	1	1	1	1	1	1
F02261	F00050	1	1	1	1	1	1	1
F02262	F00015	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

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

## Appendix 17-2 (Continued) Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm													
		Ease of removal from cage							Ease of handling						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02252	F00067	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02253	F00059	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02254	F00047	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02255	F00020	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02256	F00061	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02257	F00005	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02258	F00048	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02259	F00071	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02260	F00019	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02261	F00050	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02262	F00015	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-2 (Continued) Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm													
		Muscle tone							Fur conditions						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02252	F00067	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02253	F00059	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02254	F00047	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02255	F00020	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02256	F00061	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02257	F00005	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02258	F00048	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02259	F00071	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02260	F00019	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02261	F00050	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02262	F00015	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

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

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

## Appendix 17-2 (Continued) Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm														
		Lacrimation							Salivation							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02252	F00067	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02253	F00059	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02254	F00047	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02255	F00020	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02256	F00061	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02257	F00005	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02258	F00048	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02259	F00071	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02260	F00019	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02261	F00050	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F02262	F00015	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

## Appendix 17-2 (Continued) Individual FOB of female rats

		(bumetizole group at 62.5 mg/kg)						
Female No.	Blind No.	Observation of animals on observer's palm						
		Respiration						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	1	1	1	1	1	1	1
F02252	F00067	1	1	1	1	1	1	1
F02253	F00059	1	1	1	1	1	1	1
F02254	F00047	1	1	1	1	1	1	1
F02255	F00020	1	1	1	1	1	1	1
F02256	F00061	1	1	1	1	1	1	1
F02257	F00005	1	1	1	1	1	1	1
F02258	F00048	1	1	1	1	1	1	1
F02259	F00071	1	1	1	1	1	1	1
F02260	F00019	1	1	1	1	1	1	1
F02261	F00050	1	1	1	1	1	1	1
F02262	F00015	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 17-2 (Continued) Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	6	4	4	5	8	5	5	0	0	0	0	0	0	0
F02252	F00067	7	6	7	4	5	4	6	0	0	0	0	0	0	0
F02253	F00059	11	13	11	11	2	15	4	0	0	0	0	0	0	1
F02254	F00047	14	11	13	8	14	7	6	0	0	0	0	0	0	0
F02255	F00020	15	11	13	15	4	10	7	0	0	0	0	0	0	0
F02256	F00061	7	5	10	8	3	8	3	0	0	0	0	0	0	0
F02257	F00005	11	9	14	4	10	8	13	0	0	0	0	0	0	0
F02258	F00048	15	9	3	4	9	4	7	0	0	0	0	0	0	1
F02259	F00071	6	8	4	7	5	5	6	0	0	0	0	0	0	0
F02260	F00019	6	10	0	1	3	3	4	0	0	0	0	0	0	2
F02261	F00050	7	11	4	4	7	8	3	0	0	0	0	0	0	0
F02262	F00015	1	5	6	4	3	0	4	0	0	0	0	0	0	0
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		8.8	8.5	7.4	6.3	6.1	6.4	5.7	0.0	0.0	0.0	0.0	0.0	0.0	0.3
S.D.		4.3	2.9	4.6	3.8	3.6	3.8	2.7	0.0	0.0	0.0	0.0	0.0	0.0	0.7
Significance															
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	UA	UA	UA	DU	UA	DT

P: Pregnancy, L: lactation.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

## Appendix 17-2 (Continued) Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Open-field test							Palpebral closure							Day 1(P)				Day 8(P)			Day 15(P)				Day 3(L)		
		Gait				Pre			Day 8				Day 15			Day 1(P)				Day 8(P)			Day 15(P)				Day 3(L)		
F02251	F00060	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02252	F00067	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02253	F00059	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02254	F00047	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02255	F00020	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02256	F00061	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02257	F00005	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02258	F00048	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02259	F00071	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02260	F00019	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02261	F00050	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
F02262	F00015	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12				
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0				
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
Significance																													
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA					

P: Pregnancy, L: lactation.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

(Continued)

## Appendix 17-2 (Continued) Individual FOB of female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Open-field test													
		Consciousness							Behavioral abnormalities						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02252	F00067	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02253	F00059	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02254	F00047	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02255	F00020	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02256	F00061	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02257	F00005	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02258	F00048	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02259	F00071	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02260	F00019	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02261	F00050	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F02262	F00015	2	2	2	2	2	2	2	1	1	1	1	1	1	1
288	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Range	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-2 (Continued) Individual FOB of female rats

		(bumetizole group at 62.5 mg/kg)						
Female No.	Blind No.	Open-field test						
		Righting reflex						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F02251	F00060	1	1	1	1	1	1	1
F02252	F00067	1	1	1	1	1	1	1
F02253	F00059	1	1	1	1	1	1	1
F02254	F00047	1	1	1	1	1	1	1
F02255	F00020	1	1	1	1	1	1	1
F02256	F00061	1	1	1	1	1	1	1
F02257	F00005	1	1	1	1	1	1	1
F02258	F00048	1	1	1	1	1	1	1
F02259	F00071	1	1	1	1	1	1	1
F02260	F00019	1	1	1	1	1	1	1
F02261	F00050	1	1	1	1	1	1	1
F02262	F00015	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Righting reflex

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

## Appendix 17-3 Individual FOB of female rats

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals in cages														
		Posture							Palpebral closure							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03352	F00053	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03353	F00068	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03354	F00028	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03355	F00022	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03356	F00003	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03357	F00051	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03358	F00036	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03359	F00063	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03360	F00040	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03361	F00002	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03362	F00029	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-3 (Continued) Individual FOB of female rats

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals in cages														
		Biting behavior							Clonic convulsions							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03352	F00053	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03353	F00068	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03354	F00028	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03355	F00022	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03356	F00003	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03357	F00051	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03358	F00036	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03359	F00063	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03360	F00040	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03361	F00002	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03362	F00029	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 17-3 (Continued) Individual FOB of female rats

		Observation of animals in cages						
		Tonic convulsions						
Female No.	Blind No.	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	1	1	1	1	1	1	1
F03352	F00053	1	1	1	1	1	1	1
F03353	F00068	1	1	1	1	1	1	1
F03354	F00028	1	1	1	1	1	1	1
F03355	F00022	1	1	1	1	1	1	1
F03356	F00003	1	1	1	1	1	1	1
F03357	F00051	1	1	1	1	1	1	1
F03358	F00036	1	1	1	1	1	1	1
F03359	F00063	1	1	1	1	1	1	1
F03360	F00040	1	1	1	1	1	1	1
F03361	F00002	1	1	1	1	1	1	1
F03362	F00029	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

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

## Appendix 17-3 (Continued) Individual FOB of female rats

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm														
		Ease of removal from cage							Ease of handling							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03352	F00053	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03353	F00068	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03354	F00028	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03355	F00022	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03356	F00003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03357	F00051	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03358	F00036	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03359	F00063	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03360	F00040	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03361	F00002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03362	F00029	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-3 (Continued) Individual FOB of female rats

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm														
		Muscle tone							Fur conditions							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03352	F00053	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03353	F00068	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03354	F00028	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03355	F00022	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03356	F00003	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03357	F00051	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03358	F00036	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03359	F00063	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03360	F00040	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03361	F00002	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03362	F00029	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

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

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

## Appendix 17-3 (Continued) Individual FOB of female rats

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm														
		Lacrimation							Salivation							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03352	F00053	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03353	F00068	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03354	F00028	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03355	F00022	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03356	F00003	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03357	F00051	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03358	F00036	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03359	F00063	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03360	F00040	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03361	F00002	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03362	F00029	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

## Appendix 17-3 (Continued) Individual FOB of female rats

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm						
		Respiration						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	1	1	1	1	1	1	1
F03352	F00053	1	1	1	1	1	1	1
F03353	F00068	1	1	1	1	1	1	1
F03354	F00028	1	1	1	1	1	1	1
F03355	F00022	1	1	1	1	1	1	1
F03356	F00003	1	1	1	1	1	1	1
F03357	F00051	1	1	1	1	1	1	1
F03358	F00036	1	1	1	1	1	1	1
F03359	F00063	1	1	1	1	1	1	1
F03360	F00040	1	1	1	1	1	1	1
F03361	F00002	1	1	1	1	1	1	1
F03362	F00029	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 17-3 (Continued) Individual FOB of female rats

		(bumetizole group at 250 mg/kg)													
Female No. Blind No.		Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	2	4	4	1	8	2	5	0	0	0	0	0	0	1
F03352	F00053	18	15	8	9	13	11	2	0	0	0	0	0	0	0
F03353	F00068	9	9	8	5	8	9	4	0	0	0	0	0	0	0
F03354	F00028	9	11	7	5	6	10	13	0	0	0	0	0	0	1
F03355	F00022	5	12	7	7	10	11	7	0	0	0	0	0	0	0
F03356	F00003	14	8	13	13	9	11	10	0	0	0	0	0	0	0
F03357	F00051	6	3	6	6	7	8	7	2	0	0	0	0	0	0
F03358	F00036	15	5	8	2	7	12	1	0	0	0	0	0	0	1
F03359	F00063	10	4	4	1	2	0	3	0	0	0	0	0	0	0
F03360	F00040	4	1	3	3	7	1	5	0	0	0	0	0	0	0
F03361	F00002	8	1	2	1	1	2	5	0	0	0	0	0	0	3
F03362	F00029	1	1	2	0	7	0	0	0	0	0	0	0	0	0
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		8.4	6.2	6.0	4.4	7.1	6.4	5.2	0.2	0.0	0.0	0.0	0.0	0.0	0.5
S.D.		5.2	4.7	3.2	3.9	3.2	4.9	3.7	0.6	0.0	0.0	0.0	0.0	0.0	0.9
Significance															
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	UA	UA	UA	DU	UA	DT

P: Pregnancy, L: lactation.

(Continued)

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 17-3 (Continued) Individual FOB of female rats

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Open-field test							Palpebral closure						
		Gait							Palpebral closure						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03352	F00053	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03353	F00068	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03354	F00028	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03355	F00022	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03356	F00003	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03357	F00051	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03358	F00036	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03359	F00063	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03360	F00040	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03361	F00002	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03362	F00029	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-3 (Continued) Individual FOB of female rats

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Open-field test														
		Consciousness							Behavioral abnormalities							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F03351	F00049	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03352	F00053	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03353	F00068	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03354	F00028	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03355	F00022	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03356	F00003	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03357	F00051	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03358	F00036	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03359	F00063	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03360	F00040	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03361	F00002	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F03362	F00029	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
- 299 -	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Range	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
Significance																(Continued)
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-3 (Continued) Individual FOB of female rats

(bumetizole group at 250 mg/kg)							
Female No.	Blind No.	Open-field test					
		Righting reflex					
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)
F03351	F00049	1	1	1	1	1	1
F03352	F00053	1	1	1	1	1	1
F03353	F00068	1	1	1	1	1	1
F03354	F00028	1	1	1	1	1	1
F03355	F00022	1	1	1	1	1	1
F03356	F00003	1	1	1	1	1	1
F03357	F00051	1	1	1	1	1	1
F03358	F00036	1	1	1	1	1	1
F03359	F00063	1	1	1	1	1	1
F03360	F00040	1	1	1	1	1	1
F03361	F00002	1	1	1	1	1	1
F03362	F00029	1	1	1	1	1	1
Number of females		12	12	12	12	12	12
Mean		1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1
Significance							
Statistical method		UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Righting reflex

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

## Appendix 17-4 Individual FOB of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals in cages														
		Posture							Palpebral closure							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04452	F00013	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04453	F00030	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04454	F00054	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04455	F00014	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04456	F00070	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04457	F00021	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04458	F00031	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04459	F00056	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04460	F00016	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04461	F00058	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04462	F00073	2	2	2	Non-pregnancy				1	1	1	Non-pregnancy				
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11	11
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-4 (Continued) Individual FOB of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals in cages													
		Biting behavior							Clonic convulsions						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04452	F00013	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04453	F00030	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04454	F00054	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04455	F00014	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04456	F00070	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04457	F00021	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04458	F00031	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04459	F00056	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04460	F00016	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04461	F00058	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04462	F00073	1	1	1	Non-pregnancy			1	1	1	1	Non-pregnancy			
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Biting behavior      1: Not observed, 2: observed.

Clonic convulsions    1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 17-4 (Continued) Individual FOB of female rats

		Observation of animals in cages						
		Tonic convulsions						
Female No.	Blind No.	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	1	1	1	1	1	1	1
F04452	F00013	1	1	1	1	1	1	1
F04453	F00030	1	1	1	1	1	1	1
F04454	F00054	1	1	1	1	1	1	1
F04455	F00014	1	1	1	1	1	1	1
F04456	F00070	1	1	1	1	1	1	1
F04457	F00021	1	1	1	1	1	1	1
F04458	F00031	1	1	1	1	1	1	1
F04459	F00056	1	1	1	1	1	1	1
F04460	F00016	1	1	1	1	1	1	1
F04461	F00058	1	1	1	1	1	1	1
F04462	F00073	1	1	1	Non-pregnancy			
Number of females		12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

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

## Appendix 17-4 (Continued) Individual FOB of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm														
		Ease of removal from cage							Ease of handling							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04452	F00013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04453	F00030	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04454	F00054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04455	F00014	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04456	F00070	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04457	F00021	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04458	F00031	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04459	F00056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04460	F00016	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04461	F00058	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04462	F00073	2	2	2	Non-pregnancy				2	2	2	2	Non-pregnancy			
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11	11
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Significance																(Continued)
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 17-4 (Continued) Individual FOB of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm														
		Muscle tone							Fur conditions							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04452	F00013	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04453	F00030	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04454	F00054	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04455	F00014	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04456	F00070	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04457	F00021	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04458	F00031	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04459	F00056	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04460	F00016	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04461	F00058	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04462	F00073	2	2	2	Non-pregnancy				1	1	1	Non-pregnancy				
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11	11
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
Significance																
Statistical method																

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

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

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

## Appendix 17-4 (Continued) Individual FOB of female rats

		(bumetizole group at 1000 mg/kg)													
Female No.	Blind No.	Lacrimation							Observation of animals on observer's palm						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04452	F00013	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04453	F00030	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04454	F00054	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04455	F00014	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04456	F00070	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04457	F00021	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04458	F00031	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04459	F00056	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04460	F00016	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04461	F00058	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04462	F00073	1	1	1	Non-pregnancy			1	1	1	Non-pregnancy			1	1
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

## Appendix 17-4 (Continued) Individual FOB of female rats

		Observation of animals on observer's palm						
Female No.	Blind No.	Respiration						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	1	1	1	1	1	1	1
F04452	F00013	1	1	1	1	1	1	1
F04453	F00030	1	1	1	1	1	1	1
F04454	F00054	1	1	1	1	1	1	1
F04455	F00014	1	1	1	1	1	1	1
F04456	F00070	1	1	1	1	1	1	1
F04457	F00021	1	1	1	1	1	1	1
F04458	F00031	1	1	1	1	1	1	1
F04459	F00056	1	1	1	1	1	1	1
F04460	F00016	1	1	1	1	1	1	1
F04461	F00058	1	1	1	1	1	1	1
F04462	F00073	1	1	1	Non-pregnancy			
Number of females		12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Respiration                    1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 17-4 (Continued) Individual FOB of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	19	23	30	9	3	8	3	1	0	0	0	0	0	0
F04452	F00013	11	9	12	10	18	23	14	0	0	0	0	1	0	0
F04453	F00030	7	4	2	1	3	3	2	0	0	0	0	2	0	0
F04454	F00054	12	15	10	10	13	5	10	0	0	0	0	0	0	0
F04455	F00014	15	10	7	7	7	7	4	0	0	0	0	0	0	0
F04456	F00070	3	4	5	2	3	8	5	0	0	0	0	0	0	1
F04457	F00021	17	11	8	8	5	7	5	0	0	0	0	0	0	0
F04458	F00031	9	8	2	1	6	4	4	0	0	0	0	0	0	0
F04459	F00056	12	7	6	5	4	7	7	0	0	0	0	0	0	0
F04460	F00016	3	7	5	0	5	10	1	0	0	0	0	0	0	0
F04461	F00058	6	8	10	4	7	11	2	0	0	0	0	0	0	0
F04462	F00073	4	1	11	Non-pregnancy		0	0	0	Non-pregnancy					
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		9.8	8.9	9.0	5.2	6.7	8.5	5.2	0.1	0.0	0.0	0.0	0.3	0.0	0.1
S.D.		5.4	5.7	7.4	3.8	4.7	5.4	3.9	0.3	0.0	0.0	0.0	0.6	0.0	0.3
Significance															
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	UA	UA	UA	DU	UA	DT

P: Pregnancy, L: lactation.

(Continued)

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 17-4 (Continued) Individual FOB of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Open-field test							Palpebral closure						
		Gait			Pre Day 8 Day 15 Day 1(P) Day 8(P) Day 15(P) Day 3(L)				Pre Day 8 Day 15 Day 1(P) Day 8(P) Day 15(P) Day 3(L)						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)	Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04452	F00013	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04453	F00030	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04454	F00054	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04455	F00014	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04456	F00070	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04457	F00021	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04458	F00031	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04459	F00056	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04460	F00016	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04461	F00058	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04462	F00073	1	1	1	1	Non-pregnancy				1	1	1	1	Non-pregnancy	
Number of females		12	12	12	11	11	11	11	12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

(Continued)

## Appendix 17-4 (Continued) Individual FOB of female rats

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Open-field test							Behavioral abnormalities							
		Consciousness							Behavioral abnormalities							
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04452	F00013	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04453	F00030	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04454	F00054	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04455	F00014	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04456	F00070	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04457	F00021	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04458	F00031	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04459	F00056	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04460	F00016	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04461	F00058	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
F04462	F00073	2	2	2	Non-pregnancy				1	1	1	Non-pregnancy				
10 13	Number of females	12	12	12	11	11	11	11	12	12	12	11	11	11	11	11
	Mean	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Range	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

(Continued)

## Appendix 18-1 Individual FOB of female rats (recovery group)

(Control group)		Female No.	Blind No.	Observation of animals in cages															
				Posture							Palpebral closure								
				Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42		
F01171	F00087	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1		
F01172	F00096	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1		
F01173	F00074	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1		
F01174	F00092	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1		
F01175	F00083	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1		
F01176	F00090	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1		
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0		
Range		2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1		

Findings were graded as follows

(Continued)

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.

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group)		Observation of animals in cages						
Female No.	Blind No.	Tonic convulsions						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F01171	F00087	1	1	1	1	1	1	1
F01172	F00096	1	1	1	1	1	1	1
F01173	F00074	1	1	1	1	1	1	1
F01174	F00092	1	1	1	1	1	1	1
F01175	F00083	1	1	1	1	1	1	1
F01176	F00090	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

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

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group)		Observation of animals on observer's palm											
Female No.	Blind No.	Ease of removal from cage						Ease of handling					
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29
F01171	F00087	2	2	2	2	2	2	2	2	2	2	2	2
F01172	F00096	2	2	2	2	2	2	2	2	2	2	2	2
F01173	F00074	2	2	2	2	2	2	2	2	2	2	2	2
F01174	F00092	2	2	2	2	2	2	2	2	2	2	2	2
F01175	F00083	2	2	2	2	2	2	2	2	2	2	2	2
F01176	F00090	2	2	2	2	2	2	2	2	2	2	2	2
Number of females		6	6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2

Findings were graded as follows

(Continued)

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.

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group)

Female No.	Blind No.	Observation of animals on observer's palm													
		Muscle tone						Fur conditions							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F01171	F00087	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01172	F00096	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01173	F00074	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01174	F00092	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01175	F00083	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01176	F00090	2	2	2	2	2	2	2	1	1	1	1	1	1	
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	

Findings were graded as follows

(Continued)

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

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

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group)		Female No.	Blind No.	Observation of animals on observer's palm											
				Lacrimation						Salivation					
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F01171	F00087	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01172	F00096	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01173	F00074	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01174	F00092	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01175	F00083	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01176	F00090	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

Lacrimation            1: None, 2: mild, 3: marked.  
 Salivation            1: None, 2: mild, 3: marked.

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group)		Observation of animals on observer's palm						
Female No.	Blind No.	Respiration						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F01171	F00087	1	1	1	1	1	1	1
F01172	F00096	1	1	1	1	1	1	1
F01173	F00074	1	1	1	1	1	1	1
F01174	F00092	1	1	1	1	1	1	1
F01175	F00083	1	1	1	1	1	1	1
F01176	F00090	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group) Female No. Blind No.		Open-field test												
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)					
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 36	Day 42
F01171	F00087	5	10	5	9	9	5	10	0	0	0	0	0	0
F01172	F00096	5	9	2	5	1	1	10	0	0	0	0	0	0
F01173	F00074	10	0	3	4	6	4	7	0	0	0	0	0	0
F01174	F00092	5	10	15	11	7	6	11	0	0	0	0	0	0
F01175	F00083	1	0	5	1	1	2	6	0	0	0	0	0	0
F01176	F00090	7	0	6	0	3	3	10	0	0	0	0	0	0
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		5.5	4.8	6.0	5.0	4.5	3.5	9.0	0.0	0.0	0.0	0.0	0.0	0.0
S.D.		2.9	5.3	4.6	4.3	3.3	1.9	2.0	0.0	0.0	0.0	0.0	0.0	0.0

(Continued)

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

## (Control group)

Female No.	Blind No.	Open-field test													
		Gait			Palpebral closure										
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F01171	F00087	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01172	F00096	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01173	F00074	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01174	F00092	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01175	F00083	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F01176	F00090	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1

Findings were graded as follows

(Continued)

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.

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group)		Female No.	Blind No.	Open-field test													
				Consciousness						Behavioral abnormalities							
				Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F01171	F00087	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01172	F00096	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01173	F00074	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01174	F00092	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01175	F00083	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	
F01176	F00090	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	
Range		2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	

Findings were graded as follows

(Continued)

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.

## Appendix 18-1 (Continued) Individual FOB of female rats (recovery group)

(Control group)		Open-field test						
Female No.	Blind No.	Righting reflex						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	
F01171	F00087	1	1	1	1	1	1	1
F01172	F00096	1	1	1	1	1	1	1
F01173	F00074	1	1	1	1	1	1	1
F01174	F00092	1	1	1	1	1	1	1
F01175	F00083	1	1	1	1	1	1	1
F01176	F00090	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1

Findings were graded as follows

Righting reflex

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

## Appendix 18-2 Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals in cages													
		Posture						Palpebral closure							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F03371	F00082	2	2	2	2	2	2	2	1	1	1	1	1	1	
F03372	F00097	2	2	2	2	2	2	2	1	1	1	1	1	1	
F03373	F00088	2	2	2	2	2	2	2	1	1	1	1	1	1	
F03374	F00095	2	2	2	2	2	2	2	1	1	1	1	1	1	
F03375	F00086	2	2	2	2	2	2	2	1	1	1	1	1	1	
F03376	F00093	2	2	2	2	2	2	2	1	1	1	1	1	1	
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	

## Significance

Statistical method	UA													
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(Continued)

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UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals in cages												
		Biting behavior						Clonic convulsions						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36
F03371	F00082	1	1	1	1	1	1	1	1	1	1	1	1	1
F03372	F00097	1	1	1	1	1	1	1	1	1	1	1	1	1
F03373	F00088	1	1	1	1	1	1	1	1	1	1	1	1	1
F03374	F00095	1	1	1	1	1	1	1	1	1	1	1	1	1
F03375	F00086	1	1	1	1	1	1	1	1	1	1	1	1	1
F03376	F00093	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1
Significance		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

		Observation of animals in cages						
		Tonic convulsions						
Female No.	Blind No.	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F03371	F00082	1	1	1	1	1	1	1
F03372	F00097	1	1	1	1	1	1	1
F03373	F00088	1	1	1	1	1	1	1
F03374	F00095	1	1	1	1	1	1	1
F03375	F00086	1	1	1	1	1	1	1
F03376	F00093	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

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

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm													
		Ease of removal from cage						Ease of handling							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F03371	F00082	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03372	F00097	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03373	F00088	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03374	F00095	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03375	F00086	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03376	F00093	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm													
		Muscle tone						Fur conditions							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F03371	F00082	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03372	F00097	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03373	F00088	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03374	F00095	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03375	F00086	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03376	F00093	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

## Significance

Statistical method	UA													
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(Continued)

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UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

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

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

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm														
		Lacrimation							Salivation							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F03371	F00082	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03372	F00097	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03373	F00088	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03374	F00095	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03375	F00086	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03376	F00093	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Lacrimation      1: None, 2: mild, 3: marked.

Salivation      1: None, 2: mild, 3: marked.

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

		(bumetizole group at 250 mg/kg)					
Female No. Blind No.		Observation of animals on observer's palm					
		Respiration					
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36
F03371	F00082	1	1	1	1	1	1
F03372	F00097	1	1	1	1	1	1
F03373	F00088	1	1	1	1	1	1
F03374	F00095	1	1	1	1	1	1
F03375	F00086	1	1	1	1	1	1
F03376	F00093	1	1	1	1	1	1
Number of females		6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1
Significance							
Statistical method		UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F03371	F00082	15	7	4	0	9	12	6	0	0	0	0	0	0	0
F03372	F00097	8	11	14	11	14	16	18	0	0	0	0	0	0	0
F03373	F00088	11	5	14	10	3	10	11	0	0	0	0	0	2	0
F03374	F00095	12	9	14	11	14	16	10	0	0	0	0	0	0	0
F03375	F00086	11	3	5	7	5	5	14	0	0	0	0	1	0	0
F03376	F00093	7	1	2	3	8	8	10	0	0	0	0	0	0	0
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		10.7	6.0	8.8	7.0	8.8	11.2	11.5	0.0	0.0	0.0	0.0	0.2	0.3	0.0
S.D.		2.9	3.7	5.7	4.6	4.5	4.4	4.1	0.0	0.0	0.0	0.0	0.4	0.8	0.0
Significance		*						**							
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	UA	UA	UA	DU	DU	UA

Significantly different from control group (\*: P&lt;0.05, \*\*: P&lt;0.01).

(Continued)

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Open-field test													
		Gait							Palpebral closure						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F03371	F00082	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03372	F00097	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03373	F00088	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03374	F00095	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03375	F00086	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F03376	F00093	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)

Female No.	Blind No.	Open-field test													
		Consciousness							Behavioral abnormalities						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F03371	F00082	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03372	F00097	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03373	F00088	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03374	F00095	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03375	F00086	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F03376	F00093	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

## Significance

Statistical method	UA														
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(Continued)

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UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 18-2 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 250 mg/kg)							
Female No.	Blind No.	Open-field test					
		Righting reflex					
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36
F03371	F00082	1	1	1	1	1	1
F03372	F00097	1	1	1	1	1	1
F03373	F00088	1	1	1	1	1	1
F03374	F00095	1	1	1	1	1	1
F03375	F00086	1	1	1	1	1	1
F03376	F00093	1	1	1	1	1	1
Number of females		6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1
Significance							
Statistical method		UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Righting reflex

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

## Appendix 18-3 Individual FOB of female rats (recovery group)

		(bumetizole group at 1000 mg/kg)													
Female No.	Blind No.	Observation of animals in cages													
		Posture						Palpebral closure							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04472	F00077	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04473	F00080	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04474	F00079	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04475	F00099	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04476	F00081	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals in cages														
		Biting behavior							Clonic convulsions							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04472	F00077	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04473	F00080	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04474	F00079	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04475	F00099	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04476	F00081	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

## Appendix 17-4 (Continued) Individual FOB of female rats

		(bumetizole group at 1000 mg/kg)						
Female No.	Blind No.	Open-field test						
		Righting reflex						
		Pre	Day 8	Day 15	Day 1(P)	Day 8(P)	Day 15(P)	Day 3(L)
F04451	F00001	1	1	1	1	1	1	1
F04452	F00013	1	1	1	1	1	1	1
F04453	F00030	1	1	1	1	1	1	1
F04454	F00054	1	1	1	1	1	1	1
F04455	F00014	1	1	1	1	1	1	1
F04456	F00070	1	1	1	1	1	1	1
F04457	F00021	1	1	1	1	1	1	1
F04458	F00031	1	1	1	1	1	1	1
F04459	F00056	1	1	1	1	1	1	1
F04460	F00016	1	1	1	1	1	1	1
F04461	F00058	1	1	1	1	1	1	1
F04462	F00073	1	1	1	Non-pregnancy			
Number of females		12	12	12	11	11	11	11
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

P: Pregnancy, L: lactation.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Righting reflex

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

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

		(bumetizole group at 1000 mg/kg)						
Female No.	Blind No.	Observation of animals in cages						
		Tonic convulsions						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	1	1	1	1	1	1	1
F04472	F00077	1	1	1	1	1	1	1
F04473	F00080	1	1	1	1	1	1	1
F04474	F00079	1	1	1	1	1	1	1
F04475	F00099	1	1	1	1	1	1	1
F04476	F00081	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

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

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm														
		Ease of removal from cage							Ease of handling							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04472	F00077	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04473	F00080	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04474	F00079	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04475	F00099	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04476	F00081	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Significance																
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm													
		Muscle tone						Fur conditions							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04472	F00077	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04473	F00080	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04474	F00079	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04475	F00099	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04476	F00081	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1

## Significance

Statistical method	UA													
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(Continued)

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UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

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

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

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm													
		Lacrimation						Salivation							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	1	1	1	1	1	1	1	1	1	1	1	1	1	
F04472	F00077	1	1	1	1	1	1	1	1	1	1	1	1	1	
F04473	F00080	1	1	1	1	1	1	1	1	1	1	1	1	1	
F04474	F00079	1	1	1	1	1	1	1	1	1	1	1	1	1	
F04475	F00099	1	1	1	1	1	1	1	1	1	1	1	1	1	
F04476	F00081	1	1	1	1	1	1	1	1	1	1	1	1	1	
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	
Significance		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Lacrimation      1: None, 2: mild, 3: marked.

Salivation      1: None, 2: mild, 3: marked.

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Observation of animals on observer's palm						
		Respiration						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	1	1	1	1	1	1	1
F04472	F00077	1	1	1	1	1	1	1
F04473	F00080	1	1	1	1	1	1	1
F04474	F00079	1	1	1	1	1	1	1
F04475	F00099	1	1	1	1	1	1	1
F04476	F00081	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1
Significance								
Statistical method		UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Open-field test													
		Frequency of rearing (during a 2-minute period)							Frequency of grooming (during a 2-minute period)						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	1	1	1	0	7	8	1	1	0	0	0	0	2	0
F04472	F00077	8	6	9	7	6	9	6	0	0	0	0	0	0	0
F04473	F00080	3	3	4	5	5	10	12	0	0	0	0	0	0	0
F04474	F00079	9	1	4	7	3	3	7	0	0	0	0	0	0	0
F04475	F00099	8	6	12	8	13	11	16	0	0	0	0	0	0	0
F04476	F00081	8	3	6	7	11	5	9	0	0	0	0	0	0	0
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		6.2	3.3	6.0	5.7	7.5	7.7	8.5	0.2	0.0	0.0	0.0	0.0	0.3	0.0
S.D.		3.3	2.3	3.9	2.9	3.8	3.1	5.2	0.4	0.0	0.0	0.0	0.0	0.8	0.0
Significance															
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	UA	UA	UA	DU	DU	UA

DU: Analysis by Dunnett's test.

(Continued)

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Gait							Open-field test							Palpebral closure							
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	
F04471	F00084	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04472	F00077	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04473	F00080	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04474	F00079	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04475	F00099	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F04476	F00081	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Significance																							
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)															
Female No.		Open-field test													
	Blind No.	Consciousness							Behavioral abnormalities						
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42	Pre	Day 8	Day 15	Day 22	Day 29	Day 36	Day 42
F04471	F00084	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04472	F00077	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04473	F00080	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04474	F00079	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04475	F00099	2	2	2	2	2	2	2	1	1	1	1	1	1	1
F04476	F00081	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	2	2	1	1	1	1	1	1	1
Significance															
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

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.

## Appendix 18-3 (Continued) Individual FOB of female rats (recovery group)

(bumetizole group at 1000 mg/kg)							
Female No.	Blind No.	Open-field test					
		Righting reflex					
		Pre	Day 8	Day 15	Day 22	Day 29	Day 36
F04471	F00084	1	1	1	1	1	1
F04472	F00077	1	1	1	1	1	1
F04473	F00080	1	1	1	1	1	1
F04474	F00079	1	1	1	1	1	1
F04475	F00099	1	1	1	1	1	1
F04476	F00081	1	1	1	1	1	1
Number of females		6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1
Significance							
Statistical method		UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows

Righting reflex

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

## Appendix 19-1 Individual sensory response of male rats on termination of administration period

(Control group)

Male No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
M01101	M00059	1	2	2	2	3
M01102	M00055	1	2	2	2	3
M01103	M00037	1	2	2	2	3
M01104	M00070	1	2	2	2	3
M01105	M00010	1	2	2	2	3
M01106	M00039	1	2	2	2	3
Number of males		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	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.

## Appendix 19-2 Individual sensory response of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Male No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
M02201	M00023	1	2	2	2	3
M02202	M00029	1	2	2	2	3
M02203	M00020	1	2	2	2	3
M02204	M00060	1	2	2	2	3
M02205	M00035	1	2	2	2	3
M02206	M00046	1	2	2	2	3
Number of males		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance						
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 19-3 Individual sensory response of male rats on termination of administration period

(bumetizole group at 250 mg/kg)						
Male No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
M03301	M00011	1	2	2	2	3
M03302	M00044	1	2	2	2	3
M03303	M00047	1	2	2	2	3
M03304	M00012	1	2	2	2	3
M03305	M00017	1	2	2	2	3
M03306	M00073	1	2	2	2	3
Number of males		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance						
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 19-4 Individual sensory response of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Male No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
M04401	M00004	1	2	2	2	3
M04402	M00028	1	2	2	2	3
M04403	M00032	1	2	2	2	3
M04404	M00019	1	2	2	2	3
M04405	M00045	1	2	2	2	3
M04406	M00034	1	2	2	2	3
Number of males		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance						
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 20-1 Individual sensory response of female rats on termination of administration period

## (Control group)

Female No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
F01151	F00052	1	2	2	2	3
F01152	F00006	1	2	2	2	3
F01153	F00039	1	2	2	2	3
F01154	F00041	1	2	2	2	3
F01155	F00034	1	2	2	2	3
F01156	F00043	1	2	2	2	3
Number of females		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	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.

## Appendix 20-2 Individual sensory response of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Female No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
F02251	F00060	1	2	2	2	3
F02252	F00067	1	2	2	2	3
F02253	F00059	1	2	2	2	3
F02254	F00047	1	2	2	2	3
F02255	F00020	1	2	2	2	3
F02256	F00061	1	2	2	2	3
Number of females		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance						
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 20-3 Individual sensory response of female rats on termination of administration period

(bumetizole group at 250 mg/kg)						
Female No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
F03351	F00049	1	2	2	2	3
F03352	F00053	1	2	2	2	3
F03353	F00068	1	2	2	2	3
F03354	F00028	1	2	2	2	3
F03355	F00022	1	2	2	2	3
F03356	F00003	1	2	2	2	3
Number of females		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance						
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 20-4 Individual sensory response of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Female No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
F04451	F00001	1	2	2	2	3
F04452	F00013	1	2	2	2	3
F04453	F00030	1	2	2	2	3
F04454	F00054	1	2	2	2	3
F04455	F00014	1	2	2	2	3
F04456	F00070	1	2	2	2	3
Number of females		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance						
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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.

## Appendix 21-1 Individual grip strength (g) of male rats on termination of administration period

(Control group)		
Male No.	Forelimb	Hindlimb
M01101	1034	122
M01102	1076	127
M01103	1216	68
M01104	488	78
M01105	903	193
M01106	1456	117
Number of males	6	6
Mean	1029	118
S.D.	325	44

## Appendix 21-2 Individual grip strength (g) of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)		
Male No.	Forelimb	Hindlimb
M02201	1017	75
M02202	840	45
M02203	1097	101
M02204	1336	146
M02205	1511	192
M02206	929	330
Number of males	6	6
Mean	1122	148
S.D.	255	103
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 21-3 Individual grip strength (g) of male rats on termination of administration period

(bumetizole group at 250 mg/kg)		
Male No.	Forelimb	Hindlimb
M03301	954	130
M03302	848	58
M03303	1487	214
M03304	1512	114
M03305	1037	194
M03306	880	112
Number of males	6	6
Mean	1120	137
S.D.	301	58
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 21-4 Individual grip strength (g) of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)		
Male No.	Forelimb	Hindlimb
M04401	706	158
M04402	1051	63
M04403	1323	140
M04404	640	156
M04405	942	95
M04406	1059	88
Number of males	6	6
Mean	954	117
S.D.	252	40
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 22-1 Individual grip strength (g) of female rats on termination of administration period

(Control group)		
Female No.	Forelimb	Hindlimb
F01151	956	123
F01152	1301	81
F01153	746	206
F01154	910	140
F01155	958	78
F01156	882	97
Number of females	6	6
Mean	959	121
S.D.	185	48

## Appendix 22-2 Individual grip strength (g) of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)		
Female No.	Forelimb	Hindlimb
F02251	923	100
F02252	746	60
F02253	703	91
F02254	815	171
F02255	699	62
F02256	857	76
Number of females	6	6
Mean	791	93
S.D.	90	41
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 22-3 Individual grip strength (g) of female rats on termination of administration period

(bumetizole group at 250 mg/kg)		
Female No.	Forelimb	Hindlimb
F03351	550	63
F03352	870	73
F03353	897	73
F03354	788	108
F03355	733	74
F03356	954	55
Number of females	6	6
Mean	799	74
S.D.	145	18
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 22-4 Individual grip strength (g) of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)		
Female No.	Forelimb	Hindlimb
F04451	927	219
F04452	1062	89
F04453	864	103
F04454	1126	99
F04455	473	50
F04456	708	145
Number of females	6	6
Mean	860	118
S.D.	240	58
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 23-1 Individual spontaneous motor activity of male rats on termination of administration period

(Control group)

Male No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	10	20	30	40	50	60		10	20	30	40	50	60	
M01101	1167	527	343	634	243	322	3236	89	41	25	33	30	20	238
M01102	1485	304	135	0	0	75	1999	45	9	6	0	0	5	65
M01103	590	181	65	3	0	642	1481	71	32	3	0	0	32	138
M01104	1980	51	0	54	11	33	2129	74	6	0	2	0	1	83
M01105	1395	1111	154	214	18	72	2964	58	26	3	10	0	0	97
M01106	513	193	63	180	79	78	1106	36	16	7	16	5	6	86
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	1188	395	127	181	59	204	2153	62	22	7	10	6	11	118
S.D.	561	386	120	240	95	239	825	20	14	9	13	12	13	64

## Appendix 23-2 Individual spontaneous motor activity of male rats on termination of administration period

Male No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	10	20	30	40	50	60		10	20	30	40	50	60	
M02201	959	266	197	6	21	0	1449	60	22	9	0	0	0	91
M02202	1896	5449	2079	408	132	159	10123	88	37	62	31	10	5	233
M02203	452	0	33	91	127	0	703	30	0	2	4	2	0	38
M02204	1173	481	110	40	63	711	2578	27	19	1	0	2	19	68
M02205	1197	631	174	330	512	38	2882	92	49	14	24	11	4	194
M02206	585	178	211	252	51	107	1384	59	13	12	0	0	0	84
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	1044	1168	467	188	151	169	3187	59	23	17	10	4	5	118
S.D.	517	2109	792	166	182	273	3493	28	17	23	14	5	7	77
Significance														
Statistical method	DU	DT	DT	DU	DT	DT	DT	DU	DU	DU	DT	DU	DT	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 23-3 Individual spontaneous motor activity of male rats on termination of administration period

Male No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	10	20	30	40	50	60		10	20	30	40	50	60	
M03301	572	196	269	245	28	0	1310	74	45	29	26	1	0	175
M03302	1506	326	700	182	289	0	3003	48	19	29	6	12	0	114
M03303	394	20	0	0	176	1	591	67	2	0	0	15	0	84
M03304	585	196	185	94	16	0	1076	67	50	17	1	0	0	135
M03305	1246	770	279	622	106	0	3023	49	30	11	36	5	0	131
M03306	965	457	126	0	30	10	1588	45	23	6	0	0	0	74
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	878	328	260	191	108	2	1765	58	28	15	12	6	0	119
S.D.	436	261	239	233	108	4	1020	12	18	12	16	7	0	37
Significance	*													*
Statistical method	DU	DT	DT	DU	DT	DT	DT	DU	DU	DU	DT	DU	DT	DU

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Significantly different from control group (\*: P&lt;0.05).

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 23-4 Individual spontaneous motor activity of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Male No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	10	20	30	40	50	60		10	20	30	40	50	60	
M04401	562	108	29	40	0	0	739	42	10	1	4	0	0	57
M04402	450	45	208	0	92	80	875	32	4	4	0	0	0	40
M04403	1309	4048	705	740	846	700	8348	71	33	10	0	0	3	117
M04404	593	595	474	55	160	122	1999	38	15	19	1	14	6	93
M04405	441	216	6	96	39	9	807	15	8	0	5	0	0	28
M04406	710	213	8	3	2	3	939	43	18	0	1	0	0	62
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	678	871	238	156	190	152	2285	40	15	6	2	2	2	66
S.D.	325	1568	292	288	327	273	3007	18	10	8	2	6	3	33
Significance														
Statistical method	DU	DT	DT	DU	DT	DT	DT	DU	DU	DU	DT	DU	DT	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 24-1 Individual spontaneous motor activity of female rats on termination of administration period

(Control group)		Ambulatory counts							Vertical counts						
Female No.		Minutes after administration						Minutes after administration							
		10	20	30	40	50	60	Total	10	20	30	40	50	60	Total
F01151		1608	301	11	0	42	55	2017	37	7	0	0	0	0	44
F01152		1420	1318	390	158	320	0	3606	35	32	29	6	7	0	109
F01153		1153	4	0	24	0	0	1181	25	0	0	0	0	0	25
F01154		1040	0	0	0	13	1	1054	33	0	0	0	2	0	35
F01155		332	103	1	450	33	0	919	14	5	0	11	0	0	30
F01156		537	262	37	10	0	0	846	33	11	0	0	0	0	44
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		1015	331	73	107	68	9	1604	30	9	5	3	2	0	48
S.D.		496	500	156	179	125	22	1068	9	12	12	5	3	0	31

## Appendix 24-2 Individual spontaneous motor activity of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Female No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	10	20	30	40	50	60	10	20	30	40	50	60		
F02251	1367	950	442	395	199	556	3909	44	26	12	11	5	14	112
F02252	489	0	0	1	11	0	501	25	0	0	0	0	0	25
F02253	965	298	1	0	1	2	1267	91	22	0	0	0	0	113
F02254	856	0	0	0	0	3	859	30	0	0	0	0	0	30
F02255	1100	282	7	4	0	0	1393	38	6	0	0	0	0	44
F02256	754	43	2	0	0	0	799	21	0	0	0	0	0	21
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	922	262	75	67	35	94	1455	42	9	2	2	1	2	58
S.D.	301	363	180	161	80	227	1246	26	12	5	4	2	6	43
Significance														
Statistical method	DT	DT	DT	DT	DT	DT	DT	DT	DT	DU	DU	DU	DT	DT

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DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

## Appendix 24-3 Individual spontaneous motor activity of female rats on termination of administration period

Female No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	10	20	30	40	50	60		10	20	30	40	50	60	
F03351	459	88	0	0	0	0	547	7	8	0	0	0	0	15
F03352	535	26	4	23	0	0	588	25	0	0	0	0	0	25
F03353	1505	708	756	570	479	302	4320	45	29	26	27	13	11	151
F03354	874	33	290	270	141	2	1610	41	2	15	11	8	0	77
F03355	595	1	0	0	0	7	603	13	0	0	0	0	0	13
F03356	1376	1120	101	123	5162	0	7882	30	24	3	0	1	0	58
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	891	329	192	164	964	52	2592	27	11	7	6	4	2	57
S.D.	450	472	298	224	2065	123	2969	15	13	11	11	6	4	53
Significance														
Statistical method	DT	DT	DT	DT	DT	DT	DT	DT	DT	DU	DU	DU	DT	DT

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

## Appendix 24-4 Individual spontaneous motor activity of female rats on termination of administration period

Female No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	10	20	30	40	50	60		10	20	30	40	50	60	
F04451	340	1129	27	0	0	37	1533	7	15	1	0	0	1	24
F04452	679	167	12	177	60	9	1104	95	537	46	10	0	0	688
F04453	1736	1340	1064	809	726	920	6595	42	0	13	1	6	0	62
F04454	3724	6517	3999	3216	3151	3145	23752	63	14	0	0	0	0	77
F04455	565	447	0	151	0	0	1163	16	22	0	3	0	0	41
F04456	288	1	0	0	1	1	291	4	0	0	0	0	0	4
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	1222	1600	850	726	656	685	5740	38	98	10	2	1	0	149
S.D.	1334	2466	1599	1256	1255	1259	9110	36	215	18	4	2	0	265
Significance														
Statistical method	DT	DT	DT	DT	DT	DT	DT	DT	DT	DU	DU	DU	DT	DT

368 DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

## Appendix 25-1 Individual urinary examination of male rats on termination of administration period

(Control group)		
Male No.	UV mL	S.G.
M01101	20.8	1.041
M01102	9.1	1.048
M01103	20.9	1.042
M01104	16.1	1.046
M01105	20.8	1.037
M01106	14.2	1.052
Number of males	6	6
Mean	17.0	1.044
S.D.	4.8	0.005

(Continued)

## Appendix 25-1 (Continued) Individual urinary examination of male rats on termination of administration period

(Control group)

Male No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M01101	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-
M01102	Light yellow	8.5	±	-	-	-	-	±	±	±	±	-	-
M01103	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	+
M01104	Light yellow	8.5	++	-	-	-	±	±	±	±	±	-	-
M01105	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	+
M01106	Light yellow	8.5	+	-	-	-	±	±	±	±	±	-	-
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, ++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, ++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, ++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, ++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, ++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 25-2 Individual urinary examination of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Male No.	UV mL	S.G.
M02201	24.7	1.027
M02202	21.8	1.025
M02203	13.3	1.048
M02204	20.9	1.032
M02205	22.9	1.038
M02206	36.3	1.022
Number of males	6	6
Mean	23.3	1.032
S.D.	7.5	0.010
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 25-2 (Continued) Individual urinary examination of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)										Urinary sediments				
Male No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen						
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals	
M02201	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-	
M02202	Light yellow	8.5	++	-	+	-	-	±	±	±	±	-	+	
M02203	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-	
M02204	Light yellow	8.5	±	-	-	-	-	±	±	±	±	-	+	
M02205	Light yellow	8.5	+	-	-	-	±	±	±	±	±	-	+	
M02206	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-	
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, ++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, ++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, ++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, ++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, ++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 25-3 Individual urinary examination of male rats on termination of administration period

(bumetizole group at 250 mg/kg)

Male No.	UV mL	S.G.
M03301	24.9	1.037
M03302	16.1	1.048
M03303	17.8	1.045
M03304	11.7	1.060
M03305	14.8	1.047
M03306	17.7	1.044
Number of males	6	6
Mean	17.2	1.047
S.D.	4.4	0.008
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 25-3 (Continued) Individual urinary examination of male rats on termination of administration period

(bumetizole group at 250 mg/kg)													
Male No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M03301	Light yellow	9.0	++	-	-	-	-	±	±	±	±	-	-
M03302	Light yellow	9.0	+	-	-	-	-	±	±	±	±	-	-
M03303	Light yellow	8.5	+	-	-	-	+	±	±	±	±	-	+
M03304	Light yellow	8.5	+	-	+	-	-	±	±	±	±	-	+
M03305	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-
M03306	Light yellow	9.0	++	-	-	-	-	±	±	±	±	-	-
Number of males		6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, +++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields +++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields +++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 25-4 Individual urinary examination of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)		
Male No.	UV mL	S.G.
M04401	12.9	1.050
M04402	17.6	1.045
M04403	16.1	1.052
M04404	9.3	1.080
M04405	19.1	1.041
M04406	12.4	1.056
Number of males	6	6
Mean	14.6	1.054
S.D.	3.7	0.014
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 25-4 (Continued) Individual urinary examination of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Male No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M04401	Light yellow	8.5	++	-	-	-	±	±	±	±	±	-	-
M04402	Light yellow	8.5	++	-	+	-	±	±	±	±	±	-	+
M04403	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-
M04404	Light yellow	8.5	++	-	+	-	-	+	±	±	±	-	+
M04405	Light yellow	8.5	++	-	-	-	±	±	±	±	±	-	-
M04406	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	+
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, +++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields +++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields +++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 26-1 Individual urinary examination of female rats on termination of administration period

(Control group)

Female No.	UV mL	S.G.
F01151	31.4	1.034
F01152	33.5	1.030
F01153	24.3	1.038
F01154	30.0	1.031
F01155	26.5	1.033
F01156	33.4	1.024
Number of females	6	6
Mean	29.9	1.032
S.D.	3.8	0.005

(Continued)

Appendix 26-1 (Continued) Individual urinary examination of female rats on termination of administration period

(Control group) Female No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F01151	Light yellow	6.5	±	—	—	—	—	±	±	±	±	—	+
F01152	Light yellow	6.0	±	—	—	—	—	±	±	±	±	—	+
F01153	Light yellow	6.5	±	—	—	—	—	±	±	±	±	—	—
F01154	Light yellow	6.5	—	—	—	—	—	±	±	±	±	—	+
F01155	Light yellow	8.0	±	—	—	—	—	±	±	±	±	—	+
F01156	Light yellow	7.5	—	—	—	—	—	±	±	±	±	—	+
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: —; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, ++++; 1000 mg/dL.

Glucose: —; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, ++++; 2000 mg/dL.

Ketone body: —; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: —; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: —; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, ++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, ++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, ++++; ≥501 cells/100 fields.

Casts: —; not observed, +; observed.

Crystals: —; not observed, +; observed.

## Appendix 26-2 Individual urinary examination of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Female No.	UV mL	S.G.
F02251	20.2	1.041
F02252	28.5	1.028
F02253	29.1	1.034
F02254	24.7	1.038
F02255	20.2	1.034
F02256	22.6	1.042
Number of females	6	6
Mean	24.2	1.036
S.D.	3.9	0.005
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 26-2 (Continued) Individual urinary examination of female rats on termination of administration period

Female No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F02251	Light yellow	5.5	++	-	-	-	-	+	±	±	±	-	+
F02252	Light yellow	7.5	±	-	-	-	-	±	±	±	±	-	+
F02253	Light yellow	7.5	-	-	-	-	-	±	±	±	±	-	+
F02254	Light yellow	6.5	-	-	-	-	-	±	±	±	±	--	-
F02255	Light yellow	6.5	-	-	-	-	-	±	±	±	±	-	-
F02256	Light yellow	5.5	+	-	-	-	-	±	±	±	±	-	-
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, ++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 26-3 Individual urinary examination of female rats on termination of administration period

(bumetizole group at 250 mg/kg)

Female No.	UV mL	S.G.
F03351	37.0	1.029
F03352	24.3	1.038
F03353	36.2	1.027
F03354	20.8	1.039
F03355	24.0	1.032
F03356	26.8	1.032
Number of females	6	6
Mean	28.2	1.033
S.D.	6.8	0.005
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 26-3 (Continued) Individual urinary examination of female rats on termination of administration period

(bumetizole group at 250 mg/kg)

Female No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F03351	Light yellow	8.0	-	-	-	-	-	±	±	±	±	-	+
F03352	Light yellow	7.0	+	-	+	-	-	+	±	±	±	-	+
F03353	Light yellow	5.5	-	-	-	-	-	±	±	±	±	-	-
F03354	Light yellow	8.5	-	-	-	-	-	±	±	±	±	-	+
F03355	Light yellow	7.0	-	-	-	-	-	±	±	±	±	-	+
F03356	Light yellow	7.0	-	-	-	-	-	±	±	±	±	-	-
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, +++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 26-4 Individual urinary examination of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Female No.	UV mL	S.G.
F04451	40.5	1.026
F04452	36.9	1.029
F04453	50.4	1.019
F04454	38.1	1.023
F04455	26.5	1.034
F04456	22.9	1.028
Number of females	6	6
Mean	35.9	1.027
S.D.	9.9	0.005
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 26-4 (Continued) Individual urinary examination of female rats on termination of administration period

Female No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F04451	Light yellow	6.5	—	—	—	—	—	±	±	±	±	—	+
F04452	Light yellow	7.0	—	—	—	—	—	±	±	±	±	—	+
F04453	Light yellow	6.5	—	—	—	—	—	±	±	±	±	—	+
F04454	Light yellow	7.5	—	—	—	—	—	±	±	±	±	—	+
F04455	Light yellow	7.5	—	—	—	—	—	±	±	±	±	—	+
F04456	Light yellow	6.5	—	—	—	—	—	±	±	±	±	—	—
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: —; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, +++++; 1000 mg/dL.

Glucose: —; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++++; 2000 mg/dL.

Ketone body: —; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: —; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: —; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields +++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields +++++; ≥501 cells/100 fields.

Casts: —; not observed, +; observed.

Crystals: —; not observed, +; observed.

## Appendix 27-1 Individual urinary examination of male rats on termination of recovery period

(Control group)

Male No.	UV mL	S.G.
M01107	16.6	1.046
M01108	35.5	1.014
M01109	10.9	1.068
M01110	12.7	1.062
M01111	18.1	1.038
M01112	25.9	1.030
Number of males	6	6
Mean	20.0	1.043
S.D.	9.2	0.020

(Continued)

## Appendix 27-1 (Continued) Individual urinary examination of male rats on termination of recovery period

(Control group) Male No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M01107	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-
M01108	Light yellow	8.5	++	-	-	-	±	±	±	±	±	-	-
M01109	Light yellow	8.5	++	-	-	-	-	±	±	±	±	-	+
M01110	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-
M01111	Light yellow	8.5	++	-	-	-	-	±	±	±	±	-	+
M01112	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, +++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 27-2 Individual urinary examination of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)

Male No.	UV mL	S.G.
M02207	31.4	1.025
M02208	19.5	1.040
M02209	13.1	1.050
M02210	16.0	1.054
M02211	22.2	1.036
M02212	16.7	1.048
Number of males	6	6
Mean	19.8	1.042
S.D.	6.5	0.011
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 27-2 (Continued) Individual urinary examination of male rats on termination of recovery period

Male No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M02207	Light yellow	8.5	±	—	—	—	—	±	±	±	±	—	—
M02208	Light yellow	8.5	++	—	—	—	—	±	±	±	±	—	+
M02209	Light yellow	8.5	++	—	—	—	—	±	±	±	±	—	—
M02210	Light yellow	8.5	+	—	—	—	—	±	±	±	±	—	—
M02211	Light yellow	8.5	+	—	—	—	—	±	±	±	±	—	+
M02212	Light yellow	8.5	++	—	—	—	±	±	±	±	±	—	—
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: —; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, ++++; 1000 mg/dL.

Glucose: —; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; 2000 mg/dL.

Ketone body: —; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: —; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: —; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: —; not observed, +; observed.

Crystals: —; not observed, +; observed.

## Appendix 27-3 Individual urinary examination of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)

Male No.	UV mL	S.G.
M03307	15.3	1.040
M03308	21.0	1.042
M03309	14.1	1.048
M03310	13.6	1.058
M03311	20.8	1.042
M03312	6.5	1.080
Number of males	6	6
Mean	15.2	1.052
S.D.	5.4	0.015
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 27-3 (Continued) Individual urinary examination of male rats on termination of recovery period

Male No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M03307	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-
M03308	Light yellow	8.5	++	-	-	-	-	±	±	±	±	-	+
M03309	Light yellow	7.5	+	-	-	-	-	±	±	±	±	-	-
M03310	Light yellow	9.0	++	-	-	-	-	±	±	±	±	-	-
M03311	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	-
M03312	Light yellow	8.0	+	-	-	-	-	±	±	±	±	-	+
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, ++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, ++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, ++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, ++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, ++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 27-4 Individual urinary examination of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)

Male No.	UV mL	S.G.
M04407	14.1	1.056
M04408	12.8	1.058
M04409	8.4	1.064
M04410	12.9	1.054
M04411	14.2	1.041
M04412	14.0	1.062
Number of males	6	6
Mean	12.7	1.056
S.D.	2.2	0.008
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 27-4 (Continued) Individual urinary examination of male rats on termination of recovery period

Male No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M04407	Light yellow	8.5	+	-	-	-	-	±	±	±	±	-	+
M04408	Light yellow	8.5	++	-	-	-	-	±	±	±	±	-	-
M04409	Light yellow	8.5	++	-	+	-	-	±	±	±	±	-	-
M04410	Light yellow	8.5	++	-	-	-	-	±	±	±	±	-	+
M04411	Light yellow	8.5	++	-	-	-	-	±	±	±	±	-	-
M04412	Light yellow	8.5	++	-	+	-	-	±	±	±	±	-	+
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, ++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, ++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 28-1 Individual urinary examination of female rats on termination of recovery period

(Control group)		
Female No.	UV mL	S.G.
F01171	10.6	1.054
F01172	15.3	1.044
F01173	11.3	1.054
F01174	14.8	1.033
F01175	16.6	1.042
F01176	5.6	1.072
Number of females	6	6
Mean	12.4	1.050
S.D.	4.1	0.013

(Continued)

## Appendix 28-1 (Continued) Individual urinary examination of female rats on termination of recovery period

(Control group) Female No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F01171	Light yellow	8.5	-	-	-	-	-	±	±	±	±	-	-
F01172	Light yellow	9.0	+	-	-	-	-	±	±	±	±	-	+
F01173	Light yellow	8.5	-	-	-	-	-	±	±	±	±	-	+
F01174	Light yellow	8.5	±	-	-	-	±	±	±	±	±	-	-
F01175	Light yellow	8.5	-	-	-	-	-	±	±	±	±	-	+
F01176	Light yellow	8.5	±	-	-	-	-	±	±	±	±	-	+
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, ++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 28-2 Individual urinary examination of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)

Female No.	UV mL	S.G.
F03371	11.1	1.056
F03372	9.7	1.043
F03373	14.7	1.043
F03374	11.3	1.045
F03375	17.9	1.043
F03376	15.3	1.043
Number of females	6	6
Mean	13.3	1.046
S.D.	3.1	0.005
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 28-2 (Continued) Individual urinary examination of female rats on termination of recovery period

Female No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen	Urinary sediments				
									Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F03371	Light yellow	8.5	-	-	-	-	-	±	±	±	±	-	+
F03372	Light yellow	8.5	±	-	-	-	-	±	±	±	±	-	-
F03373	Light yellow	9.0	-	-	-	-	-	±	±	±	±	-	-
F03374	Light yellow	9.0	+	-	-	-	-	±	±	±	±	-	-
F03375	Light yellow	8.5	-	-	-	-	-	±	±	±	±	-	+
F03376	Light yellow	8.5	±	-	-	-	±	±	±	±	±	-	+
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, +++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields, +++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 28-3 Individual urinary examination of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)		
Female No.	UV mL	S.G.
F04471	5.7	1.070
F04472	10.9	1.056
F04473	9.6	1.060
F04474	13.5	1.048
F04475	13.6	1.048
F04476	6.4	1.064
Number of females	6	6
Mean	10.0	1.058
S.D.	3.4	0.009
Significance		
Statistical method	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 28-3 (Continued) Individual urinary examination of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)										Urinary sediments					
Female No.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobilinogen			Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F04471	Light yellow	8.5	-	-	-	-	-	±	±	±	±	-	-	-	
F04472	Light yellow	9.0	±	-	-	-	-	±	±	±	±	-	-	+	
F04473	Light yellow	7.0	±	-	-	-	-	±	±	±	±	-	-	-	
F04474	Light yellow	9.0	±	-	-	-	-	±	±	±	±	-	-	-	
F04475	Light yellow	9.0	-	-	-	-	-	±	±	±	±	-	-	+	
F04476	Light yellow	8.5	-	-	-	-	-	±	±	±	±	-	-	+	
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	

Protein: -; negative, ±; 10~20 mg/dL, +; 30 mg/dL, ++; 100 mg/dL, +++; 300 mg/dL, +++++; 1000 mg/dL.

Glucose: -; negative, ±; 40~60 mg/dL, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++++; 2000 mg/dL.

Ketone body: -; negative, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; 0.5 mg/dL, ++; 1.0 mg/dL, +++; 2.0 mg/dL.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Urobilinogen: ±; normal, +; 1 mg/dL, ++; 4 mg/dL, +++; 8 mg/dL, +++++; 12 mg/dL.

Epithelial cells: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields +++++; ≥501 cells/100 fields.

Leukocytes: ±; 0~20 cells/100 fields, +; 21~100 cells/100 fields, ++; 101~200 cells/100 fields, +++; 201~500 cells/100 fields +++++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

## Appendix 29-1 Individual hematological examination of male rats on termination of administration period

(Control group)	Male No.	RBC 10 <sup>6</sup> /µL	HGB g/dL	HCT %	MCV fl	MCH pg	MCHC g/dL	PLT 10 <sup>6</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
	M01101	847	15.8	46.3	54.7	18.7	34.1	99.6	28	19.0	23.6	211.2
	M01102	853	16.2	47.6	55.8	19.0	34.0	83.1	29	20.9	24.5	189.4
	M01103	849	15.4	44.9	52.9	18.1	34.3	105.8	31	15.7	21.7	204.8
	M01104	806	15.2	44.4	55.1	18.9	34.2	111.9	30	18.7	21.1	232.9
	M01105	910	16.7	49.0	53.8	18.4	34.1	94.2	28	21.1	23.8	211.2
	M01106	929	15.9	48.3	52.0	17.1	32.9	92.2	27	23.5	22.8	198.8
Number of males		6	6	6	6	6	6	6	6	6	6	6
Mean		866	15.9	46.8	54.1	18.4	33.9	97.8	29	19.8	22.9	208.1
S.D.		45	0.5	1.9	1.4	0.7	0.5	10.3	1	2.7	1.3	14.7

(Continued)

## Appendix 29-1 (Continued) Individual hematological examination of male rats on termination of administration period

(Control group)						
Male No.	WBC $10^2/\mu\text{L}$	L %	N %	E %	B %	M %
M01101	40	87	12	1	0	0
M01102	51	86	13	0	0	1
M01103	56	83	16	1	0	0
M01104	57	87	13	0	0	0
M01105	54	83	17	0	0	0
M01106	76	91	7	2	0	0
Number of males	6	6	6	6	6	6
Mean	56	86.2	13.0	0.7	0.0	0.2
S.D.	12	3.0	3.5	0.8	0.0	0.4

## Appendix 29-2 Individual hematological examination of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)											
Male No.	RBC 10 <sup>6</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>6</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
M02201	876	15.8	47.8	54.6	18.0	33.1	85.1	27	21.1	24.9	196.8
M02202	895	16.0	47.8	53.4	17.9	33.5	113.5	37	24.8	25.6	211.2
M02203	903	17.1	50.7	56.1	18.9	33.7	105.4	37	23.6	25.8	213.4
M02204	892	15.9	46.4	52.0	17.8	34.3	89.0	29	24.0	23.7	211.2
M02205	823	15.5	45.4	55.2	18.8	34.1	89.7	33	20.2	24.5	225.2
M02206	854	16.1	46.6	54.6	18.9	34.5	101.2	38	15.9	19.0	204.8
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	874	16.1	47.5	54.3	18.4	33.9	97.3	34	21.6	23.9	210.4
S.D.	30	0.5	1.8	1.4	0.5	0.5	11.1	5	3.3	2.5	9.4
Significance											
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 29-2 (Continued) Individual hematological examination of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Male No.	WBC 10 <sup>2</sup> /μL	L %	N %	E %	B %	M %
M02201	74	81	17	2	0	0
M02202	45	92	8	0	0	0
M02203	56	83	14	2	0	1
M02204	54	92	8	0	0	0
M02205	67	87	12	0	0	1
M02206	64	89	10	0	0	1
Number of males	6	6	6	6	6	6
Mean	60	87.3	11.5	0.7	0.0	0.5
S.D.	10	4.6	3.6	1.0	0.0	0.5
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 29-3 Individual hematological examination of male rats on termination of administration period

(bumetizole group at 250 mg/kg)											
Male No.	RBC 10 <sup>4</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>4</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
M03301	882	16.2	48.0	54.4	18.4	33.8	106.0	32	19.9	21.5	211.2
M03302	853	16.8	48.2	56.5	19.7	34.9	113.6	26	19.7	22.9	213.4
M03303	857	16.6	47.7	55.7	19.4	34.8	97.5	38	23.8	25.4	202.7
M03304	831	15.9	46.4	55.8	19.1	34.3	94.8	35	17.6	22.2	215.7
M03305	837	16.2	47.9	57.2	19.4	33.8	76.7	25	16.2	22.6	200.7
M03306	838	15.7	46.3	55.3	18.7	33.9	109.8	36	23.2	24.2	215.7
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	850	16.2	47.4	55.8	19.1	34.3	99.7	32	20.1	23.1	209.9
S.D.	19	0.4	0.8	1.0	0.5	0.5	13.4	5	3.0	1.4	6.6
Significance											
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 29-3 (Continued) Individual hematological examination of male rats on termination of administration period

(bumetizole group at 250 mg/kg)

Male No.	WBC 10 <sup>3</sup> /µL	L %	N %	E %	B %	M %
M03301	44	88	11	0	0	1
M03302	53	85	14	0	0	1
M03303	54	93	6	1	0	0
M03304	60	86	14	0	0	0
M03305	46	84	16	0	0	0
M03306	97	91	9	0	0	0
Number of males	6	6	6	6	6	6
Mean	59	87.8	11.7	0.2	0.0	0.3
S.D.	19	3.5	3.7	0.4	0.0	0.5
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 29-4 Individual hematological examination of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)											
Male No.	RBC 10 <sup>4</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>4</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
M04401	795	15.4	45.1	56.7	19.4	34.1	100.8	33	17.1	22.9	193.0
M04402	905	16.4	47.9	52.9	18.1	34.2	93.2	23	19.3	22.5	202.7
M04403	919	17.0	49.9	54.3	18.5	34.1	89.9	30	20.8	22.8	191.2
M04404	817	14.8	43.7	53.5	18.1	33.9	95.4	27	17.4	19.4	204.8
M04405	912	16.5	48.7	53.4	18.1	33.9	90.5	34	27.4	30.8	189.4
M04406	817	15.5	45.1	55.2	19.0	34.4	94.1	29	16.0	22.4	196.8
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	861	15.9	46.7	54.3	18.5	34.1	94.0	29	19.7	23.5	196.3
S.D.	57	0.8	2.4	1.4	0.6	0.2	3.9	4	4.2	3.8	6.3
Significance											
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 29-4 (Continued) Individual hematological examination of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Male No.	WBC 10 <sup>2</sup> /µL	L %	N %	E %	B %	M %
M04401	55	82	17	0	0	1
M04402	67	88	9	2	0	1
M04403	84	89	10	1	0	0
M04404	59	93	6	0	0	1
M04405	61	84	15	0	0	1
M04406	57	89	11	0	0	0
Number of males	6	6	6	6	6	6
Mean	64	87.5	11.3	0.5	0.0	0.7
S.D.	11	3.9	4.0	0.8	0.0	0.5
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 30-1 Individual hematological examination of female rats on termination of administration period

(Control group)											
Female No.	RBC 10 <sup>6</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>3</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
F01151	662	14.2	39.7	50.0	21.5	35.8	119.6	63	16.9	15.8	200.1
F01152	712	14.5	41.9	58.8	20.4	34.6	108.5	65	16.1	16.8	264.4
F01153	756	15.4	43.5	57.5	20.4	35.4	105.3	51	15.9	16.9	202.1
F01154	708	14.7	42.2	59.6	20.8	34.8	107.6	57	15.8	17.5	231.2
F01155	736	14.5	43.0	58.4	19.7	33.7	115.0	74	15.4	15.7	222.8
F01156	758	14.8	41.9	55.3	19.5	35.3	99.6	44	15.4	16.9	224.9
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	722	14.7	42.0	58.3	20.4	34.9	109.3	59	15.9	16.6	224.3
S.D.	36	0.4	1.3	1.7	0.7	0.7	7.1	11	0.6	0.7	23.4

(Continued)

## Appendix 30-1 (Continued) Individual hematological examination of female rats on termination of administration period

(Control group)						
Female No.	WBC $10^2/\mu\text{L}$	L %	N %	E %	B %	M %
F01151	54	82	18	0	0	0
F01152	68	86	12	1	0	1
F01153	46	88	10	2	0	0
F01154	32	82	17	0	0	1
F01155	29	87	9	2	0	2
F01156	46	79	20	0	0	1
Number of females	6	6	6	6	6	6
Mean	46	84.0	14.3	0.8	0.0	0.8
S.D.	14	3.5	4.6	1.0	0.0	0.8

## Appendix 30-2 Individual hematological examination of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)											
Female No.	RBC $10^4/\mu\text{L}$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT $10^4/\mu\text{L}$	RET %	PT sec.	APTT sec.	Fbg mg/dL
F02251	637	13.5	38.0	59.7	21.2	35.5	97.4	53	16.1	17.7	204.2
F02252	741	14.9	42.7	57.6	20.1	34.9	71.1	60	15.7	16.7	180.4
F02253	690	13.6	38.9	56.4	19.7	35.0	103.3	53	16.5	15.1	226.3
F02254	694	14.2	40.2	57.9	20.5	35.3	85.4	55	16.6	17.1	208.7
F02255	691	14.6	43.0	62.2	21.1	34.0	98.4	72	15.8	15.7	180.0
F02256	666	14.1	38.1	57.2	21.2	37.0	82.5	62	16.5	18.3	270.2
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	687	14.2	40.2	58.5	20.6	35.3	89.7	59	16.2	16.8	211.6
S.D.	34	0.5	2.2	2.1	0.6	1.0	12.1	7	0.4	1.2	33.7
Significance	**										
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

Significantly different from control group (\*\*: P&lt;0.01).

(Continued)

DU: Analysis by Dunnett's test.

## Appendix 30-2 (Continued) Individual hematological examination of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)						
Female No.	WBC 10 <sup>2</sup> /µL	L %	N %	E %	B %	M %
F02251	55	76	23	0	0	1
F02252	30	86	14	0	0	0
F02253	34	91	8	0	0	1
F02254	29	95	5	0	0	0
F02255	44	79	17	2	0	2
F02256	44	83	16	0	0	1
Number of females	6	6	6	6	6	6
Mean	39	85.0	13.8	0.3	0.0	0.8
S.D.	10	7.2	6.5	0.8	0.0	0.8
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 30-3 Individual hematological examination of female rats on termination of administration period

(bumetizole group at 250 mg/kg)											
Female No.	RBC 10 <sup>6</sup> /μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>3</sup> /μL	RET %	PT sec.	APTT sec.	Fbg mg/dL
F03351	768	15.4	44.4	57.8	20.1	34.7	102.7	57	15.6	17.9	250.0
F03352	699	13.5	40.1	57.4	19.3	33.7	96.2	71	15.7	16.8	173.1
F03353	723	14.3	41.4	57.3	19.8	34.5	94.9	74	16.3	17.3	253.5
F03354	726	14.2	40.4	55.6	19.6	35.1	94.3	60	15.9	17.7	192.9
F03355	693	13.6	40.8	58.9	19.6	33.3	77.4	75	16.4	15.7	206.4
F03356	704	13.5	39.7	56.4	19.2	34.0	104.3	73	16.5	17.4	212.8
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	719	14.1	41.1	57.2	19.6	34.2	95.0	68	16.1	17.1	214.8
S.D.	27	0.7	1.7	1.1	0.3	0.7	9.6	8	0.4	0.8	31.7
Significance	*										
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

Significantly different from control group (\*: P&lt;0.05).

(Continued)

DU: Analysis by Dunnett's test.

## Appendix 30-3 (Continued) Individual hematological examination of female rats on termination of administration period

(bumetizole group at 250 mg/kg)						
Female No.	WBC 10 <sup>3</sup> /μL	L %	N %	E %	B %	M %
F03351	49	81	16	1	0	2
F03352	36	80	19	0	0	1
F03353	54	75	22	1	0	2
F03354	42	86	14	0	0	0
F03355	36	91	9	0	0	0
F03356	41	89	11	0	0	0
Number of females	6	6	6	6	6	6
Mean	43	83.7	15.2	0.3	0.0	0.8
S.D.	7	6.1	4.9	0.5	0.0	1.0
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 30-4 Individual hematological examination of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)											
Female No.	RBC 10 <sup>6</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>3</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
F04451	773	15.6	45.2	58.5	20.2	34.5	84.0	49	15.2	17.2	184.5
F04452	754	15.3	44.1	58.5	20.3	34.7	97.0	70	15.4	16.1	220.3
F04453	681	14.2	41.6	61.1	20.9	34.1	104.1	92	16.6	18.1	241.2
F04454	716	14.4	40.5	56.6	20.1	35.6	98.5	64	15.9	17.7	224.9
F04455	680	13.5	39.1	57.5	19.9	34.5	91.9	61	15.5	17.6	212.6
F04456	721	14.3	41.5	57.6	19.8	34.5	102.3	70	17.1	15.9	193.5
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	721	14.6	42.0	58.3	20.2	34.7	96.3	68	16.0	17.1	212.8
S.D.	38	0.8	2.3	1.5	0.4	0.5	7.4	14	0.8	0.9	20.9
Significance											
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 30-4 (Continued) Individual hematological examination of female rats on termination of administration period

## (bumetizole group at 1000 mg/kg)

Female No.	WBC 10 <sup>2</sup> /µL	L %	N %	E %	B %	M %
F04451	51	82	15	2	0	1
F04452	32	86	11	2	0	1
F04453	39	87	12	0	0	1
F04454	40	86	13	1	0	0
F04455	34	85	14	0	0	1
F04456	35	91	8	1	0	0
Number of females	6	6	6	6	6	6
Mean	39	86.2	12.2	1.0	0.0	0.7
S.D.	7	2.9	2.5	0.9	0.0	0.5
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 31-1 Individual hematological examination of male rats on termination of recovery period

(Control group)	Male No.	RBC 10 <sup>6</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>6</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
	M01107	915	16.3	48.3	52.8	17.8	33.7	98.8	24	18.5	19.1	191.2
	M01108	900	16.0	48.0	53.3	17.8	33.3	96.9	27	22.8	25.3	198.4
	M01109	844	15.9	45.7	54.1	18.8	34.8	102.5	31	17.2	22.6	206.1
	M01110	834	15.2	45.2	54.2	18.2	33.6	96.9	34	17.0	19.0	184.5
	M01111	866	16.1	47.1	54.4	18.6	34.2	86.9	25	20.1	24.8	212.4
	M01112	847	15.7	46.2	54.5	18.5	34.0	113.7	25	20.5	22.3	202.2
Number of males		6	6	6	6	6	6	6	6	6	6	6
Mean		868	15.9	46.8	53.9	18.3	33.9	99.3	28	19.4	22.2	199.1
S.D.		33	0.4	1.3	0.7	0.4	0.5	8.8	4	2.2	2.7	10.1

(Continued)

## Appendix 31-1 (Continued) Individual hematological examination of male rats on termination of recovery period

(Control group)

Male No.	WBC $10^2/\mu\text{L}$	L %	N %	E %	B %	M %
M01107	53	86	12	1	0	1
M01108	68	93	7	0	0	0
M01109	58	86	13	0	0	1
M01110	48	89	10	1	0	0
M01111	47	86	12	1	0	1
M01112	73	92	7	0	0	1
Number of males	6	6	6	6	6	6
Mean	58	88.7	10.2	0.5	0.0	0.7
S.D.	11	3.2	2.6	0.5	0.0	0.5

## Appendix 31-2 Individual hematological examination of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)											
Male No.	RBC 10 <sup>4</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>4</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
M02207	871	16.1	47.7	54.8	18.5	33.8	92.8	27	16.2	21.5	181.3
M02208	770	15.5	44.1	57.3	20.1	35.1	92.9	26	19.0	23.4	189.5
M02209	842	15.4	45.3	53.8	18.3	34.0	96.7	27	15.8	22.1	196.5
M02210	829	14.1	42.6	51.4	17.0	33.1	104.7	29	18.4	20.4	189.5
M02211	854	15.8	46.2	54.1	18.5	34.2	110.6	32	18.7	21.9	206.1
M02212	878	16.2	47.8	54.4	18.5	33.9	114.5	19	16.1	21.8	212.4
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	841	15.5	45.6	54.3	18.5	34.0	102.0	27	17.4	21.9	195.9
S.D.	39	0.8	2.0	1.9	1.0	0.6	9.3	4	1.5	1.0	11.6
Significance											
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 31-2 (Continued) Individual hematological examination of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)

Male No.	WBC 10 <sup>3</sup> /µL	L %	N %	E %	B %	M %
M02207	63	93	5	1	0	1
M02208	54	81	18	1	0	0
M02209	52	91	7	1	0	1
M02210	80	86	13	1	0	0
M02211	49	85	14	0	0	1
M02212	69	83	15	0	0	2
Number of males	6	6	6	6	6	6
Mean	61	86.5	12.0	0.7	0.0	0.8
S.D.	12	4.6	5.0	0.5	0.0	0.8
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 31-3 Individual hematological examination of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)											
Male No.	RBC 10 <sup>4</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>4</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
M03307	875	15.6	46.5	53.1	17.8	33.5	100.7	43	19.5	21.9	194.7
M03308	880	16.2	48.1	54.7	18.4	33.7	104.3	34	17.4	23.7	204.1
M03309	827	14.9	44.7	54.1	18.0	33.3	118.2	34	19.3	20.6	181.3
M03310	856	15.9	46.9	54.8	18.6	33.9	113.9	40	16.7	20.8	169.6
M03311	835	15.5	45.3	54.3	18.6	34.2	90.5	24	16.4	22.1	202.2
M03312	882	16.6	49.7	56.3	18.8	33.4	98.2	22	20.7	22.2	189.5
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	859	15.8	46.9	54.6	18.4	33.7	104.3	33	18.3	21.9	190.2
S.D.	24	0.6	1.8	1.1	0.4	0.3	10.3	8	1.7	1.1	13.1
Significance											
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 31-3 (Continued) Individual hematological examination of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)

Male No.	WBC 10 <sup>3</sup> /µL	L %	N %	E %	B %	M %
M03307	91	93	7	0	0	0
M03308	67	85	14	1	0	0
M03309	72	89	10	0	0	1
M03310	55	89	8	2	0	1
M03311	47	75	23	1	0	1
M03312	44	91	9	0	0	0
Number of males	6	6	6	6	6	6
Mean	63	87.0	11.8	0.7	0.0	0.5
S.D.	18	6.4	6.0	0.8	0.0	0.5
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 31-4 Individual hematological examination of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)											
Male No.	RBC 10 <sup>6</sup> /µL	HGB g/dL	HCT %	MCV fl	MCH pg	MCHC g/dL	PLT 10 <sup>6</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
M04407	794	15.0	44.4	55.9	18.9	33.8	100.1	39	19.6	21.6	176.7
M04408	856	14.5	44.0	51.4	16.9	33.0	109.1	25	18.6	22.6	194.7
M04409	881	16.3	49.1	55.7	18.5	33.2	106.9	29	21.5	22.3	196.5
M04410	787	14.8	43.0	54.6	18.8	34.4	81.6	19	21.3	23.2	189.5
M04411	875	15.6	46.6	53.3	17.8	33.5	115.4	26	19.0	23.7	191.2
M04412	881	16.1	47.6	54.0	18.3	33.8	87.0	36	20.1	24.5	172.4
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	846	15.4	45.8	54.2	18.2	33.6	100.0	29	20.0	23.0	186.8
S.D.	44	0.7	2.4	1.7	0.7	0.5	13.2	7	1.2	1.0	9.9
Significance											
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 31-4 (Continued) Individual hematological examination of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)						
Male No.	WBC 10 <sup>2</sup> /µL	L %	N %	E %	B %	M %
M04407	45	95	5	0	0	0
M04408	83	90	8	0	0	2
M04409	57	84	14	2	0	0
M04410	59	88	10	1	0	1
M04411	59	87	12	0	0	1
M04412	60	83	14	2	0	1
Number of males	6	6	6	6	6	6
Mean	61	87.8	10.5	0.8	0.0	0.8
S.D.	12	4.4	3.6	1.0	0.0	0.8
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 32-1 Individual hematological examination of female rats on termination of recovery period

(Control group)											
Female No.	RBC 10 <sup>4</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>4</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
F01171	777	15.6	44.9	57.8	20.1	34.7	104.5	21	15.9	17.1	165.2
F01172	729	14.5	42.6	58.4	19.9	34.0	94.5	30	16.9	19.7	146.5
F01173	754	15.2	43.0	57.0	20.2	35.3	90.8	23	14.7	19.0	163.9
F01174	773	14.7	42.2	54.6	19.0	34.8	125.2	35	15.2	17.7	167.9
F01175	778	15.4	44.6	57.3	19.8	34.5	70.4	20	13.8	17.1	161.3
F01176	755	14.6	42.3	56.0	19.3	34.5	81.6	32	14.7	16.9	150.7
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	761	15.0	43.3	56.9	19.7	34.6	94.5	27	15.2	17.9	159.3
S.D.	19	0.5	1.2	1.4	0.5	0.4	19.0	6	1.1	1.2	8.6

(Continued)

## Appendix 32-1 (Continued) Individual hematological examination of female rats on termination of recovery period

## (Control group)

Female No.	WBC $10^2/\mu\text{L}$	L %	N %	E %	B %	M %
F01171	26	81	18	0	0	1
F01172	27	90	9	0	0	1
F01173	39	86	12	0	0	2
F01174	35	83	17	0	0	0
F01175	33	84	14	1	0	1
F01176	23	79	21	0	0	0
Number of females	6	6	6	6	6	6
Mean	31	83.8	15.2	0.2	0.0	0.8
S.D.	6	3.9	4.4	0.4	0.0	0.8

## Appendix 32-2 Individual hematological examination of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)											
Female No.	RBC 10 <sup>6</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>6</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
F03371	759	15.5	43.4	57.2	20.4	35.7	88.2	28	14.8	19.5	161.3
F03372	785	15.1	42.8	54.5	19.2	35.3	97.0	28	15.8	17.5	170.6
F03373	761	15.0	42.0	55.2	19.7	35.7	98.6	20	15.2	16.3	165.2
F03374	762	14.2	40.7	53.4	18.6	34.9	94.1	26	14.8	16.0	155.3
F03375	705	14.0	39.2	55.6	19.9	35.7	97.5	25	15.0	17.2	166.5
F03376	687	13.8	38.9	56.6	20.1	35.5	93.1	35	15.2	17.2	157.7
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	743	14.6	41.2	55.4	19.7	35.5	94.8	27	15.1	17.3	162.8
S.D.	38	0.7	1.9	1.4	0.7	0.3	3.8	5	0.4	1.2	5.7
Significance	**										
Statistical method	DU	DU	DU	DU	DU	DU	DT	DU	DT	DU	DU

Significantly different from control group (\*\*: P&lt;0.01).

(Continued)

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 32-2 (Continued) Individual hematological examination of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)						
Female No.	WBC 10 <sup>3</sup> /µL	L %	N %	E %	B %	M %
F03371	20	80	19	1	0	0
F03372	31	92	7	1	0	0
F03373	31	87	11	1	0	1
F03374	23	89	10	0	0	1
F03375	50	87	11	1	0	1
F03376	41	83	15	1	0	1
Number of females	6	6	6	6	6	6
Mean	33	86.3	12.2	0.8	0.0	0.7
S.D.	11	4.3	4.2	0.4	0.0	0.5
Significance						
Statistical method	DU	DU	DU	DU	UA	DU

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 32-3 Individual hematological examination of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)											
Female No.	RBC 10 <sup>4</sup> /µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10 <sup>4</sup> /µL	RET %	PT sec.	APTT sec.	Fbg mg/dL
F04471	739	14.2	41.0	55.5	19.2	34.6	104.8	22	15.1	17.3	162.6
F04472	764	15.1	43.7	57.2	19.8	34.6	85.2	30	15.5	18.1	165.2
F04473	800	15.4	45.0	56.3	19.3	34.2	89.6	22	14.8	17.8	160.1
F04474	765	15.0	42.6	55.7	19.6	35.2	100.6	22	14.9	16.4	169.3
F04475	764	14.9	42.6	55.8	19.5	35.0	97.5	32	15.6	15.5	170.6
F04476	727	14.4	41.5	57.1	19.8	34.7	79.4	25	15.2	16.7	155.3
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	760	14.8	42.7	56.3	19.5	34.7	92.9	26	15.2	17.0	163.9
S.D.	25	0.5	1.5	0.7	0.3	0.3	9.7	4	0.3	1.0	5.8
Significance											
Statistical method	DU	DU	DU	DU	DU	DU	DT	DU	DT	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

(Continued)

## Appendix 32-3 (Continued) Individual hematological examination of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)

Female No.	WBC 10 <sup>2</sup> /μL	L %	N %	E %	B %	M %
F04471	28	93	5	2	0	0
F04472	27	93	6	0	0	1
F04473	32	87	10	2	0	1
F04474	46	85	15	0	0	0
F04475	26	89	10	0	0	1
F04476	41	90	9	1	0	0
Number of females	6	6	6	6	6	6
Mean	33	89.5	9.2	0.8	0.0	0.5
S.D.	8	3.2	3.5	1.0	0.0	0.5
Significance	*	*				
Statistical method	DU	DU	DU	DU	UA	DU

Significantly different from control group (\*: P&lt;0.05).

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 33-1 Individual blood chemical examination of male rats on termination of administration period

(Control group)	Male No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
	M01101	87.5	27.5	351.6	0.12
	M01102	72.0	22.3	371.3	0.15
	M01103	75.2	21.3	212.8	0.43
	M01104	97.0	26.7	371.4	0.63
	M01105	79.9	20.3	390.7	0.58
	M01106	63.8	13.8	278.6	0.23
	Number of males	6	6	6	6
	Mean	79.2	22.0	329.4	0.36
	S.D.	11.8	5.0	69.2	0.22

(Continued)

## Appendix 33-1 (Continued) Individual blood chemical examination of male rats on termination of administration period

(Control group)			
Male No.	TP g/dL	Alb g/dL	A/G
M01101	5.87	3.02	1.06
M01102	5.41	2.68	0.98
M01103	5.80	2.78	0.92
M01104	5.68	2.87	1.02
M01105	5.81	2.92	1.01
M01106	5.74	2.74	0.92
Number of males	6	6	6
Mean	5.72	2.84	0.99
S.D.	0.16	0.13	0.06

(Continued)

## Appendix 33-1 (Continued) Individual blood chemical examination of male rats on termination of administration period

(Control group)	Male No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
	M01101	0.14	16.5	0.34	104.8	49.2	66.3
	M01102	0.12	20.0	0.34	122.4	45.9	29.3
	M01103	0.13	16.4	0.31	107.8	61.9	35.3
	M01104	0.14	19.0	0.26	121.0	81.0	43.4
	M01105	0.14	19.6	0.28	116.5	61.7	39.7
	M01106	0.13	19.0	0.26	117.8	47.6	24.4
Number of males		6	6	6	6	6	6
Mean		0.13	18.4	0.30	115.1	57.9	39.7
S.D.		0.01	1.6	0.04	7.2	13.3	14.7

(Continued)

## Appendix 33-1 (Continued) Individual blood chemical examination of male rats on termination of administration period

(Control group)	Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
	M01101	143.6	4.13	104.3	9.8	6.4
	M01102	145.7	4.15	106.3	9.5	6.5
	M01103	143.6	4.51	104.7	9.6	7.4
	M01104	143.5	4.68	105.4	9.8	8.3
	M01105	144.2	4.29	107.4	9.9	6.9
	M01106	146.2	4.13	105.7	9.8	7.5
	Number of males	6	6	6	6	6
	Mean	144.5	4.32	105.6	9.7	7.2
	S.D.	1.2	0.23	1.1	0.2	0.7

## Appendix 33-2 Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Male No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
M02201	91.1	29.8	353.0	0.23
M02202	70.2	19.8	439.6	0.26
M02203	82.8	27.6	344.1	0.45
M02204	90.1	20.6	396.5	0.22
M02205	76.2	20.4	302.1	0.20
M02206	84.8	25.4	387.2	0.46
Number of males	6	6	6	6
Mean	82.5	23.9	370.4	0.30
S.D.	8.1	4.3	47.8	0.12
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 33-2 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)			
Male No.	TP g/dL	Alb g/dL	A/G
M02201	5.60	2.96	1.12
M02202	5.39	2.84	1.11
M02203	5.65	2.67	0.90
M02204	5.07	2.56	1.02
M02205	5.12	2.68	1.10
M02206	5.63	2.84	1.02
Number of males	6	6	6
Mean	5.41	2.76	1.05
S.D.	0.26	0.15	0.08
Significance	*		
Statistical method	DU	DU	DU

Significantly different from control group (\*: P&lt;0.05).

(Continued)

DU: Analysis by Dunnett's test.

## Appendix 33-2 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)						
Male No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
M02201	0.11	17.7	0.31	122.4	38.1	33.4
M02202	0.12	18.9	0.35	107.5	44.8	50.0
M02203	0.13	19.5	0.29	115.4	55.8	26.6
M02204	0.12	17.3	0.26	121.0	42.9	46.1
M02205	0.11	15.5	0.30	120.2	52.7	41.9
M02206	0.12	18.8	0.29	110.9	74.4	19.8
Number of males	6	6	6	6	6	6
Mean	0.12	18.0	0.30	116.2	51.5	36.3
S.D.	0.01	1.5	0.03	6.0	13.0	11.7
Significance	*					
Statistical method	DU	DU	DU	DU	DU	DU

Significantly different from control group (\*: P&lt;0.05).

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 33-2 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
M02201	146.2	4.61	107.2	9.3	6.5
M02202	145.5	4.29	106.8	9.6	7.3
M02203	146.0	4.58	107.8	9.4	6.7
M02204	145.0	4.21	106.8	9.2	7.8
M02205	146.0	4.39	106.9	9.6	7.0
M02206	146.5	4.42	106.6	9.7	8.5
Number of males	6	6	6	6	6
Mean	145.9	4.42	107.0	9.5	7.3
S.D.	0.5	0.16	0.4	0.2	0.7
Significance			*		
Statistical method	DU	DU	DU	DU	DU

Significantly different from control group (\*: P&lt;0.05).

DU: Analysis by Dunnett's test.

## Appendix 33-3 Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 250 mg/kg)

Male No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
M03301	78.8	26.6	438.0	0.22
M03302	74.5	34.3	513.6	0.36
M03303	100.3	17.3	313.0	0.35
M03304	86.7	24.3	357.4	0.76
M03305	69.5	16.5	317.3	0.00
M03306	89.4	19.6	342.6	0.25
Number of males	6	6	6	6
Mean	83.2	23.1	380.3	0.32
S.D.	11.2	6.8	79.4	0.25
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 33-3 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 250 mg/kg)			
Male No.	TP g/dL	Alb g/dL	A/G
M03301	5.63	2.81	1.00
M03302	5.73	3.01	1.11
M03303	5.46	2.83	1.08
M03304	5.27	2.67	1.03
M03305	5.50	2.80	1.04
M03306	5.54	3.01	1.19
Number of males	6	6	6
Mean	5.52	2.86	1.08
S.D.	0.16	0.13	0.07
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 33-3 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 250 mg/kg)						
Male No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
M03301	0.13	19.0	0.30	116.8	41.3	55.4
M03302	0.11	17.8	0.29	108.9	54.2	50.3
M03303	0.11	19.6	0.29	129.9	46.4	18.3
M03304	0.14	18.2	0.26	133.0	60.1	59.2
M03305	0.12	17.9	0.28	121.6	73.8	40.2
M03306	0.12	13.7	0.29	91.9	59.5	23.7
Number of males	6	6	6	6	6	6
Mean	0.12	17.7	0.29	117.0	55.9	41.2
S.D.	0.01	2.1	0.01	15.1	11.5	17.0
Significance						
Statistical method	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 33-3 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 250 mg/kg)					
Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
M03301	144.4	4.13	106.8	9.4	7.0
M03302	144.7	4.20	106.9	9.8	7.1
M03303	145.5	4.30	104.8	9.5	8.4
M03304	145.3	4.07	106.5	9.7	7.6
M03305	146.5	4.19	106.4	9.6	7.6
M03306	144.5	4.66	106.9	9.6	7.4
Number of males	6	6	6	6	6
Mean	145.2	4.26	106.4	9.6	7.5
S.D.	0.8	0.21	0.8	0.1	0.5
Significance					
Statistical method	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 33-4 Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)				
Male No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L
M04401	87.1	33.0	297.7	0.48
M04402	80.8	21.3	412.7	0.47
M04403	100.1	46.4	373.5	0.37
M04404	132.0	28.8	362.2	0.85
M04405	76.8	23.1	318.8	0.26
M04406	69.8	14.8	272.8	0.34
Number of males	6	6	6	6
Mean	91.1	27.9	339.6	0.46
S.D.	22.5	11.0	52.3	0.21
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 33-4 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)			
Male No.	TP g/dL	Alb g/dL	A/G
M04401	5.42	2.78	1.05
M04402	5.43	2.79	1.05
M04403	5.77	2.98	1.07
M04404	5.38	2.70	1.00
M04405	5.28	2.66	1.02
M04406	5.67	3.00	1.12
Number of males	6	6	6
Mean	5.49	2.82	1.05
S.D.	0.19	0.14	0.04
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 33-4 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Male No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
M04401	0.11	17.6	0.32	104.8	54.2	25.6
M04402	0.11	18.4	0.30	122.6	67.6	67.4
M04403	0.13	19.4	0.30	136.5	62.6	106.0
M04404	0.13	18.9	0.29	131.5	44.5	33.6
M04405	0.10	18.8	0.27	112.2	32.8	51.7
M04406	0.11	16.2	0.27	107.8	62.4	43.0
Number of males	6	6	6	6	6	6
Mean	0.12	18.2	0.29	119.2	54.0	54.6
S.D.	0.01	1.2	0.02	13.0	13.2	29.1
Significance	*					
Statistical method	DU	DU	DU	DU	DU	DU

Significantly different from control group (\*: P&lt;0.05).

(Continued)

DU: Analysis by Dunnett's test.

## Appendix 33-4 (Continued) Individual blood chemical examination of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)					
Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
M04401	145.0	4.31	105.4	9.3	6.3
M04402	143.9	4.33	107.2	9.5	7.1
M04403	144.3	4.08	106.5	9.9	8.0
M04404	144.2	4.34	105.5	9.6	7.8
M04405	146.1	4.22	106.6	9.3	8.6
M04406	147.0	4.09	105.9	9.8	7.4
Number of males	6	6	6	6	6
Mean	145.1	4.23	106.2	9.6	7.5
S.D.	1.2	0.12	0.7	0.3	0.8
Significance					
Statistical method	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 34-1 Individual blood chemical examination of female rats on termination of administration period

(Control group)	Female No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
	F01151	94.4	20.5	126.7	0.32
	F01152	89.0	20.0	156.2	0.61
	F01153	84.2	14.5	124.0	0.81
	F01154	95.1	16.8	151.4	0.57
	F01155	87.2	18.2	117.2	0.54
	F01156	62.4	15.3	133.5	0.46
	Number of females	6	6	6	6
	Mean	85.4	17.6	134.8	0.55
	S.D.	12.0	2.5	15.7	0.16

(Continued)

## Appendix 34-1 (Continued) Individual blood chemical examination of female rats on termination of administration period

(Control group)			
Female No.	TP g/dL	Alb g/dL	A/G
F01151	5.56	2.72	0.96
F01152	6.02	2.87	0.91
F01153	6.00	3.19	1.13
F01154	6.08	2.89	0.90
F01155	6.44	3.45	1.15
F01156	5.78	2.81	0.95
Number of females	6	6	6
Mean	5.98	2.99	1.00
S.D.	0.30	0.28	0.11

(Continued)

## Appendix 34-1 (Continued) Individual blood chemical examination of female rats on termination of administration period

(Control group)						
Female No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
F01151	0.13	28.0	0.44	105.4	75.7	24.6
F01152	0.13	22.5	0.41	109.3	67.8	30.4
F01153	0.12	23.2	0.37	122.3	76.3	36.8
F01154	0.11	19.6	0.37	108.3	67.4	40.9
F01155	0.13	24.8	0.39	100.8	73.5	24.0
F01156	0.12	22.6	0.40	125.4	65.2	27.4
Number of females	6	6	6	6	6	6
Mean	0.12	23.5	0.40	111.9	71.0	30.7
S.D.	0.01	2.8	0.03	9.8	4.8	6.8

(Continued)

## Appendix 34-1 (Continued) Individual blood chemical examination of female rats on termination of administration period

(Control group)					
Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
F01151	140.1	4.38	105.7	10.4	7.1
F01152	139.6	4.34	104.1	10.3	6.6
F01153	139.6	4.19	104.8	10.1	6.0
F01154	139.3	4.23	102.5	10.2	6.4
F01155	139.5	4.57	104.2	10.4	6.1
F01156	138.5	3.88	100.8	10.3	6.9
Number of females	6	6	6	6	6
Mean	139.4	4.27	103.7	10.3	6.5
S.D.	0.5	0.23	1.8	0.1	0.4

## Appendix 34-2 Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Female No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
F02251	77.0	29.8	201.7	0.48
F02252	84.3	15.4	119.2	0.60
F02253	89.5	18.3	214.3	0.58
F02254	61.9	16.4	146.7	0.50
F02255	81.9	12.9	225.9	0.42
F02256	86.9	26.1	188.5	0.85
Number of females	6	6	6	6
Mean	80.3	19.8	182.7	0.57
S.D.	10.0	6.6	41.4	0.15
Significance				
Statistical method	DU	DT	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 34-2 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)			
Female No.	TP g/dL	Alb g/dL	A/G
F02251	6.21	3.14	1.03
F02252	5.79	3.00	1.07
F02253	6.40	3.30	1.06
F02254	6.45	3.13	0.94
F02255	6.26	3.35	1.15
F02256	6.13	2.70	0.79
Number of females	6	6	6
Mean	6.21	3.10	1.01
S.D.	0.24	0.23	0.13
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 34-2 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)						
Female No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
F02251	0.14	22.5	0.36	122.8	91.0	36.6
F02252	0.12	22.0	0.38	118.3	92.2	50.2
F02253	0.13	23.4	0.38	114.5	83.1	31.6
F02254	0.11	25.1	0.41	113.4	73.7	17.2
F02255	0.14	22.0	0.38	125.7	62.4	21.9
F02256	0.14	24.4	0.38	112.0	62.6	34.1
Number of females	6	6	6	6	6	6
Mean	0.13	23.2	0.38	117.8	77.5	31.9
S.D.	0.01	1.3	0.02	5.5	13.4	11.6
Significance						
Statistical method	DU	DU	DU	DU	DT	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 34-2 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)					
Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
F02251	139.5	3.82	102.3	10.8	7.0
F02252	140.9	4.01	105.0	10.2	5.9
F02253	138.0	4.41	102.5	10.3	6.8
F02254	140.4	4.00	104.3	10.5	7.2
F02255	141.7	3.98	107.5	10.1	6.5
F02256	139.0	4.08	99.9	10.5	7.5
Number of females	6	6	6	6	6
Mean	139.9	4.05	103.6	10.4	6.8
S.D.	1.3	0.20	2.6	0.3	0.6
Significance					
Statistical method	DT	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 34-3 Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 250 mg/kg)				
Female No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L
F03351	74.7	15.0	208.6	0.69
F03352	71.7	13.3	80.9	0.25
F03353	75.5	16.2	157.6	0.59
F03354	81.9	18.3	109.4	0.32
F03355	89.0	15.6	180.9	0.55
F03356	80.0	18.3	164.8	0.60
Number of females	6	6	6	6
Mean	78.8	16.1	150.4	0.50
S.D.	6.2	1.9	47.1	0.17
Significance				
Statistical method	DU	DT	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 34-3 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 250 mg/kg)			
Female No.	TP g/dL	Alb g/dL	A/G
F03351	6.58	3.20	0.95
F03352	5.62	2.77	0.97
F03353	5.99	3.02	1.02
F03354	6.14	3.20	1.09
F03355	5.99	2.97	0.98
F03356	6.34	3.27	1.06
Number of females	6	6	6
Mean	6.11	3.07	1.01
S.D.	0.33	0.19	0.05
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 34-3 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 250 mg/kg)						
Female No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
F03351	0.13	20.2	0.33	109.5	80.4	80.5
F03352	0.11	23.7	0.38	113.6	53.6	18.3
F03353	0.12	30.2	0.42	117.3	120.7	36.8
F03354	0.12	20.5	0.36	103.0	70.8	19.2
F03355	0.13	22.1	0.37	107.3	67.0	25.6
F03356	0.12	24.3	0.36	107.8	101.0	28.4
Number of females	6	6	6	6	6	6
Mean	0.12	23.5	0.37	109.8	82.3	34.8
S.D.	0.01	3.7	0.03	5.0	24.6	23.4
Significance						
Statistical method	DU	DU	DU	DU	DT	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 34-3 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 250 mg/kg)					
Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
F03351	140.1	4.14	103.8	10.7	7.7
F03352	137.8	4.38	103.8	9.9	7.1
F03353	140.3	3.90	103.5	11.0	7.8
F03354	140.1	4.21	106.2	9.9	5.8
F03355	142.6	4.28	105.4	10.0	6.7
F03356	140.3	4.63	102.4	10.4	6.8
Number of females	6	6	6	6	6
Mean	140.2	4.26	104.2	10.3	7.0
S.D.	1.5	0.24	1.4	0.5	0.7
Significance					
Statistical method	DT	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 34-4 Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)				
Female No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
F04451	76.7	27.4	205.2	0.37
F04452	78.3	16.9	176.2	0.48
F04453	93.9	18.5	164.9	0.44
F04454	63.0	15.3	158.9	0.64
F04455	76.4	19.9	138.5	0.56
F04456	87.3	17.9	149.6	0.82
Number of females	6	6	6	6
Mean	79.3	19.3	165.6	0.55
S.D.	10.6	4.3	23.3	0.16
Significance				
Statistical method	DU	DT	DU	DU

DU: Analysis by Dunnnett's test.

DT: Analysis by Dunnett type mean rank test.

(Continued)

## Appendix 34-4 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)			
Female No.	TP g/dL	Alb g/dL	A/G
F04451	6.45	3.48	1.17
F04452	6.02	2.88	0.92
F04453	6.13	3.05	0.99
F04454	6.34	3.29	1.08
F04455	6.16	3.01	0.96
F04456	5.82	2.88	0.98
Number of females	6	6	6
Mean	6.15	3.10	1.02
S.D.	0.22	0.24	0.09
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 34-4 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)						
Female No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
F04451	0.15	19.2	0.35	133.6	83.8	25.6
F04452	0.13	22.9	0.40	113.7	76.2	24.6
F04453	0.14	23.9	0.41	121.2	55.3	32.6
F04454	0.12	17.9	0.39	121.9	102.5	35.5
F04455	0.11	23.0	0.39	112.7	81.9	25.0
F04456	0.12	16.0	0.37	126.8	83.1	62.7
Number of females	6	6	6	6	6	6
Mean	0.13	20.5	0.39	121.7	80.5	34.3
S.D.	0.01	3.2	0.02	7.9	15.2	14.6
Significance						
Statistical method	DU	DU	DU	DU	DT	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 34-4 (Continued) Individual blood chemical examination of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
F04451	140.3	4.46	102.6	10.6	6.9
F04452	140.2	4.15	105.3	10.5	6.6
F04453	140.0	4.09	104.8	10.6	7.2
F04454	139.8	3.99	104.1	10.4	4.9
F04455	141.3	3.73	104.5	10.4	6.2
F04456	140.0	4.53	102.5	9.9	7.5
Number of females	6	6	6	6	6
Mean	140.3	4.16	104.0	10.4	6.6
S.D.	0.5	0.30	1.2	0.3	0.9
Significance					
Statistical method	DT	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 35-1 Individual blood chemical examination of male rats on termination of recovery period

(Control group)				
Male No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
M01107	91.4	30.9	333.1	0.40
M01108	74.9	33.7	276.7	0.37
M01109	67.2	26.1	225.8	0.31
M01110	100.9	33.2	259.8	0.42
M01111	84.4	31.3	329.8	0.82
M01112	75.5	37.7	299.7	0.44
Number of males	6	6	6	6
Mean	82.4	32.2	287.5	0.46
S.D.	12.3	3.8	41.7	0.18

(Continued)

## Appendix 35-1 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(Control group)			
Male No.	TP g/dL	Alb g/dL	A/G
M01107	5.64	2.90	1.06
M01108	5.49	2.66	0.94
M01109	5.50	2.83	1.05
M01110	5.16	2.51	0.95
M01111	5.30	2.75	1.08
M01112	5.61	2.65	0.89
Number of males	6	6	6
Mean	5.45	2.72	1.00
S.D.	0.19	0.14	0.08

(Continued)

## Appendix 35-1 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(Control group)	Male No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
	M01107	0.11	19.7	0.31	132.9	50.4	74.2
	M01108	0.11	22.8	0.33	122.7	56.1	28.6
	M01109	0.11	17.0	0.32	120.7	60.2	55.4
	M01110	0.09	20.6	0.32	131.9	63.1	34.6
	M01111	0.10	15.0	0.28	101.7	59.2	67.7
	M01112	0.11	17.0	0.29	136.7	47.3	26.8
	Number of males	6	6	6	6	6	6
	Mean	0.11	18.7	0.31	124.4	56.1	47.9
	S.D.	0.01	2.9	0.02	12.7	6.1	20.7

(Continued)

## Appendix 35-1 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(Control group)	Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
	M01107	143.0	4.37	103.4	9.3	5.2
	M01108	143.7	4.39	104.8	9.2	6.4
	M01109	143.8	4.18	105.7	9.3	6.0
	M01110	144.3	4.89	106.0	9.3	6.8
	M01111	145.0	4.08	106.7	9.5	7.0
	M01112	146.7	4.13	105.5	10.1	8.7
	Number of males	6	6	6	6	6
	Mean	144.4	4.34	105.4	9.5	6.7
	S.D.	1.3	0.30	1.1	0.3	1.2

## Appendix 35-2 Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)

Male No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
M02207	69.1	27.5	210.9	0.10
M02208	87.8	37.5	322.1	0.51
M02209	68.8	27.0	273.1	0.24
M02210	77.6	30.4	264.9	0.26
M02211	78.0	33.2	289.8	0.44
M02212	87.6	32.5	290.6	0.42
Number of males	6	6	6	6
Mean	78.2	31.4	275.2	0.33
S.D.	8.4	3.9	37.1	0.15
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 35-2 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)			
Male No.	TP g/dL	Alb g/dL	A/G
M02207	5.53	2.84	1.06
M02208	5.20	2.60	1.00
M02209	5.10	2.56	1.00
M02210	5.30	2.53	0.91
M02211	5.73	2.69	0.88
M02212	5.86	2.81	0.92
Number of males	6	6	6
Mean	5.45	2.67	0.96
S.D.	0.30	0.13	0.07
Significance			
Statistical method	DU	DT	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 35-2 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)						
Male No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
M02207	0.12	19.5	0.30	116.9	55.6	28.3
M02208	0.11	18.5	0.28	104.5	50.8	44.8
M02209	0.10	17.6	0.32	124.2	52.9	36.6
M02210	0.11	15.6	0.28	117.9	51.9	65.0
M02211	0.10	16.3	0.33	111.9	51.2	54.7
M02212	0.14	17.7	0.30	125.6	59.8	29.4
Number of males	6	6	6	6	6	6
Mean	0.11	17.5	0.30	116.8	53.7	43.1
S.D.	0.02	1.4	0.02	7.9	3.4	14.6
Significance						
Statistical method	DU	DU	DU	DU	DT	DU

DU: Analysis by Dunnnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 35-2 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)

Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
M02207	144.3	4.12	105.6	9.7	6.1
M02208	143.1	4.31	104.8	9.2	6.3
M02209	145.0	4.61	104.8	9.3	7.4
M02210	146.3	4.40	107.0	9.2	6.8
M02211	145.8	4.66	105.9	9.5	6.6
M02212	146.3	4.66	104.4	9.8	7.7
Number of males	6	6	6	6	6
Mean	145.1	4.46	105.4	9.5	6.8
S.D.	1.3	0.22	1.0	0.3	0.6
Significance					
Statistical method	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 35-3 Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)

Male No.	AST IU/L	ALT IU/L	ALP IU/L	$\gamma$ -GTP IU/L
M03307	75.0	28.6	324.7	0.38
M03308	85.2	34.2	259.6	0.41
M03309	81.1	30.6	332.1	0.40
M03310	79.1	31.2	300.8	0.47
M03311	74.7	31.4	296.5	0.25
M03312	82.1	38.4	365.7	0.44
Number of males	6	6	6	6
Mean	79.5	32.4	313.2	0.39
S.D.	4.1	3.4	36.2	0.08
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 35-3 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)			
Male No.	TP g/dL	Alb g/dL	A/G
M03307	5.11	2.70	1.12
M03308	5.34	2.68	1.00
M03309	5.51	2.71	0.97
M03310	5.16	2.76	1.15
M03311	5.81	2.71	0.87
M03312	5.53	2.70	0.95
Number of males	6	6	6
Mean	5.41	2.71	1.01
S.D.	0.26	0.03	0.11
Significance			
Statistical method	DU	DT	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 35-3 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)						
Male No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
M03307	0.11	19.8	0.33	124.6	42.7	25.2
M03308	0.10	22.8	0.35	106.6	56.2	45.1
M03309	0.13	17.5	0.29	96.9	57.2	57.1
M03310	0.13	18.1	0.33	133.9	70.2	60.7
M03311	0.12	16.6	0.32	109.9	71.1	62.4
M03312	0.12	19.0	0.32	147.3	56.7	40.0
Number of males	6	6	6	6	6	6
Mean	0.12	19.0	0.32	119.9	59.0	48.4
S.D.	0.01	2.2	0.02	18.8	10.5	14.4
Significance						
Statistical method	DU	DU	DU	DU	DT	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 35-3 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)					
Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
M03307	143.6	4.25	107.1	8.9	6.1
M03308	143.4	4.66	105.2	9.3	7.1
M03309	143.9	4.60	103.9	9.5	6.3
M03310	144.3	4.28	106.6	9.2	6.4
M03311	145.2	4.34	105.3	9.7	6.2
M03312	145.5	4.59	105.0	9.6	7.1
Number of males	6	6	6	6	6
Mean	144.3	4.45	105.5	9.4	6.5
S.D.	0.9	0.18	1.2	0.3	0.5
Significance					
Statistical method	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 35-4 Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)				
Male No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L
M04407	79.8	33.9	303.8	0.22
M04408	69.5	34.1	294.7	0.31
M04409	84.2	26.7	279.5	0.42
M04410	97.8	41.8	281.7	0.51
M04411	87.5	32.8	317.7	0.47
M04412	82.2	34.1	389.5	0.31
Number of males	6	6	6	6
Mean	83.5	33.9	311.2	0.37
S.D.	9.3	4.8	40.9	0.11
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 35-4 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)			
Male No.	TP g/dL	Alb g/dL	A/G
M04407	5.20	2.61	1.00
M04408	5.73	2.91	1.03
M04409	5.28	2.52	0.91
M04410	5.22	2.80	1.15
M04411	5.24	2.46	0.89
M04412	5.34	2.76	1.07
Number of males	6	6	6
Mean	5.34	2.68	1.01
S.D.	0.20	0.17	0.10
Significance			
Statistical method	DU	DT	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 35-4 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)

Male No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
M04407	0.11	17.6	0.30	134.1	46.7	36.3
M04408	0.12	22.4	0.33	104.6	67.2	52.2
M04409	0.12	17.9	0.30	103.3	28.1	27.8
M04410	0.11	18.5	0.33	124.6	39.4	18.8
M04411	0.11	16.5	0.32	135.7	50.0	47.0
M04412	0.11	18.5	0.25	113.8	38.2	48.5
Number of males	6	6	6	6	6	6
Mean	0.11	18.6	0.31	119.4	44.9	38.4
S.D.	0.01	2.0	0.03	14.3	13.3	13.2
Significance						
Statistical method	DU	DU	DU	DU	DT	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 35-4 (Continued) Individual blood chemical examination of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)					
Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
M04407	143.1	4.36	104.6	8.8	6.1
M04408	144.2	4.46	107.1	9.3	6.2
M04409	143.7	4.73	106.6	9.5	7.2
M04410	144.7	4.47	105.1	9.3	7.4
M04411	145.1	4.84	105.9	9.7	6.7
M04412	146.5	4.49	105.6	9.6	7.1
Number of males	6	6	6	6	6
Mean	144.6	4.56	105.8	9.4	6.8
S.D.	1.2	0.18	0.9	0.3	0.5
Significance					
Statistical method	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 36-1 Individual blood chemical examination of female rats on termination of recovery period

(Control group)				
Female No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L
F01171	64.0	24.6	172.6	0.49
F01172	85.6	23.8	106.0	0.09
F01173	64.5	21.5	186.5	0.97
F01174	59.4	28.0	166.4	0.54
F01175	67.9	29.2	133.4	0.84
F01176	85.7	33.9	122.5	0.55
Number of females	6	6	6	6
Mean	71.2	26.8	147.9	0.58
S.D.	11.5	4.5	31.8	0.31

(Continued)

## Appendix 36-1 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(Control group)			
Female No.	TP g/dL	Alb g/dL	A/G
F01171	6.66	3.87	1.39
F01172	5.92	3.43	1.38
F01173	5.86	3.15	1.16
F01174	6.49	3.47	1.15
F01175	6.49	3.67	1.30
F01176	6.81	3.90	1.34
Number of females	6	6	6
Mean	6.37	3.58	1.29
S.D.	0.39	0.29	0.11

(Continued)

## Appendix 36-1 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(Control group)						
Female No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
F01171	0.17	18.0	0.37	124.9	62.1	22.2
F01172	0.14	22.1	0.54	151.0	61.1	37.9
F01173	0.12	13.8	0.37	125.6	59.3	44.5
F01174	0.14	17.5	0.37	112.4	97.1	47.0
F01175	0.13	16.0	0.31	122.5	85.7	24.4
F01176	0.14	18.5	0.39	113.5	98.2	36.6
Number of females	6	6	6	6	6	6
Mean	0.14	17.7	0.39	125.0	77.3	35.4
S.D.	0.02	2.8	0.08	14.0	18.5	10.2

(Continued)

## Appendix 36-1 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(Control group)	Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
	F01171	141.4	4.05	105.6	10.0	3.6
	F01172	142.8	4.17	106.8	9.5	5.3
	F01173	142.1	4.13	107.4	9.3	5.4
	F01174	142.5	4.17	106.7	9.9	4.3
	F01175	142.9	3.98	106.1	10.0	6.3
	F01176	143.0	4.21	106.3	10.3	5.6
Number of females		6	6	6	6	6
Mean		142.5	4.12	106.5	9.8	5.1
S.D.		0.6	0.09	0.6	0.4	1.0

## Appendix 36-2 Individual blood chemical examination of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)				
Female No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L
F03371	78.8	20.7	111.5	0.71
F03372	68.4	23.8	127.4	0.49
F03373	74.7	29.9	174.7	0.64
F03374	76.2	26.2	141.2	0.51
F03375	101.3	46.2	167.3	0.66
F03376	62.0	16.3	130.7	0.44
Number of females	6	6	6	6
Mean	76.9	27.2	142.1	0.58
S.D.	13.4	10.4	24.4	0.11
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 36-2 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)

Female No.	TP g/dL	Alb g/dL	A/G
F03371	6.94	4.03	1.38
F03372	6.57	3.64	1.24
F03373	6.39	3.44	1.17
F03374	6.24	3.36	1.16
F03375	5.77	3.00	1.08
F03376	5.65	3.23	1.33
Number of females	6	6	6
Mean	6.26	3.45	1.23
S.D.	0.49	0.36	0.11
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 36-2 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)						
Female No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
F03371	0.11	15.9	0.41	128.6	67.9	53.0
F03372	0.13	21.4	0.36	117.4	70.6	43.7
F03373	0.14	17.6	0.39	123.7	85.0	26.3
F03374	0.16	22.6	0.35	121.2	74.6	15.2
F03375	0.14	23.3	0.40	133.4	66.7	16.5
F03376	0.12	19.7	0.37	119.1	59.9	20.2
Number of females	6	6	6	6	6	6
Mean	0.13	20.1	0.38	123.9	70.8	29.2
S.D.	0.02	2.9	0.02	6.1	8.5	15.6
Significance						
Statistical method	DU	DU	DT	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

DT: Analysis by Dunnett type mean rank test.

## Appendix 36-2 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)					
Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
F03371	141.3	4.48	107.2	9.9	3.4
F03372	142.9	4.02	106.3	10.0	4.6
F03373	141.8	4.43	107.1	9.4	3.9
F03374	142.9	4.07	106.2	9.6	7.3
F03375	142.0	4.19	106.3	9.4	6.8
F03376	144.6	4.01	107.3	9.3	6.7
Number of females	6	6	6	6	6
Mean	142.6	4.20	106.7	9.6	5.5
S.D.	1.2	0.21	0.5	0.3	1.7
Significance					
Statistical method	DU	DU	DT	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 36-3 Individual blood chemical examination of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)				
Female No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L
F04471	87.7	31.9	127.3	0.45
F04472	66.2	25.6	106.0	0.42
F04473	77.3	24.8	146.5	0.36
F04474	74.9	36.1	109.1	0.84
F04475	72.9	27.9	132.2	0.43
F04476	74.2	20.2	113.0	0.60
Number of females	6	6	6	6
Mean	75.5	27.8	122.4	0.52
S.D.	7.0	5.6	15.7	0.18
Significance				
Statistical method	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 36-3 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)			
Female No.	TP g/dL	Alb g/dL	A/G
F04471	6.68	3.83	1.35
F04472	6.68	3.96	1.46
F04473	6.00	3.32	1.24
F04474	6.32	3.44	1.20
F04475	6.06	3.62	1.49
F04476	5.75	3.21	1.26
Number of females	6	6	6
Mean	6.25	3.56	1.33
S.D.	0.38	0.29	0.12
Significance			
Statistical method	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 36-3 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)						
Female No.	T-Bil mg/dL	UN mg/dL	CRE mg/dL	Glu mg/dL	T-Cho mg/dL	TG mg/dL
F04471	0.13	17.7	0.38	116.7	81.1	34.5
F04472	0.16	17.3	0.38	119.7	68.8	41.5
F04473	0.12	25.5	0.41	102.2	60.3	19.8
F04474	0.16	13.7	0.33	115.7	81.4	22.3
F04475	0.16	17.9	0.39	126.3	70.4	16.3
F04476	0.11	23.2	0.43	111.9	58.1	8.9
Number of females	6	6	6	6	6	6
Mean	0.14	19.2	0.39	115.4	70.0	23.9
S.D.	0.02	4.3	0.03	8.1	9.9	12.0
Significance						
Statistical method	DU	DU	DT	DU	DU	DU

DU: Analysis by Dunnnett's test.

DT: Analysis by Dunnett type mean rank test.

(Continued)

## Appendix 36-3 (Continued) Individual blood chemical examination of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)

Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
F04471	142.5	4.38	105.9	9.6	4.2
F04472	143.6	3.85	106.6	10.3	4.8
F04473	142.6	4.38	106.7	9.9	6.1
F04474	141.5	3.98	105.8	10.2	5.4
F04475	144.4	4.46	109.6	9.9	6.5
F04476	145.3	4.15	108.2	9.4	7.5
Number of females	6	6	6	6	6
Mean	143.3	4.20	107.1	9.9	5.8
S.D.	1.4	0.25	1.5	0.3	1.2
Significance					
Statistical method	DU	DU	DT	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 37-1 Individual necropsy findings of male rats on termination of administration period

(Control group)					
Male No.	Dead or alive	Copulation or non-copulation	Fertilization or non-fertilization	Day of necropsy	Findings
M01101	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M01102	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M01103	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal Epididymis: Yellowish white nodule, left cauda
M01104	Alive	Copulation	Fertilization	Day 43 of administration	Other organs and tissues: Normal
M01105	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M01106	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal

## Appendix 37-2 Individual necropsy findings of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Male No.	Dead or alive	Copulation or non-copulation	Fertilization or non-fertilization	Day of necropsy	Findings
M02201	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M02202	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M02203	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M02204	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M02205	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M02206	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal

## Appendix 37-3 Individual necropsy findings of male rats on termination of administration period

(bumetizole group at 250 mg/kg)

Male No.	Dead or alive	Copulation or non-copulation	Fertilization or non-fertilization	Day of necropsy	Findings
M03301	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M03302	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M03303	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M03304	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M03305	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M03306	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal

## Appendix 37-4 Individual necropsy findings of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Male No.	Dead or alive	Copulation or non-copulation	Fertilization or non-fertilization	Day of necropsy	Findings
M04401	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M04402	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M04403	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M04404	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M04405	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal
M04406	Alive	Copulation	Fertilization	Day 43 of administration	Whole organs and tissues: Normal

## Appendix 38-1 Individual necropsy findings of female rats on termination of administration period

(Control group)					
Female No.	Dead or alive	Copulation or non-copulation	Pregnancy or non-pregnancy	Day of necropsy	Findings
F01151	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01152	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01153	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01154	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01155	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01156	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01157	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01158	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01159	Alive	Copulation	Non-pregnancy	Day 25 after copulation	Whole organs and tissues: Normal
F01160	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01161	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F01162	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal

## Appendix 38-2 Individual necropsy findings of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)					
Female No.	Dead or alive	Copulation or non-copulation	Pregnancy or non-pregnancy	Day of necropsy	Findings
F02251	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02252	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02253	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02254	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02255	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02256	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02257	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02258	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02259	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02260	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02261	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F02262	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal

## Appendix 38-3 Individual necropsy findings of female rats on termination of administration period

(bumetizole group at 250 mg/kg)					
Female No.	Dead or alive	Copulation or non-copulation	Pregnancy or non-pregnancy	Day of necropsy	Findings
F03351	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03352	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03353	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03354	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03355	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03356	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03357	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03358	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03359	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03360	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03361	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F03362	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal

## Appendix 38-4 Individual necropsy findings of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)					
Female No.	Dead or alive	Copulation or non-copulation	Pregnancy or non-pregnancy	Day of necropsy	Findings
F04451	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04452	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04453	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04454	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04455	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04456	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04457	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04458	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04459	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04460	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04461	Alive	Copulation	Pregnancy	Day 7 of lactation	Whole organs and tissues: Normal
F04462	Alive	Copulation	Non-pregnancy	Day 25 after copulation	Whole organs and tissues: Normal

## Appendix 39-1 Individual necropsy findings of male rats on termination of recovery period

(Control group)					
Male No.	Dead or alive	Copulation or non-copulation	Fertilization or non-fertilization	Day of necropsy	Findings
M01107	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M01108	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M01109	Alive	Copulation	Non-fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M01110	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M01111	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M01112	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal

## Appendix 39-2 Individual necropsy findings of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)

Male No.	Dead or alive	Copulation or non-copulation	Fertilization or non-fertilization	Day of necropsy	Findings
M02207	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M02208	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M02209	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M02210	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M02211	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M02212	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal

## Appendix 39-3 Individual necropsy findings of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)					
Male No.	Dead or alive	Copulation or non-copulation	Fertilization or non-fertilization	Day of necropsy	Findings
M03307	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M03308	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M03309	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M03310	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M03311	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M03312	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal

## Appendix 39-4 Individual necropsy findings of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)					
Male No.	Dead or alive	Copulation or non-copulation	Fertilization or non-fertilization	Day of necropsy	Findings
M04407	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M04408	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M04409	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M04410	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M04411	Alive	Copulation	Fertilization	Day 15 of recovery	Whole organs and tissues: Normal
M04412	Alive	Copulation	Non-fertilization	Day 15 of recovery	Whole organs and tissues: Normal

## Appendix 40-1 Individual necropsy findings of female rats on termination of recovery period

(Control group)			
Female No.	Dead or alive	Day of necropsy	Findings
F01171	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F01172	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F01173	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F01174	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F01175	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F01176	Alive	Day 15 of recovery	Whole organs and tissues: Normal

## Appendix 40-2 Individual necropsy findings of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)			
Female No.	Dead or alive	Day of necropsy	Findings
F03371	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F03372	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F03373	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F03374	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F03375	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F03376	Alive	Day 15 of recovery	Whole organs and tissues: Normal

## Appendix 40-3 Individual necropsy findings of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)			
Female No.	Dead or alive	Day of necropsy	Findings
F04471	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F04472	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F04473	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F04474	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F04475	Alive	Day 15 of recovery	Whole organs and tissues: Normal
F04476	Alive	Day 15 of recovery	Whole organs and tissues: Normal

## Appendix 41-1 Individual organ weights of male rats on termination of administration period

(Control group)																	
Male No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
M01101	486	2.03	0.42	12.4	2.6	22.5	4.6	306	63	1.38	0.28	10.69	2.20	0.72	0.15	2.71	0.56
M01102	412	1.99	0.48	12.9	3.1	23.5	5.7	168	41	1.24	0.30	10.01	2.43	0.66	0.16	2.69	0.65
M01103	448	2.06	0.46	15.1	3.4	16.6	3.7	272	61	1.34	0.30	11.23	2.51	0.61	0.14	2.98	0.67
M01104	455	2.18	0.48	16.1	3.5	18.2	4.0	204	45	1.45	0.32	11.39	2.50	0.76	0.17	3.13	0.69
M01105	457	2.11	0.46	13.6	3.0	18.4	4.0	250	55	1.28	0.28	11.84	2.59	0.69	0.15	2.93	0.64
M01106	493	2.27	0.46	16.3	3.3	29.2	5.9	261	53	1.53	0.31	11.86	2.41	0.85	0.17	3.39	0.69
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	459	2.11	0.46	14.4	3.2	21.4	4.7	244	53	1.37	0.30	11.17	2.44	0.72	0.16	2.97	0.65
S.D.	29	0.10	0.02	1.7	0.3	4.7	0.9	50	9	0.11	0.02	0.71	0.13	0.08	0.01	0.26	0.05

(Continued)

## Appendix 41-1 (Continued) Individual organ weights of male rats on termination of administration period

(Control group)

Male No.	Adrenals		Testes		Epididymides	
	(mg)	(mg%)	(g)	(g%)	(g)	(g%)
M01101	60.3	12.4	3.53	0.73	1.31	0.27
M01102	59.3	14.4	3.17	0.77	1.24	0.30
M01103	62.0	13.8	2.96	0.66	1.14	0.25
M01104	62.8	13.8	3.23	0.71	1.37	0.30
M01105	58.5	12.8	3.42	0.75	1.26	0.28
M01106	78.3	15.9	3.65	0.74	1.39	0.28
Number of males	6	6	6	6	6	6
Mean	63.5	13.9	3.33	0.73	1.29	0.28
S.D.	7.4	1.2	0.25	0.04	0.09	0.02

## Appendix 41-2 Individual organ weights of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)																	
Male No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
M02201	444	2.02	0.45	11.1	2.5	20.9	4.7	282	64	1.68	0.38	10.38	2.34	0.80	0.18	2.79	0.63
M02202	445	2.07	0.47	10.9	2.4	21.6	4.9	256	58	1.31	0.29	11.14	2.50	0.64	0.14	2.60	0.58
M02203	473	2.26	0.48	11.5	2.4	21.8	4.6	372	79	1.57	0.33	12.59	2.66	0.72	0.15	3.05	0.64
M02204	458	2.01	0.44	12.8	2.8	27.9	6.1	194	42	1.59	0.35	11.03	2.41	0.63	0.14	2.98	0.65
M02205	506	2.15	0.42	16.0	3.2	21.1	4.2	437	86	1.64	0.32	12.77	2.52	0.93	0.18	2.84	0.56
M02206	439	2.19	0.50	15.4	3.5	22.6	5.1	170	39	1.35	0.31	10.35	2.36	0.56	0.13	2.88	0.66
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	461	2.12	0.46	13.0	2.8	22.7	4.9	285	61	1.52	0.33	11.38	2.47	0.71	0.15	2.86	0.62
S.D.	25	0.10	0.03	2.2	0.5	2.6	0.6	103	19	0.16	0.03	1.06	0.12	0.13	0.02	0.16	0.04
Significance																	
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 41-2 (Continued) Individual organ weights of male rats on termination of administration period

(bumetizole group at 62.5 mg/kg)

Male No.	Adrenals		Testes		Epididymides	
	(mg)	(mg%)	(g)	(g%)	(g)	(g%)
M02201	55.5	12.5	2.84	0.64	1.18	0.27
M02202	67.6	15.2	2.92	0.66	1.11	0.25
M02203	52.9	11.2	3.39	0.72	1.28	0.27
M02204	72.9	15.9	3.73	0.81	1.24	0.27
M02205	69.4	13.7	3.68	0.73	1.45	0.29
M02206	54.1	12.3	3.29	0.75	1.29	0.29
Number of males	6	6	6	6	6	6
Mean	62.1	13.5	3.31	0.72	1.26	0.27
S.D.	8.9	1.8	0.37	0.06	0.12	0.02
Significance						
Statistical method	DU	DU	DT	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 41-3 Individual organ weights of male rats on termination of administration period

(bumetizole group at 250 mg/kg)

Male No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
M03301	456	2.06	0.45	12.7	2.8	27.3	6.0	213	47	1.25	0.27	10.58	2.32	0.62	0.14	2.81	0.62
M03302	466	2.15	0.46	13.2	2.8	18.7	4.0	181	39	1.43	0.31	11.93	2.56	0.86	0.18	3.19	0.68
M03303	455	2.22	0.49	13.1	2.9	19.4	4.3	231	51	1.47	0.32	10.80	2.37	0.78	0.17	3.06	0.67
M03304	455	2.11	0.46	12.6	2.8	22.8	5.0	247	54	1.36	0.30	11.67	2.56	0.71	0.16	2.80	0.62
M03305	475	2.14	0.45	11.3	2.4	16.1	3.4	199	42	1.39	0.29	12.46	2.62	0.91	0.19	3.15	0.66
M03306	437	2.11	0.48	12.4	2.8	19.9	4.6	298	68	1.43	0.33	9.96	2.28	0.75	0.17	2.88	0.66
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	457	2.13	0.47	12.6	2.8	20.7	4.6	228	50	1.39	0.30	11.23	2.45	0.77	0.17	2.98	0.65
S.D.	13	0.05	0.02	0.7	0.2	3.9	0.9	41	10	0.08	0.02	0.94	0.15	0.10	0.02	0.17	0.03
Significance																	
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 41-3 (Continued) Individual organ weights of male rats on termination of administration period

(bumetizole group at 250 mg/kg)

Male No.	Adrenals		Testes		Epididymides	
	(mg)	(mg%)	(g)	(g%)	(g)	(g%)
M03301	32.4	7.1	3.48	0.76	1.16	0.25
M03302	64.1	13.8	3.51	0.75	1.38	0.30
M03303	67.9	14.9	3.41	0.75	1.19	0.26
M03304	70.2	15.4	3.34	0.73	1.24	0.27
M03305	62.9	13.2	3.51	0.74	1.46	0.31
M03306	58.0	13.3	3.55	0.81	1.33	0.30
Number of males	6	6	6	6	6	6
Mean	59.3	13.0	3.47	0.76	1.29	0.28
S.D.	13.8	3.0	0.08	0.03	0.12	0.02

## Significance

Statistical method    DU    DU    DT    DU    DU    DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 41-4 Individual organ weights of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Male No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
M04401	455	2.05	0.45	13.0	2.9	17.4	3.8	168	37	1.34	0.29	10.71	2.35	0.77	0.17	3.10	0.68
M04402	446	1.93	0.43	10.9	2.4	15.4	3.5	111	25	1.42	0.32	11.97	2.68	0.48	0.11	2.69	0.60
M04403	481	2.05	0.43	9.4	2.0	18.1	3.8	208	43	1.45	0.30	12.31	2.56	0.70	0.15	2.66	0.55
M04404	467	2.16	0.46	13.0	2.8	22.0	4.7	343	73	1.55	0.33	10.75	2.30	0.66	0.14	3.38	0.72
M04405	442	2.10	0.48	13.4	3.0	20.2	4.6	254	57	1.45	0.33	11.06	2.50	0.69	0.16	3.03	0.69
M04406	474	2.06	0.43	14.7	3.1	20.7	4.4	210	44	1.60	0.34	11.82	2.49	0.69	0.15	3.12	0.66
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	461	2.06	0.45	12.4	2.7	19.0	4.1	216	47	1.47	0.32	11.44	2.48	0.67	0.15	3.00	0.65
S.D.	16	0.08	0.02	1.9	0.4	2.4	0.5	79	17	0.09	0.02	0.68	0.14	0.10	0.02	0.28	0.06
Significance																	
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 41-4 (Continued) Individual organ weights of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Male No.	Adrenals		Testes		Epididymides	
	(mg)	(mg%)	(g)	(g%)	(g)	(g%)
M04401	65.8	14.5	3.20	0.70	1.16	0.25
M04402	51.5	11.5	2.60	0.58	1.11	0.25
M04403	62.8	13.1	3.49	0.73	1.28	0.27
M04404	74.4	15.9	3.19	0.68	1.15	0.25
M04405	68.7	15.5	3.32	0.75	1.27	0.29
M04406	62.8	13.2	3.55	0.75	1.25	0.26
Number of males	6	6	6	6	6	6
Mean	64.3	14.0	3.23	0.70	1.20	0.26
S.D.	7.6	1.7	0.34	0.06	0.07	0.02
Significance						
Statistical method	DU	DU	DT	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 42-1 Individual organ weights of female rats on termination of administration period

(Control group)																		
Female No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys		
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	
F01151	284	1.94	0.68	17.3	6.1	21.6	7.6	180	63	0.94	0.33	10.02	3.53	0.66	0.23	1.90	0.67	
F01152	311	1.96	0.63	18.8	6.0	20.9	6.7	398	128	1.04	0.33	8.89	2.86	0.74	0.24	1.93	0.62	
F01153	343	1.98	0.58	16.3	4.8	17.0	5.0	394	115	1.06	0.31	10.21	2.98	0.74	0.22	2.01	0.59	
F01154	319	2.00	0.63	17.8	5.6	20.1	6.3	278	87	1.16	0.36	9.10	2.85	0.80	0.25	1.97	0.62	
F01155	281	1.91	0.68	18.9	6.7	16.2	5.8	144	51	0.81	0.29	8.41	2.99	0.48	0.17	1.77	0.63	
F01156	314	2.08	0.66	18.0	5.7	19.8	6.3	263	84	1.10	0.35	9.82	3.13	0.78	0.25	2.10	0.67	
F01157	326	2.00	0.61	22.2	6.8	20.4	6.3	315	97	1.20	0.37	10.10	3.10	0.85	0.26	2.30	0.71	
F01158	300	1.92	0.64	17.3	5.8	16.9	5.6	300	100	1.09	0.36	9.31	3.10	0.63	0.21	2.17	0.72	
F01159	Non-pregnancy																	
F01160	316	1.92	0.61	22.0	7.0	15.7	5.0	183	58	1.05	0.33	9.71	3.07	0.63	0.20	1.98	0.63	
F01161	297	2.11	0.71	16.3	5.5	16.1	5.4	301	101	1.00	0.34	8.77	2.95	0.58	0.20	1.93	0.65	
F01162	283	1.85	0.65	15.5	5.5	16.8	5.9	209	74	0.97	0.34	7.80	2.76	0.54	0.19	1.95	0.69	
- 512 -	Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
	Mean	307	1.97	0.64	18.2	6.0	18.3	6.0	270	87	1.04	0.34	9.29	3.03	0.68	0.22	2.00	0.65
	S.D.	20	0.08	0.04	2.2	0.7	2.2	0.8	84	24	0.11	0.02	0.77	0.20	0.12	0.03	0.14	0.04

(Continued)

## Appendix 42-1 (Continued) Individual organ weights of female rats on termination of administration period

(Control group)						
Female No.	Adrenals		Ovaries		Uterus	
	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)
F01151	90.1	31.7	100.4	35.4	0.50	0.18
F01152	70.7	22.7	94.7	30.5	0.50	0.16
F01153	77.5	22.6	92.2	26.9	0.44	0.13
F01154	70.8	22.2	116.9	36.6	0.51	0.16
F01155	58.5	20.8	79.0	28.1	0.48	0.17
F01156	94.7	30.2	95.4	30.4	0.51	0.16
F01157	91.4	28.0	114.7	35.2	0.49	0.15
F01158	79.2	26.4	81.7	27.2	0.77	0.26
F01159	Non-pregnancy					
F01160	64.1	20.3	119.7	37.9	0.68	0.22
F01161	74.1	24.9	87.5	29.5	0.58	0.20
F01162	71.1	25.1	103.0	36.4	0.48	0.17
513	Number of females	11	11	11	11	11
	Mean	76.6	25.0	98.7	32.2	0.54
	S.D.	11.5	3.8	13.9	4.1	0.10
						0.04

## Appendix 42-2 Individual organ weights of female rats on termination of administration period

(bumetizole group at 62.5 mg/kg)																		
Female No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys		
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	
F02251	301	1.99	0.66	13.9	4.6	20.6	6.8	296	98	0.97	0.32	9.48	3.15	0.61	0.20	1.91	0.63	
F02252	312	1.99	0.64	16.3	5.2	20.4	6.5	338	108	1.02	0.33	9.41	3.02	0.80	0.26	1.97	0.63	
F02253	302	2.01	0.67	20.3	6.7	17.7	5.9	394	130	0.99	0.33	9.82	3.25	0.72	0.24	2.05	0.68	
F02254	310	2.05	0.66	23.2	7.5	25.6	8.3	387	125	1.00	0.32	10.56	3.41	0.89	0.29	2.12	0.68	
F02255	294	1.87	0.64	17.7	6.0	18.3	6.2	382	130	1.09	0.37	8.44	2.87	0.55	0.19	1.88	0.64	
F02256	287	1.93	0.67	18.0	6.3	17.7	6.2	185	64	0.91	0.32	9.21	3.21	0.65	0.23	2.07	0.72	
F02257	324	2.02	0.62	19.9	6.1	19.7	6.1	265	82	1.11	0.34	11.11	3.43	0.89	0.27	2.12	0.65	
F02258	309	2.04	0.66	15.0	4.9	21.1	6.8	378	122	0.92	0.30	9.96	3.22	0.70	0.23	2.09	0.68	
F02259	292	1.94	0.66	15.4	5.3	16.1	5.5	316	108	0.99	0.34	8.64	2.96	0.70	0.24	1.84	0.63	
F02260	295	1.91	0.65	21.0	7.1	14.4	4.9	315	107	0.94	0.32	9.84	3.34	0.79	0.27	2.03	0.69	
F02261	270	1.90	0.70	14.2	5.3	11.9	4.4	289	107	0.92	0.34	7.74	2.87	0.67	0.25	2.02	0.75	
F02262	353	2.00	0.57	19.5	5.5	13.9	3.9	382	108	1.16	0.33	12.14	3.44	0.88	0.25	2.44	0.69	
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
Mean		304	1.97	0.65	17.9	5.9	18.1	6.0	327	107	1.00	0.33	9.70	3.18	0.74	0.24	2.05	0.67
S.D.		21	0.06	0.03	3.0	0.9	3.7	1.2	63	19	0.08	0.02	1.19	0.21	0.11	0.03	0.15	0.04
Significance															*			
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU		

Significantly different from control group (\*: P&lt;0.05).

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 42-2 (Continued) Individual organ weights of female rats on termination of administration period

Female No.	Adrenals		Ovaries		Uterus	
	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)
F02251	70.1	23.3	77.8	25.8	0.54	0.18
F02252	83.2	26.7	84.2	27.0	0.53	0.17
F02253	75.3	24.9	98.4	32.6	0.59	0.20
F02254	74.2	23.9	113.8	36.7	0.62	0.20
F02255	81.5	27.7	83.8	28.5	1.00	0.34
F02256	79.1	27.6	102.1	35.6	0.46	0.16
F02257	80.1	24.7	99.8	30.8	0.59	0.18
F02258	72.0	23.3	94.8	30.7	0.50	0.16
F02259	68.2	23.4	97.1	33.3	0.48	0.16
F02260	68.0	23.1	88.8	30.1	0.54	0.18
F02261	71.8	26.6	82.5	30.6	0.68	0.25
F02262	83.8	23.7	107.5	30.5	0.50	0.14
Number of females	12	12	12	12	12	12
Mean	75.6	24.9	94.2	31.0	0.59	0.19
S.D.	5.8	1.8	11.0	3.2	0.14	0.05
Significance						
Statistical method	DU	DU	DU	DU	DT	DT

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 42-3 Individual organ weights of female rats on termination of administration period

(bumetizole group at 250 mg/kg)

Female No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys		
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	
F03351	319	1.96	0.61	17.6	5.5	19.0	6.0	224	70	1.05	0.33	12.29	3.85	0.77	0.24	2.35	0.74	
F03352	317	2.18	0.69	17.7	5.6	16.0	5.0	227	72	0.97	0.31	10.98	3.46	0.88	0.28	1.96	0.62	
F03353	283	2.02	0.71	20.8	7.3	18.7	6.6	177	63	0.98	0.35	11.33	4.00	0.66	0.23	2.12	0.75	
F03354	299	2.00	0.67	19.2	6.4	16.8	5.6	259	87	0.94	0.31	8.46	2.83	0.63	0.21	1.78	0.60	
F03355	278	1.96	0.71	15.5	5.6	18.9	6.8	305	110	0.97	0.35	8.65	3.11	0.76	0.27	2.04	0.73	
F03356	277	2.17	0.78	17.6	6.4	19.5	7.0	260	94	0.97	0.35	9.39	3.39	0.81	0.29	1.96	0.71	
F03357	288	1.87	0.65	18.1	6.3	14.5	5.0	261	91	0.93	0.32	8.22	2.85	0.58	0.20	1.69	0.59	
F03358	350	2.15	0.61	19.1	5.5	19.1	5.5	326	93	1.13	0.32	11.41	3.26	0.98	0.28	2.26	0.65	
F03359	288	1.95	0.68	17.7	6.1	15.0	5.2	222	77	0.92	0.32	8.67	3.01	0.69	0.24	2.09	0.73	
F03360	293	1.94	0.66	18.6	6.3	20.1	6.9	278	95	1.04	0.35	9.77	3.33	0.74	0.25	2.17	0.74	
F03361	346	2.00	0.58	19.0	5.5	19.7	5.7	393	114	1.19	0.34	10.25	2.96	0.66	0.19	2.11	0.61	
F03362	298	1.96	0.66	14.5	4.9	18.5	6.2	266	89	0.96	0.32	9.96	3.34	0.78	0.26	2.01	0.67	
516	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	Mean	303	2.01	0.67	18.0	6.0	18.0	6.0	267	88	1.00	0.33	9.95	3.28	0.75	0.25	2.05	0.68
	S.D.	25	0.10	0.05	1.7	0.6	1.9	0.7	56	15	0.08	0.02	1.33	0.37	0.11	0.03	0.19	0.06
Significance																		
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	

DU: Analysis by Dunnett's test.

(Continued)

## Appendix 42-3 (Continued) Individual organ weights of female rats on termination of administration period

(bumetizole group at 250 mg/kg)						
Female No.	Adrenals		Ovaries		Uterus	
	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)
F03351	107.7	33.8	110.3	34.6	0.60	0.19
F03352	69.7	22.0	95.5	30.1	0.60	0.19
F03353	73.2	25.9	104.0	36.7	0.58	0.20
F03354	67.3	22.5	82.3	27.5	0.54	0.18
F03355	72.2	26.0	101.5	36.5	0.51	0.18
F03356	69.5	25.1	102.8	37.1	0.61	0.22
F03357	71.8	24.9	109.2	37.9	0.61	0.21
F03358	90.9	26.0	102.7	29.3	0.50	0.14
F03359	74.4	25.8	82.1	28.5	0.54	0.19
F03360	78.0	26.6	107.7	36.8	0.54	0.18
F03361	68.7	19.9	106.2	30.7	0.57	0.16
F03362	84.9	28.5	94.4	31.7	0.58	0.19
Number of females	12	12	12	12	12	12
Mean	77.4	25.6	99.9	33.1	0.57	0.19
S.D.	11.8	3.5	9.6	3.9	0.04	0.02
Significance						
Statistical method	DU	DU	DU	DU	DT	DT

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 42-4 Individual organ weights of female rats on termination of administration period

Female No.	(bumetizole group at 1000 mg/kg)																	
	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys		
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	
F04451	367	2.00	0.54	14.3	3.9	19.6	5.3	312	85	1.01	0.28	10.00	2.72	0.70	0.19	1.91	0.52	
F04452	309	2.08	0.67	19.0	6.1	15.3	5.0	213	69	1.11	0.36	9.55	3.09	0.66	0.21	2.10	0.68	
F04453	275	2.12	0.77	17.2	6.3	19.9	7.2	204	74	0.95	0.35	8.67	3.15	0.74	0.27	2.04	0.74	
F04454	296	2.01	0.68	15.2	5.1	19.2	6.5	247	83	1.16	0.39	10.17	3.44	0.64	0.22	2.17	0.73	
F04455	270	1.92	0.71	17.8	6.6	13.4	5.0	272	101	0.98	0.36	8.95	3.31	0.56	0.21	2.02	0.75	
F04456	281	1.99	0.71	14.9	5.3	18.8	6.7	193	69	0.98	0.35	9.05	3.22	0.64	0.23	1.79	0.64	
F04457	328	1.90	0.58	17.7	5.4	21.2	6.5	372	113	1.15	0.35	11.45	3.49	0.75	0.23	2.39	0.73	
F04458	288	1.95	0.68	18.1	6.3	20.2	7.0	334	116	1.01	0.35	8.94	3.10	0.69	0.24	1.93	0.67	
F04459	305	1.84	0.60	16.0	5.2	16.9	5.5	212	70	1.06	0.35	10.98	3.60	0.86	0.28	1.97	0.65	
F04460	282	2.03	0.72	15.1	5.4	16.0	5.7	319	113	0.97	0.34	9.42	3.34	0.74	0.26	1.97	0.70	
F04461	298	1.84	0.62	15.6	5.2	15.9	5.3	247	83	0.98	0.33	10.25	3.44	0.76	0.26	2.09	0.70	
F04462	Non-pregnancy																	
815	Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11		
	Mean	300	1.97	0.66	16.4	5.5	17.9	6.0	266	89	1.03	0.35	9.77	3.26	0.70	0.24	2.03	0.68
	S.D.	28	0.09	0.07	1.6	0.8	2.5	0.8	60	19	0.08	0.03	0.89	0.25	0.08	0.03	0.16	0.07
Significance																		
Statistical method																		
DU: Analysis by Dunnett's test.																		

(Continued)

## Appendix 42-4 (Continued) Individual organ weights of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)

Female No.	Adrenals		Ovaries		Uterus	
	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)
F04451	73.4	20.0	121.0	33.0	0.47	0.13
F04452	85.5	27.7	111.4	36.1	0.54	0.17
F04453	78.4	28.5	115.6	42.0	0.52	0.19
F04454	71.1	24.0	94.1	31.8	0.49	0.17
F04455	68.1	25.2	100.0	37.0	0.82	0.30
F04456	71.2	25.3	91.0	32.4	0.48	0.17
F04457	100.4	30.6	99.2	30.2	0.60	0.18
F04458	78.6	27.3	97.0	33.7	0.64	0.22
F04459	62.6	20.5	99.0	32.5	0.55	0.18
F04460	70.9	25.1	98.2	34.8	0.53	0.19
F04461	71.0	23.8	112.5	37.8	0.54	0.18
F04462	Non-pregnancy					
Number of females	11	11	11	11	11	11
Mean	75.6	25.3	103.5	34.7	0.56	0.19
S.D.	10.2	3.2	9.8	3.4	0.10	0.04
Significance						
Statistical method	DU	DU	DU	DU	DT	DT

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 43-1 Individual organ weights of male rats on termination of recovery period

(Control group)																	
Male No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
M01107	508	2.10	0.41	12.1	2.4	18.3	3.6	260	51	1.43	0.28	12.20	2.40	0.83	0.16	2.62	0.52
M01108	487	2.09	0.43	13.3	2.7	16.2	3.3	207	43	1.79	0.37	12.07	2.48	0.91	0.19	2.76	0.57
M01109	542	2.07	0.38	14.3	2.6	18.2	3.4	198	37	1.72	0.32	13.66	2.52	0.75	0.14	3.01	0.56
M01110	523	2.15	0.41	14.1	2.7	25.2	4.8	244	47	1.48	0.28	11.87	2.27	0.67	0.13	3.13	0.60
M01111	454	2.13	0.47	12.5	2.8	24.9	5.5	250	55	1.49	0.33	10.85	2.39	0.67	0.15	3.02	0.67
M01112	509	2.20	0.43	15.4	3.0	21.2	4.2	410	81	1.39	0.27	12.45	2.45	0.91	0.18	3.23	0.63
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
Mean	504	2.12	0.42	13.6	2.7	20.7	4.1	262	52	1.55	0.31	12.18	2.42	0.79	0.16	2.96	0.59
S.D.	30	0.05	0.03	1.2	0.2	3.8	0.9	77	15	0.16	0.04	0.91	0.09	0.11	0.02	0.23	0.05

(Continued)

## Appendix 43-1 (Continued) Individual organ weights of male rats on termination of recovery period

(Control group)						
Male No.	Adrenals		Testes		Epididymides	
	(mg)	(mg%)	(g)	(g%)	(g)	(g%)
M01107	62.6	12.3	3.08	0.61	1.20	0.24
M01108	49.8	10.2	3.26	0.67	1.21	0.25
M01109	57.3	10.6	3.27	0.60	1.40	0.26
M01110	58.3	11.1	3.43	0.66	1.33	0.25
M01111	64.0	14.1	3.20	0.70	1.27	0.28
M01112	62.6	12.3	3.22	0.63	1.44	0.28
Number of males	6	6	6	6	6	6
Mean	59.1	11.8	3.24	0.65	1.31	0.26
S.D.	5.3	1.4	0.11	0.04	0.10	0.02

## Appendix 43-2 Individual organ weights of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)																	
Male No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
M02207	473	2.08	0.44	14.1	3.0	21.1	4.5	259	55	1.29	0.27	11.43	2.42	0.67	0.14	2.76	0.58
M02208	478	2.25	0.47	17.2	3.6	26.9	5.6	315	66	1.58	0.33	11.54	2.41	0.85	0.18	3.47	0.73
M02209	508	2.05	0.40	13.8	2.7	20.0	3.9	246	48	1.54	0.30	12.15	2.39	0.69	0.14	3.04	0.60
M02210	519	2.04	0.39	13.2	2.5	28.4	5.5	221	43	1.40	0.27	13.16	2.54	0.81	0.16	3.09	0.60
M02211	532	2.06	0.39	15.0	2.8	25.4	4.8	324	61	1.30	0.24	13.69	2.57	0.78	0.15	3.19	0.60
M02212	538	2.11	0.39	16.6	3.1	31.0	5.8	179	33	1.72	0.32	12.61	2.34	0.82	0.15	3.05	0.57
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	508	2.10	0.41	15.0	3.0	25.5	5.0	257	51	1.47	0.29	12.43	2.45	0.77	0.15	3.10	0.61
S.D.	27	0.08	0.03	1.6	0.4	4.2	0.7	55	12	0.17	0.03	0.90	0.09	0.07	0.02	0.23	0.06
Significance																	
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DT

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

(Continued)

## Appendix 43-2 (Continued) Individual organ weights of male rats on termination of recovery period

(bumetizole group at 62.5 mg/kg)

Male No.	Adrenals		Testes		Epididymides	
	(mg)	(mg%)	(g)	(g%)	(g)	(g%)
M02207	47.7	10.1	3.36	0.71	1.24	0.26
M02208	67.0	14.0	3.94	0.82	1.33	0.28
M02209	61.8	12.2	3.19	0.63	1.27	0.25
M02210	45.8	8.8	2.82	0.54	1.34	0.26
M02211	53.2	10.0	2.99	0.56	1.27	0.24
M02212	67.0	12.5	3.88	0.72	1.37	0.25
Number of males	6	6	6	6	6	6
Mean	57.1	11.3	3.36	0.66	1.30	0.26
S.D.	9.5	1.9	0.46	0.11	0.05	0.01
Significance						
Statistical method	DU	DU	DT	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 43-3 Individual organ weights of male rats on termination of recovery period

(bumetizole group at 250 mg/kg)																	
Male No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
M03307	441	1.95	0.44	12.3	2.8	18.4	4.2	287	65	1.33	0.30	9.86	2.24	0.68	0.15	2.41	0.55
M03308	475	2.07	0.44	12.8	2.7	14.9	3.1	243	51	1.53	0.32	11.18	2.35	0.60	0.13	2.81	0.59
M03309	488	2.18	0.45	13.1	2.7	24.0	4.9	273	56	1.29	0.26	10.96	2.25	0.77	0.16	2.71	0.56
M03310	520	2.09	0.40	16.8	3.2	20.2	3.9	286	55	1.39	0.27	13.15	2.53	0.94	0.18	3.09	0.59
M03311	548	2.03	0.37	12.1	2.2	22.5	4.1	373	68	1.46	0.27	14.20	2.59	0.89	0.16	3.06	0.56
M03312	491	2.16	0.44	13.7	2.8	28.1	5.7	193	39	1.69	0.34	12.59	2.56	0.74	0.15	3.01	0.61
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	494	2.08	0.42	13.5	2.7	21.4	4.3	276	56	1.45	0.29	11.99	2.42	0.77	0.16	2.85	0.58
S.D.	37	0.08	0.03	1.7	0.3	4.6	0.9	59	10	0.15	0.03	1.60	0.16	0.13	0.02	0.26	0.02
Significance																	
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DT	

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

(Continued)

## Appendix 43-3 (Continued) Individual organ weights of male rats on termination of recovery period

Male No.	Adrenals		Testes		Epididymides	
	(mg)	(mg%)	(g)	(g%)	(g)	(g%)
M03307	52.9	12.0	3.34	0.76	1.15	0.26
M03308	45.9	9.7	3.56	0.75	1.51	0.32
M03309	45.5	9.3	4.24	0.87	1.53	0.31
M03310	52.2	10.0	3.69	0.71	1.33	0.26
M03311	67.6	12.3	3.33	0.61	1.31	0.24
M03312	54.6	11.1	3.38	0.69	1.33	0.27
Number of males	6	6	6	6	6	6
Mean	53.1	10.7	3.59	0.73	1.36	0.28
S.D.	8.0	1.3	0.35	0.09	0.14	0.03
Significance						
Statistical method	DU	DU	DT	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 43-4 Individual organ weights of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)																	
Male No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
M04407	534	2.18	0.41	14.5	2.7	18.8	3.5	240	45	1.63	0.31	13.80	2.58	0.91	0.17	3.24	0.61
M04408	498	2.13	0.43	14.4	2.9	20.4	4.1	355	71	1.36	0.27	13.64	2.74	0.80	0.16	3.07	0.62
M04409	450	2.10	0.47	13.3	3.0	20.6	4.6	308	68	1.44	0.32	11.30	2.51	0.82	0.18	2.78	0.62
M04410	453	2.11	0.47	13.4	3.0	21.4	4.7	204	45	1.37	0.30	10.41	2.30	0.72	0.16	2.95	0.65
M04411	504	2.21	0.44	13.9	2.8	24.1	4.8	252	50	1.37	0.27	13.33	2.64	0.75	0.15	3.05	0.61
M04412	503	2.04	0.41	13.4	2.7	19.4	3.9	260	52	1.45	0.29	12.03	2.39	0.62	0.12	3.13	0.62
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	490	2.13	0.44	13.8	2.9	20.8	4.3	270	55	1.44	0.29	12.42	2.53	0.77	0.16	3.04	0.62
S.D.	33	0.06	0.03	0.5	0.1	1.9	0.5	54	11	0.10	0.02	1.39	0.16	0.10	0.02	0.16	0.01
Significance																	
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DT	

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

(Continued)

## Appendix 43-4 (Continued) Individual organ weights of male rats on termination of recovery period

(bumetizole group at 1000 mg/kg)

Male No.	Adrenals		Testes		Epididymides	
	(mg)	(mg%)	(g)	(g%)	(g)	(g%)
M04407	59.3	11.1	3.51	0.66	1.45	0.27
M04408	48.7	9.8	3.02	0.61	1.16	0.23
M04409	60.6	13.5	3.30	0.73	1.30	0.29
M04410	56.4	12.5	3.57	0.79	1.41	0.31
M04411	55.9	11.1	3.20	0.63	1.31	0.26
M04412	57.4	11.4	3.23	0.64	1.33	0.26
Number of males	6	6	6	6	6	6
Mean	56.4	11.6	3.31	0.68	1.33	0.27
S.D.	4.2	1.3	0.21	0.07	0.10	0.03
Significance						
Statistical method	DU	DU	DT	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 44-1 Individual organ weights of female rats on termination of recovery period

(Control group)																	
Female No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
F01171	294	1.88	0.64	17.4	5.9	20.6	7.0	268	91	0.85	0.29	6.86	2.33	0.46	0.16	1.80	0.61
F01172	341	1.99	0.58	18.1	5.3	23.7	7.0	329	96	0.98	0.29	8.45	2.48	0.66	0.19	1.81	0.53
F01173	343	1.92	0.56	14.8	4.3	20.7	6.0	351	102	1.05	0.31	8.21	2.39	0.54	0.16	2.02	0.59
F01174	310	2.03	0.65	19.2	6.2	14.8	4.8	245	79	0.97	0.31	8.04	2.59	0.46	0.15	1.95	0.63
F01175	320	2.07	0.65	12.8	4.0	14.3	4.5	285	89	0.98	0.31	8.25	2.58	0.67	0.21	2.05	0.64
F01176	286	2.01	0.70	19.5	6.8	19.9	7.0	340	119	1.01	0.35	7.05	2.47	0.54	0.19	1.94	0.68
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	316	1.98	0.63	17.0	5.4	19.0	6.1	303	96	0.97	0.31	7.81	2.47	0.56	0.18	1.93	0.61
S.D.	24	0.07	0.05	2.6	1.1	3.7	1.2	43	14	0.07	0.02	0.68	0.10	0.09	0.02	0.10	0.05

(Continued)

## Appendix 44-1 (Continued) Individual organ weights of female rats on termination of recovery period

(Control group)

Female No.	Adrenals		Ovaries		Uterus	
	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)
F01171	63.2	21.5	85.0	28.9	0.65	0.22
F01172	80.1	23.5	92.7	27.2	0.85	0.25
F01173	85.2	24.8	88.5	25.8	0.43	0.13
F01174	61.5	19.8	73.8	23.8	0.49	0.16
F01175	74.5	23.3	98.9	30.9	0.43	0.13
F01176	67.5	23.6	75.8	26.5	0.38	0.13
Number of females	6	6	6	6	6	6
Mean	72.0	22.8	85.8	27.2	0.54	0.17
S.D.	9.5	1.8	9.7	2.5	0.18	0.05

## Appendix 44-2 Individual organ weights of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)																	
Female No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
F03371	351	1.83	0.52	18.8	5.4	25.9	7.4	283	81	1.17	0.33	8.27	2.36	0.57	0.16	1.94	0.55
F03372	300	2.10	0.70	16.4	5.5	12.3	4.1	305	102	0.87	0.29	7.05	2.35	0.48	0.16	1.74	0.58
F03373	350	1.99	0.57	16.7	4.8	25.3	7.2	365	104	0.96	0.27	7.70	2.20	0.49	0.14	1.85	0.53
F03374	295	2.11	0.72	20.5	6.9	20.7	7.0	236	80	0.89	0.30	6.61	2.24	0.54	0.18	1.82	0.62
F03375	309	1.90	0.61	17.6	5.7	16.0	5.2	384	124	0.90	0.29	7.58	2.45	0.61	0.20	1.88	0.61
F03376	330	2.19	0.66	19.0	5.8	14.9	4.5	380	115	1.03	0.31	8.28	2.51	0.71	0.22	2.06	0.62
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	323	2.02	0.63	18.2	5.7	19.2	5.9	326	101	0.97	0.30	7.58	2.35	0.57	0.18	1.88	0.59
S.D.	25	0.14	0.08	1.6	0.7	5.7	1.5	60	18	0.11	0.02	0.66	0.12	0.09	0.03	0.11	0.04
Significance																	
Statistical method	DU	DU	DT	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

(Continued)

## Appendix 44-2 (Continued) Individual organ weights of female rats on termination of recovery period

(bumetizole group at 250 mg/kg)

Female No.	Adrenals		Ovaries		Uterus	
	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)
F03371	67.9	19.3	72.5	20.7	0.58	0.17
F03372	62.6	20.9	74.7	24.9	0.50	0.17
F03373	58.0	16.6	73.6	21.0	0.51	0.15
F03374	65.5	22.2	64.4	21.8	0.77	0.26
F03375	63.6	20.6	82.2	26.6	0.49	0.16
F03376	78.1	23.7	77.2	23.4	0.87	0.26
Number of females	6	6	6	6	6	6
Mean	66.0	20.6	74.1	23.1	0.62	0.20
S.D.	6.8	2.4	5.9	2.3	0.16	0.05
Significance	*	*				
Statistical method	DU	DU	DU	DU	DU	DU

Significantly different from control group (\*: P&lt;0.05).

DU: Analysis by Dunnett's test.

## Appendix 44-3 Individual organ weights of female rats on termination of recovery period

(bumetizole group at 1000 mg/kg)																	
Female No.	Body weight (g)	Brain		Pituitary		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(g)	(g%)	(g)	(g%)
F04471	307	2.02	0.66	23.0	7.5	19.8	6.4	291	95	1.05	0.34	7.77	2.53	0.49	0.16	1.99	0.65
F04472	297	1.98	0.67	14.5	4.9	13.7	4.6	283	95	0.94	0.32	7.02	2.36	0.53	0.18	1.73	0.58
F04473	300	2.03	0.68	18.5	6.2	17.3	5.8	224	75	1.04	0.35	7.75	2.58	0.64	0.21	1.98	0.66
F04474	303	1.94	0.64	18.3	6.0	23.7	7.8	337	111	0.96	0.32	7.64	2.52	0.64	0.21	2.06	0.68
F04475	295	1.99	0.67	17.8	6.0	14.0	4.7	249	84	0.94	0.32	7.16	2.43	0.52	0.18	1.89	0.64
F04476	317	2.11	0.67	20.1	6.3	17.6	5.6	306	97	0.96	0.30	7.33	2.31	0.72	0.23	1.90	0.60
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	303	2.01	0.67	18.7	6.2	17.7	5.8	282	93	0.98	0.33	7.45	2.46	0.59	0.20	1.93	0.64
S.D.	8	0.06	0.01	2.8	0.8	3.7	1.2	40	12	0.05	0.02	0.32	0.11	0.09	0.03	0.11	0.04
Significance														(Continued)			
Statistical method	DU	DU	DT	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

## Appendix 44-3 (Continued) Individual organ weights of female rats on termination of recovery period

Female No.	Adrenals		Ovaries		Uterus	
	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)
F04471	73.9	24.1	78.6	25.6	0.52	0.17
F04472	71.1	23.9	80.5	27.1	0.53	0.18
F04473	69.0	23.0	90.3	30.1	0.54	0.18
F04474	68.7	22.7	66.8	22.0	0.64	0.21
F04475	75.4	25.6	82.5	28.0	0.83	0.28
F04476	69.0	21.8	80.8	25.5	0.52	0.16
Number of females	6	6	6	6	6	6
Mean	71.2	23.5	79.9	26.4	0.60	0.20
S.D.	2.9	1.3	7.6	2.7	0.12	0.04
Significance						
Statistical method	DU	DU	DU	DU	DU	DU

DU: Analysis by Dunnett's test.

## Appendix 45-1 Individual histopathological findings of male rats on termination of administration period

(Control group)		
Male No.	Organ/Tissue	Findings
M01101	Whole organs and tissues	No abnormality detected
M01102	Epididymis	Cellular infiltration, lymphoid cell: ±
	Other organs and tissues	No abnormality detected
M01103	Whole organs and tissues	No abnormality detected
M01104	Epididymis	Granuloma, spermatic, lateral: ±
	Other organs and tissues	No abnormality detected
M01105	Lung	Accumulation, foam cell: ±
	Other organs and tissues	No abnormality detected
M01106	Lung	Accumulation, foam cell: ±
	Other organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

## Appendix 45-2 Individual histopathological findings of male rats on termination of administration period

(bumetizole group at 1000 mg/kg)		
Male No.	Organ/Tissue	Findings
M04401	Whole organs and tissues	No abnormality detected
M04402	Lung	Accumulation, foam cell: ±
	Other organs and tissues	No abnormality detected
M04403	Whole organs and tissues	No abnormality detected
M04404	Whole organs and tissues	No abnormality detected
M04405	Jejunum	Mineralization, Peyer's patch: ±
	Prostate	Cellular infiltration, lymphoid cell: ±
	Other organs and tissues	No abnormality detected
M04406	Whole organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

## Appendix 46-1 Individual histopathological findings of female rats on termination of administration period

(Control group)		
Female No.	Organ/Tissue	Findings
F01151	Spleen	Hematopoiesis, extramedullary: ±
	Other organs and tissues	No abnormality detected
F01152	Spleen	Hematopoiesis, extramedullary: ±
	Other organs and tissues	No abnormality detected
F01153	Whole organs and tissues	No abnormality detected
F01154	Whole organs and tissues	No abnormality detected
F01155	Spleen	Hematopoiesis, extramedullary: ±
	Other organs and tissues	No abnormality detected
F01156	Whole organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

## Appendix 46-2 Individual histopathological findings of female rats on termination of administration period

(bumetizole group at 1000 mg/kg)		
Female No.	Organ/Tissue	Findings
F04451	Whole organs and tissues	No abnormality detected
F04452	Whole organs and tissues	No abnormality detected
F04453	Spleen	Hematopoiesis, extramedullary: ±
	Other organs and tissues	No abnormality detected
F04454	Eyeball	Dysplasia, retina, right: ±
	Other organs and tissues	No abnormality detected
F04455	Jejunum	Mineralization, Peyer's patch: ±
	Other organs and tissues	No abnormality detected
F04456	Whole organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

## Appendix 47-1 Individual reproductive functions of male rats and female rats

(Control group)

Female No.	Administration			Pairing			Copulation (+) or non-copulation (-)	Pregnancy (+) or non-pregnancy (-)	Number of days till copulation after pairing	
				Male No.	Days					
	1	7	14		Days	1	7	14		
F01151	DDPEDDPEDDPEDD	3	M01101	D+			+	+	1	
F01152	DPEDDPEDDPEDDP	3	M01102	EDDP+			+	+	4	
F01153	DDPEDDDDDDDDDD	1	M01103	DD+			+	+	2	
F01154	PEMDPEDDPEDDPE	4	M01104	DDP+			+	+	3	
F01155	DPEDDPEDDPEDDP	3	M01105	EDDP+			+	+	4	
F01156	EDDEMDPEDDPEM	4	M01106	DP+			+	+	2	
F01157	DDEMMPEDDDEDDP	3	M01107	EDDD+			+	+	4	
F01158	DPEDDPEDDPEDDP	3	M01108	EDDP+			+	+	4	
F01159	EMDPEMDPEMDPEM	4	M01109	DD+			+	-	2	
F01160	DPEDDPEDDPEDDP	3	M01110	EDDP+			+	+	4	
F01161	DPEDDPEDDPEDDP	3	M01111	EDDP+			+	+	4	
F01162	DDPEDDPEMDPEDD	3	M01112	P+			+	+	1	
Number of females		12					12	11	12	
Mean		3.1							2.9	
S.D.		0.8							1.2	
%							100.0 a)	91.7 b)		

When estrus continued for 2 consecutive days or more, it was counted only once.

a): Copulation index (%); (Number of pairs with successful copulation/number of pairs)×100.

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

P: Pro-estrus, E: Estrus, M: Meta-estrus, D: Di-estrus, +: Copulation.

## Appendix 47-2 Individual reproductive functions of male rats and female rats

(bumetizole group at 62.5 mg/kg)

Female No.	Administration			Pairing			Copulation (+) or non-copulation (-)	Pregnancy (+) or non-pregnancy (-)	Number of days till copulation after pairing		
				Male No.	Days						
	1	7	14		1	7	14				
F02251	EDDDEMDEMDEMPEM	4	M02201	DP+			+	+	2		
F02252	PEMDPEMDPEMDPE	4	M02202	DDP+			+	+	3		
F02253	EDDPEMDPEMDPEM	4	M02203	DP+			+	+	2		
F02254	PEMDDEDDPEDDPE	4	M02204	DDD+			+	+	3		
F02255	DDPEDDPEDDPEDD	3	M02205	P+			+	+	1		
F02256	MDPEDDPEMDPEDD	3	M02206	P+			+	+	1		
F02257	DPEMDPEMDPEDDP	3	M02207	EDDP+			+	+	4		
F02258	DDPEDDPEDDPEDD	3	M02208	P+			+	+	1		
F02259	EDDPEMDPEMDPEM	4	M02209	DP+			+	+	2		
F02260	EDDPEDDPEMDPEM	4	M02210	DP+			+	+	2		
F02261	DDPEDDPEDDPEMD	3	M02211	P+			+	+	1		
F02262	DDPEDDPEDDPEMD	3	M02212	P+			+	+	1		
Number of females		12					12	12	12		
Mean		3.5							1.9		
S.D.		0.5							1.0		
%							100.0 a)	100.0 b)			
Significance											
Statistical method		DU					UA	CHI-2	DT		

When estrus continued for 2 consecutive days or more, it was counted only once.

a): Copulation index (%); (Number of pairs with successful copulation/number of pairs)×100.

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

P: Pro-estrus, E: Estrus, M: Meta-estrus, D: Di-estrus, +: Copulation.

DU: Analysis by Dunnett's test.

CHI-2: Analysis by chi-square test (2×2).

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 47-3 Individual reproductive functions of male rats and female rats

(bumetizole group at 250 mg/kg)

Female No.	Administration			Pairing			Copulation (+) or non-copulation (-)	Pregnancy (+) or non-pregnancy (-)	Number of days till copulation after pairing	
				Male No.	Days					
	1	7	14		Days	1	7	14		
F03351	DDPEDDPEDDPEDD	3	M03301	P+			+	+	1	
F03352	PEDDPEDDPEDDP	4	M03302	DDP+			+	+	3	
F03353	PEDDPEDDPEDDP	4	M03303	DDP+			+	+	3	
F03354	DPEDDPEDDPEDD	3	M03304	EDDP+			+	+	4	
F03355	DDPEDDPEDDPEDD	3	M03305	P+			+	+	1	
F03356	EDDPEDDPEDMDPED	4	M03306	DP+			+	+	2	
F03357	DPEDDPEDDPEDDP	3	M03307	EDDP+			+	+	4	
F03358	DPEDDPEMDPEDD	3	M03308	EDDP+			+	+	4	
F03359	PEDDPEMDPEDDP	4	M03309	DDP+			+	+	3	
F03360	DDPEDDPEDDPEDD	3	M03310	P+			+	+	1	
F03361	DPEMDPEMDPEDD	3	M03311	EDDP+			+	+	4	
F03362	PEDDPEDDPEDDP	4	M03312	DDP+			+	+	3	
Number of females		12					12	12	12	
Mean		3.4							2.8	
S.D.		0.5							1.2	
%							100.0 a)	100.0 b)		
Significance										
Statistical method		DU					UA	CHI-2	DT	

When estrus continued for 2 consecutive days or more, it was counted only once.

a): Copulation index (%); (Number of pairs with successful copulation/number of pairs)×100.

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

P: Pro-estrus, E: Estrus, M: Meta-estrus, D: Di-estrus, +: Copulation.

DU: Analysis by Dunnett's test.

CHI-2: Analysis by chi-square test (2×2).

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

## Appendix 47-4 Individual reproductive functions of male rats and female rats

(bumetizole group at 1000 mg/kg)

Female No.	Administration			Pairing			Copulation (+) or non-copulation (-)	Pregnancy (+) or non-pregnancy (-)	Number of days till copulation after pairing	
				Male No.	Days					
	1	7	14			1	7	14		
F04451	DPEDDPEMDPEDDP	3		M04401	B	DDDDDDDDDDDD+	+	+	13	
F04452	DDEDDPEDDPEDDP	3		M04402	E	DDP+	+	+	4	
F04453	DPEDDPEMDPEDDP	3		M04403	E	DDP+	+	+	4	
F04454	DDPEDDPEDDPEDD	3		M04404	P	+	+	+	1	
F04455	DDPEDDPEDDPEDD	3		M04405	P	+	+	+	1	
F04456	EDDDEMPEMDDBD	4		M04406	D	P+	+	+	2	
F04457	EDDPEDDPEMDPEM	4		M04407	D	P+	+	+	2	
F04458	EMDPEMDPEMDPEM	4		M04408	D	P+	+	+	2	
F04459	DPEDDPEDDPEDDP	3		M04409	E	DDP+	+	+	4	
F04460	DDPEDDPEDDPEDD	3		M04410	P	+	+	+	1	
F04461	EMDPEDDPEMDPED	4		M04411	D	P+	+	+	2	
F04462	DDPEDDDDEDDDED	3		M04412	D	+	+	-	1	
Number of females		12					12	11	12	
Mean		3.3							3.1	
S.D.		0.5							3.3	
%							100.0 a)	91.7 b)		
Significance										
Statistical method		DU					UA	CHI-2	DT	

When estrus continued for 2 consecutive days or more, it was counted only once.

a): Copulation index (%); (Number of pairs with successful copulation/number of pairs)×100.

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

P: Pro-estrus, E: Estrus, M: Meta-estrus, D: Di-estrus, +: Copulation.

DU: Analysis by Dunnett's test.

CHI-2: Analysis by chi-square test (2×2).

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 48-1 Observation of pups ( $F_1$ ) from individual dams

(Control group)		Dam No.	Length of gestation (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Gestation index	Number of pups born				Delivery index (%)	Birth index (%)	Live birth index (%)	Number of live pups on Day 4 of lactation			Viability index (%)					
								Live		Male	Female	Total	Sex ratio										
								Total	Stillbirths					Male	Female	Total							
F01151	23	15	14	93	+	14	0	8	6	14	1.33	100	100	100	8	6	14	1.33	100				
F01152	22	15	14	93	+	14	0	6	8	14	0.75	100	100	100	6	8	14	0.75	100				
F01153	22	16	14	88	+	13	0	6	7	13	0.86	93	93	100	5	6	11	0.83	85				
F01154	22	19	17	89	+	16	0	8	8	16	1.00	94	94	100	8	8	16	1.00	100				
F01155	22	15	13	87	+	13	0	5	8	13	0.63	100	100	100	5	8	13	0.63	100				
F01156	22	15	13	87	+	13	0	6	7	13	0.86	100	100	100	6	7	13	0.86	100				
F01157	22	16	15	94	+	14	0	8	6	14	1.33	93	93	100	8	6	14	1.33	100				
F01158	22	17	14	82	+	13	0	7	6	13	1.17	93	93	100	7	6	13	1.17	100				
F01159	Non-pregnancy																						
F01160	23	18	16	89	+	16	2	♀2	7	7	14	1.00	88	88	88	7	7	14	1.00	100			
F01161	23	19	15	79	+	13	0	7	6	13	1.17	87	87	100	7	6	13	1.17	100				
F01162	22	15	13	87	+	13	0	8	5	13	1.60	100	100	100	8	5	13	1.60	100				
Number of dams	11	11	11	11		11	11			11	11	11	11	11	11	11	11	11					
Total		180	158		11 a)	152	2		76	74	150				75	73	148						
Mean	22.3	16.4	14.4	88.0		13.8	0.2				13.6	1.06	95.2	95.3	98.9		13.5	1.06	98.6				
S.D.	0.5	1.6	1.3	4.6		1.2	0.6				0.9	0.29	5.1	5.0	3.6		1.2	0.29	4.6				
%						100.0																	

Gestation index: +: Dams with live pups, -: Pregnant dams without live pups.

(Continued)

a): Number of dams with live pups.

Appendix 48-1 (Continued) Observation of pups ( $F_1$ ) from individual dams

(Control group) Dam No.	External abnormalities		Acaudate	
	(Number)	(%)	(Number)	(%)
F01151	0	0	0	0
F01152	0	0	0	0
F01153	0	0	0	0
F01154	0	0	0	0
F01155	0	0	0	0
F01156	0	0	0	0
F01157	0	0	0	0
F01158	0	0	0	0
F01159	Non-pregnancy			
F01160	0	0	0	0
F01161	0	0	0	0
F01162	0	0	0	0
Number of dams	11		11	
Total	0		0	
Mean		0.0		0.0
S.D.		0.0		0.0
%				

Appendix 48-2 Observation of pups ( $F_1$ ) from individual dams

Dam No.	Length of gestation (days)	Number of corpora lutea	Number of implan- tation scars	Implan- tation index (%)	Ges- ta- tion index	Number of pups born					Deli- very index (%)	Birth index (%)	Live birth index (%)	Number of live pups on Day 4 of lactation			Via- bi- li- ty index (%)			
						Live			Male	Female				Male	Female	Total				
						Total	Stillbirths	Male												
F02251	22	12	12	100	+	12	0	8	4	12	2.00	100	100	8	3	11	2.67	92		
F02252	22	15	14	93	+	11	1	♀1	3	7	10	0.43	71	71	91	3	7	10	0.43	100
F02253	23	18	17	94	+	15	0	12	3	15	4.00	88	88	100	12	3	15	4.00	100	
F02254	22	17	17	100	+	17	1	♂1	9	7	16	1.29	94	94	94	9	6	15	1.50	94
F02255	22	12	12	100	+	12	0	5	7	12	0.71	100	100	5	6	11	0.83	92		
F02256	23	18	18	100	+	16	0	8	8	16	1.00	89	89	100	8	8	16	1.00	100	
F02257	23	18	17	94	+	16	1	♀1	6	9	15	0.67	88	88	94	6	9	15	0.67	100
F02258	23	14	14	100	+	12	0	6	6	12	1.00	86	86	100	6	6	12	1.00	100	
F02259	23	16	16	100	+	14	0	10	4	14	2.50	88	88	100	10	4	14	2.50	100	
F02260	23	17	15	88	+	15	1	♂1	5	9	14	0.56	93	93	93	5	8	13	0.63	93
F02261	22	15	13	87	+	13	1	♀1	5	7	12	0.71	92	92	92	5	7	12	0.71	100
F02262	22	15	15	100	+	13	0	7	6	13	1.17	87	87	100	7	6	13	1.17	100	
Number of dams	12	12	12	12		12	12			12	12	12	12	12	12	12	12	12	12	
Total		187	180		12 a)	166	5	84	77	161				84	73	157				
Mean	22.5	15.6	15.0	96.3		13.8	0.4			13.4	1.34	89.7	89.7	97.0			13.1	1.43	97.5	
S.D.	0.5	2.2	2.0	5.0		1.9	0.5			1.9	1.04	7.5	7.5	3.8			1.9	1.08	3.7	
%					100.0															
Significance					*															
Statistical method	DU	DU	DU	DU	UA	DU	DU			DT	DT	DU	DU	DU	DU	DU	DT	DU		

Gestation index: +: Dams with live pups, -: Pregnant dams without live pups.

(Continued)

a): Number of dams with live pups.

Significantly different from control group (\*: P&lt;0.05).

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 48-2 (Continued) Observation of pups ( $F_1$ ) from individual dams

(bumetizole group at 62.5 mg/kg)				
Dam No.	External abnormalities		Acaudate	
	(Number)	(%)	(Number)	(%)
F02251	0	0	0	0
F02252	0	0	0	0
F02253	0	0	0	0
F02254	0	0	0	0
F02255	0	0	0	0
F02256	0	0	0	0
F02257	0	0	0	0
F02258	0	0	0	0
F02259	0	0	0	0
F02260	0	0	0	0
F02261	0	0	0	0
F02262	0	0	0	0
Number of dams	12		12	
Total	0		0	
Mean		0.0		0.0
S.D.		0.0		0.0
%				
Significance				
Statistical method	DU		DU	

DU: Analysis by Dunnett's test.

Appendix 48-3 Observation of pups ( $F_1$ ) from individual dams

Dam No.	Length of gestation (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Gestation index	Number of pups born						Delivery index (%)	Birth index (%)	Live birth index (%)	Number of live pups on Day 4 of lactation			Viability index (%)				
						Live			Male	Female	Total				Male	Female	Total					
						Total	Stillbirths	Male														
F03351	22	19	19	100	+	18	0	8	10	18	0.80	95	95	100	8	10	18	0.80	100			
F03352	22	18	16	89	+	13	0	9	4	13	2.25	81	81	100	9	4	13	2.25	100			
F03353	23	15	14	93	+	14	1	♀1	9	4	13	2.25	93	93	93	9	4	13	2.25	100		
F03354	22	16	13	81	+	10	1	♂1 (A)	6	3	9	2.00	69	69	90	6	3	9	2.00	100		
F03355	22	18	17	94	+	16	0	8	8	16	1.00	94	94	100	8	8	16	1.00	100			
F03356	23	21	18	86	+	17	2	♂1·♀1	5	10	15	0.50	83	83	88	5	8	13	0.63	87		
F03357	22	16	14	88	+	14	1	♀1	12	1	13	12.00	93	93	93	12	1	13	12.00	100		
F03358	22	17	16	94	+	15	0	8	7	15	1.14	94	94	100	8	7	15	1.14	100			
F03359	22	15	13	87	+	13	0	8	5	13	1.60	100	100	100	8	5	13	1.60	100			
F03360	22	18	16	89	+	15	1	♀1	6	8	14	0.75	88	88	93	6	8	14	0.75	100		
F03361	23	18	18	100	+	14	1	♀1	5	8	13	0.63	72	72	93	5	8	13	0.63	100		
F03362	23	17	14	82	+	9	0	6	3	9	2.00	64	64	100	6	3	9	2.00	100			
Number of dams	12	12	12	12		12	12			12	12	12	12	12	12	12	12	12	12			
Total		208	188		12 a)	168	7		90	71	161				90	69	159					
Mean	22.3	17.3	15.7	90.3		14.0	0.6				13.4	2.24	85.5	85.5	95.8			13.3	2.25	98.9		
S.D.	0.5	1.7	2.1	6.2		2.6	0.7				2.6	3.14	11.5	11.7	4.6			2.5	3.13	3.8		
%					100.0																	

## Significance

Statistical method DU DU DU DU UA DU DU DT DT DU DU DU DU DT DU (Continued)

Gestation index: +: Dams with live pups, -: Pregnant dams without live pups.

a): Number of dams with live pups.

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

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

A: Agnathia.

Appendix 48-3 (Continued) Observation of pups ( $F_1$ ) from individual dams

(bumetizole group at 250 mg/kg)				
Dam No.	External abnormalities	Acaudate		
	(Number)	(%)	(Number)	(%)
F03351	0	0	0	0
F03352	0	0	0	0
F03353	0	0	0	0
F03354	0	0	0	0
F03355	0	0	0	0
F03356	0	0	0	0
F03357	0	0	0	0
F03358	0	0	0	0
F03359	0	0	0	0
F03360	0	0	0	0
F03361	0	0	0	0
F03362	0	0	0	0
Number of dams	12		12	
Total	0		0	
Mean		0.0		0.0
S.D.		0.0		0.0
%				
Significance				
Statistical method		DU		DU

DU: Analysis by Dunnett's test.

Appendix 48-4 Observation of pups ( $F_1$ ) from individual dams

Dam No.	Length of gestation (days)	Number of corpora lutea	Number of implan- tation scars	Implan- tation index (%)	Ges- ta- tion index	Number of pups born					Deli- very index (%)	Birth index (%)	Live birth index (%)	Number of live pups on Day 4 of lactation			Via- bi- li- ty index (%)				
						Stillbirths		Live						Male	Female	Total	Sex ratio				
						Total	Stillbirths	Male	Female	Total											
F04451	22	17	12	71	+	12	1	♀1	5	6	11	0.83	92	92	5	6	11	0.83	100		
F04452	22	17	17	100	+	16	1	♂1	8	7	15	1.14	88	88	8	7	15	1.14	100		
F04453	22	15	15	100	+	14	0		7	7	14	1.00	93	93	6	7	13	0.86	93		
F04454	23	15	15	100	+	12	0		4	8	12	0.50	80	80	4	8	12	0.50	100		
F04455	22	17	17	100	+	16	1	♂1	8	7	15	1.14	88	88	8	6	14	1.33	93		
F04456	23	18	16	89	+	15	1	♂1	7	7	14	1.00	88	88	7	7	14	1.00	100		
F04457	22	17	16	94	+	16	0		6	10	16	0.60	100	100	6	10	16	0.60	100		
F04458	22	16	16	100	+	16	0		7	9	16	0.78	100	100	7	9	16	0.78	100		
F04459	23	19	16	84	+	16	0		12	4	16	3.00	100	100	12	4	16	3.00	100		
F04460	22	15	14	93	+	14	0		9	5	14	1.80	100	100	9	5	14	1.80	100		
F04461	22	15	15	100	+	15	0		9	6	15	1.50	100	100	9	6	15	1.50	100		
F04462	Non-pregnancy																				
1588	Number of dams	11	11	11	11		11	11		11	11	11	11	11	11	11	11	11			
	Total		181	169		11 a)	162	4		82	76	158			81	75	156				
	Mean	22.3	16.5	15.4	93.7		14.7	0.4				14.4	1.21	93.5	93.5	97.5		14.2			
	S.D.	0.5	1.4	1.4	9.3		1.6	0.5				1.6	0.70	7.0	7.0	3.4		1.7			
	%					100.0											0.71	2.8			

## Significance

Statistical method	DU	DU	DU	DU	UA	DU	DU	DT	DT	DU	DU	DU	DU	DU	DU	DT	DU
--------------------	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----

Gestation index: +: Dams with live pups, -: Pregnant dams without live pups.

(Continued)

a): Number of dams with live pups.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 48-4 (Continued) Observation of pups ( $F_1$ ) from individual dams

(bumetizole group at 1000 mg/kg)

Dam No.	External abnormalities		Acaudate	
	(Number)	(%)	(Number)	(%)
F04451	0	0	0	0
F04452	0	0	0	0
F04453	0	0	0	0
F04454	0	0	0	0
F04455	0	0	0	0
F04456	1	7	1	7
F04457	0	0	0	0
F04458	0	0	0	0
F04459	0	0	0	0
F04460	0	0	0	0
F04461	0	0	0	0
F04462	Non-pregnancy			
Number of dams	11		11	
Total	1		1	
Mean		0.6		0.6
S.D.		2.1		2.1
%				
Significance				
Statistical method	DU		DU	

DU: Analysis by Dunnett's test.

## Appendix 49-1 Delivery conditions and nursing conditions of individual dams

Dam No.	Delivery conditions	Nursing conditions				
		0	1	2	3	4
F01151	N	N	N	N	N	N
F01152	N	N	N	N	N	N
F01153	N	N	N	N	N	N
F01154	N	N	N	N	N	N
F01155	N	N	N	N	N	N
F01156	N	N	N	N	N	N
F01157	N	N	N	N	N	N
F01158	N	N	N	N	N	N
F01159	Non-pregnancy					
F01160	N	N	N	N	N	N
F01161	N	N	N	N	N	N
F01162	N	N	N	N	N	N
Number of dams	11	11	11	11	11	11
	N	11	11	11	11	11

N: Normal.

## Appendix 49-2 Delivery conditions and nursing conditions of individual dams

(bumetizole group at 62.5 mg/kg)

Dam No.	Delivery conditions	Nursing conditions				
		0	1	2	3	4
F02251	N	N	N	N	N	N
F02252	N	N	N	N	N	N
F02253	N	N	N	N	N	N
F02254	N	N	N	N	N	N
F02255	N	N	N	N	N	N
F02256	N	N	N	N	N	N
F02257	N	N	N	N	N	N
F02258	N	N	N	N	N	N
F02259	N	N	N	N	N	N
F02260	N	N	N	N	N	N
F02261	N	N	N	N	N	N
F02262	N	N	N	N	N	N
Number of dams	12	12	12	12	12	12
	N	12	12	12	12	12

N: Normal.

## Appendix 49-3 Delivery conditions and nursing conditions of individual dams

(bumetizole group at 250 mg/kg)

Dam No.	Delivery conditions	Nursing conditions				
		0	1	2	3	4
F03351	N	N	N	N	N	N
F03352	N	N	N	N	N	N
F03353	N	N	N	N	N	N
F03354	N	N	N	N	N	N
F03355	N	N	N	N	N	N
F03356	N	N	N	N	N	N
F03357	N	N	N	N	N	N
F03358	N	N	N	N	N	N
F03359	N	N	N	N	N	N
F03360	N	N	N	N	N	N
F03361	N	N	N	N	N	N
F03362	N	N	N	N	N	N
Number of dams	12	12	12	12	12	12
N	12	12	12	12	12	12

N: Normal.

## Appendix 49-4 Delivery conditions and nursing conditions of individual dams

(bumetizole group at 1000 mg/kg)

Dam No.	Delivery conditions	Nursing conditions				
		0	1	2	3	4
F04451	N	N	N	N	N	N
F04452	N	N	N	N	N	N
F04453	N	N	N	N	N	N
F04454	N	N	N	N	N	N
F04455	N	N	N	N	N	N
F04456	N	N	N	N	N	N
F04457	N	N	N	N	N	N
F04458	N	N	N	N	N	N
F04459	N	N	N	N	N	N
F04460	N	N	N	N	N	N
F04461	N	N	N	N	N	N
F04462	Non-pregnancy					
Number of dams	11	11	11	11	11	11
N	11	11	11	11	11	11

N: Normal.

Appendix 50-1 General signs of pups ( $F_1$ ) from individual dams

(Control group)		Days of lactation				
Dam No.	Number of pups and general signs	0	1	2	3	4
F01151	Number of pups	14	14	14	14	14
	Normal	14	14	14	14	14
F01152	Number of pups	14	14	14	14	14
	Normal	14	14	14	14	14
F01153	Number of pups	13	13	13	12	12
	Normal	13	13	12	12	11
	Death	0	0	1	0	1
F01154	Number of pups	16	16	16	16	16
	Normal	16	16	16	16	16
F01155	Number of pups	13	13	13	13	13
	Normal	13	13	13	13	13
F01156	Number of pups	13	13	13	13	13
	Normal	13	13	13	13	13
F01157	Number of pups	14	14	14	14	14
	Normal	14	14	14	14	14
F01158	Number of pups	13	13	13	13	13
	Normal	13	13	13	13	13
F01159	Non-pregnancy					
F01160	Number of pups	16	14	14	14	14
	Normal	14	14	14	14	14
	Death	2	0	0	0	0
F01161	Number of pups	13	13	13	13	13
	Normal	13	13	13	13	13
F01162	Number of pups	13	13	13	13	13
	Normal	13	13	13	13	13
	Number of pups	152	150	150	149	149
	Normal	150	150	149	149	148
	Death	2	0	1	0	1

Appendix 50-2 General signs of pups ( $F_1$ ) from individual dams

		(bumetizole group at 62.5 mg/kg)				
Dam No.	Number of pups and general signs	Days of lactation				
		0	1	2	3	4
F02251	Number of pups	12	12	12	12	12
	Normal	12	12	12	12	11
	Death	0	0	0	0	1
F02252	Number of pups	11	10	10	10	10
	Normal	10	10	10	10	10
	Death	1	0	0	0	0
F02253	Number of pups	15	15	15	15	15
	Normal	15	15	15	15	15
F02254	Number of pups	17	16	16	16	16
	Normal	16	16	16	16	15
	Death	1	0	0	0	1
F02255	Number of pups	12	12	12	11	11
	Normal	12	12	11	11	11
	Death	0	0	1	0	0
F02256	Number of pups	16	16	16	16	16
	Normal	16	16	16	16	16
F02257	Number of pups	16	15	15	15	15
	Normal	15	15	15	15	15
	Death	1	0	0	0	0
F02258	Number of pups	12	12	12	12	12
	Normal	12	12	12	12	12
F02259	Number of pups	14	14	14	14	14
	Normal	14	14	14	14	14
F02260	Number of pups	15	14	13	13	13
	Normal	14	13	13	13	13
	Death	1	1	0	0	0
F02261	Number of pups	13	12	12	12	12
	Normal	12	12	12	12	12
	Death	1	0	0	0	0
F02262	Number of pups	13	13	13	13	13
	Normal	13	13	13	13	13
	Number of pups	166	161	160	159	159
	Normal	161	160	159	159	157
	Death	5	1	1	0	2

Appendix 50-3 General signs of pups ( $F_1$ ) from individual dams

(bumetizole group at 250 mg/kg)

Dam No.	Number of pups and general signs	Days of lactation				
		0	1	2	3	4
F03351	Number of pups	18	18	18	18	18
	Normal	18	18	18	18	18
F03352	Number of pups	13	13	13	13	13
	Normal	13	13	13	13	13
F03353	Number of pups	14	13	13	13	13
	Normal	13	13	13	13	13
	Death	1	0	0	0	0
F03354	Number of pups	10	9	9	9	9
	Normal	9	9	9	9	9
	Death	1	0	0	0	0
F03355	Number of pups	16	16	16	16	16
	Normal	16	16	16	16	16
F03356	Number of pups	17	15	13	13	13
	Normal	15	13	13	13	13
	Death	2	2	0	0	0
F03357	Number of pups	14	13	13	13	13
	Normal	13	13	13	13	13
	Death	1	0	0	0	0
F03358	Number of pups	15	15	15	15	15
	Normal	15	15	15	15	15
F03359	Number of pups	13	13	13	13	13
	Normal	13	13	13	13	13
F03360	Number of pups	15	14	14	14	14
	Normal	14	14	14	14	14
	Death	1	0	0	0	0
F03361	Number of pups	14	13	13	13	13
	Normal	13	13	13	13	13
	Death	1	0	0	0	0
F03362	Number of pups	9	9	9	9	9
	Normal	9	9	9	9	9
	Number of pups	168	161	159	159	159
	Normal	161	159	159	159	159
	Death	7	2	0	0	0

Appendix 50-4 General signs of pups ( $F_1$ ) from individual dams

(bumetizole group at 1000 mg/kg)

Dam No.	Number of pups and general signs	Days of lactation				
		0	1	2	3	4
F04451	Number of pups	12	11	11	11	11
	Normal	11	11	11	11	11
	Death	1	0	0	0	0
F04452	Number of pups	16	15	15	15	15
	Normal	15	15	15	15	15
	Death	1	0	0	0	0
F04453	Number of pups	14	14	13	13	13
	Normal	14	13	13	13	13
	Death	0	1	0	0	0
F04454	Number of pups	12	12	12	12	12
	Normal	12	12	12	12	12
F04455	Number of pups	16	15	15	15	14
	Normal	15	15	15	14	14
	Death	1	0	0	1	0
F04456	Number of pups	15	14	14	14	14
	Normal	14	14	14	14	14
	Death	1	0	0	0	0
F04457	Number of pups	16	16	16	16	16
	Normal	16	16	16	16	16
F04458	Number of pups	16	16	16	16	16
	Normal	16	16	16	16	16
F04459	Number of pups	16	16	16	16	16
	Normal	16	16	16	16	16
F04460	Number of pups	14	14	14	14	14
	Normal	14	14	14	14	14
F04461	Number of pups	15	15	15	15	15
	Normal	15	15	15	15	15
F04462	Non-pregnancy					
	Number of pups	162	158	157	157	156
	Normal	158	157	157	156	156
	Death	4	1	0	1	0

Appendix 51-1 Body weights (g, per dam) of pups ( $F_1$ ) from individual dams

Dam No.	(Control group)													
	Days of lactation													
	Male weight		Female weight		Mean pups weight		Litter weight							
	0	4	0	4	0	4	0	4	0	4				
F01151	7.8	(8)	11.5	(8)	7.5	(6)	10.7	(6)	7.7	(14)	11.2	(14)	107.4	156.2
F01152	6.7	(6)	11.4	(6)	6.3	(8)	10.7	(8)	6.5	(14)	11.0	(14)	90.6	154.0
F01153	6.5	(6)	9.7	(6)	5.7	(7)	9.4	(6)	6.1	(13)	9.6	(12)	78.9	114.6
F01154	6.6	(8)	10.1	(8)	6.0	(8)	9.1	(8)	6.3	(16)	9.6	(16)	100.8	153.6
F01155	6.9	(5)	10.6	(5)	6.4	(8)	10.0	(8)	6.6	(13)	10.2	(13)	85.7	133.0
F01156	6.8	(6)	10.7	(6)	6.2	(7)	9.9	(7)	6.5	(13)	10.3	(13)	84.2	133.5
F01157	6.4	(8)	9.9	(8)	6.3	(6)	10.1	(6)	6.4	(14)	10.0	(14)	89.0	139.8
F01158	6.7	(7)	11.7	(7)	5.9	(6)	10.9	(6)	6.3	(13)	11.3	(13)	82.3	147.3
F01159	Non-pregnancy													
F01160	7.4	(7)	12.4	(7)	7.0	(7)	12.0	(7)	7.2	(14)	12.2	(14)	100.8	170.8
F01161	7.3	(7)	11.1	(7)	7.2	(6)	11.1	(6)	7.3	(13)	11.1	(13)	94.3	144.3
F01162	6.3	(8)	10.3	(8)	6.2	(5)	10.5	(5)	6.3	(13)	10.4	(13)	81.4	134.9
Number of dams	11		11		11		11		11		11		11	
Mean	6.9		10.9		6.4		10.4		6.7		10.6		90.5	143.8
S.D.	0.5		0.8		0.6		0.8		0.5		0.8		9.3	15.1

Figures in parentheses indicate number of pups.

Appendix 51-2 Body weights (g, per dam) of pups ( $F_1$ ) from individual dams

(bumetizole group at 62.5 mg/kg)

Dam No.	Days of lactation											
	Male weight				Female weight				Mean pups weight		Litter weight	
	0		4		0		4		0	4	0	4
F02251	6.7	(8)	11.6	(8)	6.2	(4)	11.2	(3)	6.5	(12)	11.5	(11)
F02252	7.0	(3)	11.5	(3)	6.5	(7)	11.0	(7)	6.7	(10)	11.2	(10)
F02253	7.6	(12)	11.6	(12)	7.1	(3)	10.9	(3)	7.5	(15)	11.5	(15)
F02254	6.5	(9)	10.4	(9)	6.2	(7)	9.6	(6)	6.4	(16)	10.1	(15)
F02255	6.9	(5)	11.5	(5)	6.6	(7)	11.0	(6)	6.7	(12)	11.2	(11)
F02256	7.2	(8)	10.6	(8)	6.5	(8)	9.7	(8)	6.9	(16)	10.2	(16)
F02257	8.1	(6)	10.9	(6)	7.6	(9)	10.4	(9)	7.8	(15)	10.6	(15)
F02258	8.6	(6)	13.2	(6)	8.2	(6)	12.9	(6)	8.4	(12)	13.1	(12)
F02259	7.4	(10)	10.6	(10)	7.1	(4)	9.9	(4)	7.3	(14)	10.4	(14)
F02260	7.0	(5)	10.5	(5)	6.8	(9)	10.3	(8)	6.9	(14)	10.4	(13)
F02261	6.3	(5)	10.0	(5)	6.0	(7)	9.5	(7)	6.1	(12)	9.7	(12)
F02262	6.9	(7)	11.4	(7)	6.3	(6)	10.8	(6)	6.6	(13)	11.1	(13)
Number of dams	12		12		12		12		12		12	
Mean	7.2		11.2		6.8		10.6		7.0		10.9	
S.D.	0.7		0.8		0.6		0.9		0.7		0.9	
Significance												
Statistical method	DU		DU		DU		DU		DU		DU	

Figures in parentheses indicate number of pups.

DU: Analysis by Dunnett's test.

Appendix 51-3 Body weights (g, per dam) of pups ( $F_1$ ) from individual dams

(bumetizole group at 250 mg/kg)

Dam No.	Days of lactation											
	Male weight				Female weight				Mean pups weight		Litter weight	
	0	4	0	4	0	4	0	4	0	4	0	4
F03351	6.4	(8)	10.2	(8)	6.0	(10)	9.7	(10)	6.2	(18)	9.9	(18)
F03352	7.0	(9)	10.9	(9)	6.6	(4)	9.8	(4)	6.9	(13)	10.6	(13)
F03353	7.4	(9)	12.4	(9)	7.3	(4)	12.4	(4)	7.4	(13)	12.4	(13)
F03354	6.9	(6)	11.3	(6)	6.1	(3)	10.6	(3)	6.6	(9)	11.1	(9)
F03355	6.3	(8)	10.7	(8)	6.2	(8)	10.3	(8)	6.3	(16)	10.5	(16)
F03356	7.6	(5)	11.4	(5)	6.7	(10)	10.3	(8)	7.0	(15)	10.7	(13)
F03357	6.9	(12)	10.6	(12)	5.9	(1)	9.5	(1)	6.8	(13)	10.5	(13)
F03358	6.6	(8)	10.8	(8)	6.2	(7)	10.6	(7)	6.4	(15)	10.7	(15)
F03359	6.5	(8)	10.7	(8)	6.5	(5)	10.1	(5)	6.5	(13)	10.5	(13)
F03360	6.6	(6)	10.4	(6)	6.3	(8)	9.6	(8)	6.4	(14)	9.9	(14)
F03361	8.0	(5)	12.4	(5)	7.6	(8)	11.6	(8)	7.8	(13)	11.9	(13)
F03362	8.3	(6)	15.2	(6)	8.1	(3)	14.6	(3)	8.2	(9)	15.0	(9)
Number of dams	12		12		12		12		12		12	
Mean	7.0		11.4		6.6		10.8		6.9		11.1	
S.D.	0.6		1.4		0.7		1.5		0.6		1.4	
Significance												
Statistical method	DU		DU		DU		DU		DU		DU	

Figures in parentheses indicate number of pups.

DU: Analysis by Dunnett's test.

Appendix 51-4 Body weights (g, per dam) of pups ( $F_1$ ) from individual dams

(bumetizole group at 1000 mg/kg)

Dam No.	Days of lactation											
	Male weight				Female weight				Mean pups weight		Litter weight	
	0	4	0	4	0	4	0	4	0	4	0	4
F04451	6.7	(5)	11.4	(5)	6.0	(6)	10.7	(6)	6.3	(11)	11.0	(11)
F04452	6.5	(8)	10.5	(8)	6.2	(7)	10.2	(7)	6.4	(15)	10.4	(15)
F04453	6.7	(7)	11.0	(6)	6.8	(7)	11.1	(7)	6.8	(14)	11.1	(13)
F04454	7.3	(4)	11.2	(4)	7.9	(8)	11.9	(8)	7.7	(12)	11.7	(12)
F04455	5.9	(8)	10.2	(8)	5.6	(7)	9.8	(6)	5.8	(15)	10.0	(14)
F04456	7.5	(7)	12.3	(7)	7.3	(7)	11.3	(7)	7.4	(14)	11.8	(14)
F04457	6.9	(6)	11.3	(6)	6.0	(10)	9.8	(10)	6.3	(16)	10.4	(16)
F04458	6.5	(7)	10.5	(7)	6.0	(9)	9.7	(9)	6.2	(16)	10.1	(16)
F04459	7.1	(12)	9.5	(12)	6.6	(4)	8.8	(4)	7.0	(16)	9.3	(16)
F04460	6.5	(9)	10.7	(9)	6.1	(5)	10.0	(5)	6.4	(14)	10.5	(14)
F04461	6.8	(9)	10.7	(9)	6.3	(6)	10.2	(6)	6.6	(15)	10.5	(15)
F04462	Non-pregnancy											
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11
Mean	6.8	10.8	6.4	10.3	6.6	10.6	94.8	149.6				
S.D.	0.4	0.7	0.7	0.9	0.6	0.7	10.9	13.3				
Significance												
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

Figures in parentheses indicate number of pups.

DU: Analysis by Dunnett's test.

Appendix 52-1 Individual necropsy findings of dead pups ( $F_1$ )

(Control group) Dam No.	Number of dead pups	Findings		
		Normal (Number)	Abnormal (Number)	Lack of abdominal organs (Number)
F01153	1	1	0	0
Number of dams	1			
Total	1	1	0	0

Appendix 52-2 Individual necropsy findings of dead pups (F<sub>1</sub>)

(bumetizole group at 62.5 mg/kg)

Dam No.	Number of dead pups	Findings		
		Normal (Number)	Abnormal (Number)	Lack of abdominal organs (Number)
F02255	1	1	0	0
F02257	1	1	0	0
F02260	1	1	0	0
F02261	1	1	0	0
Number of dams	4			
Total	4	4	0	0

Appendix 52-3 Individual necropsy findings of dead pups ( $F_1$ )

(bumetizole group at 250 mg/kg)

Dam No.	Number of dead pups	Findings		
		Normal (Number)	Abnormal (Number)	Lack of abdominal organs (Number)
F03353	1	1	0	0
F03354	1	0	1	1
F03356	2	2	0	0
F03357	1	1	0	0
F03361	1	1	0	0
Number of dams	5			
Total	6	5	1	1

Appendix 52-4 Individual necropsy findings of dead pups (F<sub>1</sub>)

(bumetizole group at 1000 mg/kg)

Dam No.	Number of dead pups	Findings		
		Normal (Number)	Abnormal (Number)	Lack of abdominal organs (Number)
F04451	1	1	0	0
F04452	1	1	0	0
F04455	1	1	0	0
F04456	1	1	0	0
Number of dams	4			
Total	4	4	0	0

Appendix 53-1 Individual necropsy findings of pups (F<sub>1</sub>)

(Control group)

Dam No.	Number of male pups	Findings		Number of female pups	Findings	
		Normal	Abnormal		Normal	Abnormal
		(Number)	(Number)		(Number)	(Number)
F01151	8	8	0	6	6	0
F01152	6	6	0	8	8	0
F01153	5	5	0	6	6	0
F01154	8	8	0	8	8	0
F01155	5	5	0	8	8	0
F01156	6	6	0	7	7	0
F01157	8	8	0	6	6	0
F01158	7	7	0	6	6	0
F01159	Non-pregnancy					
F01160	7	7	0	7	7	0
F01161	7	7	0	6	6	0
F01162	8	8	0	5	5	0
Number of dams	11			11		
Total	75	75	0	73	73	0

Appendix 53-2 Individual necropsy findings of pups (F<sub>1</sub>)

(bumetizole group at 62.5 mg/kg)

Dam No.	Number of male pups	Findings		Number of female pups	Findings	
		Normal	Abnormal		Normal	Abnormal
		(Number)	(Number)		(Number)	(Number)
F02251	8	8	0	3	3	0
F02252	3	3	0	7	7	0
F02253	12	12	0	3	3	0
F02254	9	9	0	6	6	0
F02255	5	5	0	6	6	0
F02256	8	8	0	8	8	0
F02257	6	6	0	9	9	0
F02258	6	6	0	6	6	0
F02259	10	10	0	4	4	0
F02260	5	5	0	8	8	0
F02261	5	5	0	7	7	0
F02262	7	7	0	6	6	0
Number of dams	12			12		
Total	84	84	0	73	73	0

Appendix 53-3 Individual necropsy findings of pups (F<sub>1</sub>)

(bumetizole group at 250 mg/kg)

Dam No.	Number of male pups	Findings		Number of female pups	Findings	
		Normal	Abnormal		Normal	Abnormal
		(Number)	(Number)		(Number)	(Number)
F03351	8	8	0	10	10	0
F03352	9	9	0	4	4	0
F03353	9	9	0	4	4	0
F03354	6	6	0	3	3	0
F03355	8	8	0	8	8	0
F03356	5	5	0	8	8	0
F03357	12	12	0	1	1	0
F03358	8	8	0	7	7	0
F03359	8	8	0	5	5	0
F03360	6	6	0	8	8	0
F03361	5	5	0	8	8	0
F03362	6	6	0	3	3	0
Number of dams	12			12		
Total	90	90	0	69	69	0

Appendix 53-4 Individual necropsy findings of pups (F<sub>1</sub>)

(bumetizole group at 1000 mg/kg)

Dam No.	Number of male pups	Findings		Number of female pups	Findings	
		Normal	Abnormal		Normal	Abnormal
		(Number)	(Number)		(Number)	(Number)
F04451	5	5	0	6	6	0
F04452	8	8	0	7	7	0
F04453	6	6	0	7	7	0
F04454	4	4	0	8	8	0
F04455	8	8	0	6	6	0
F04456	7	7	0	7	7	0
F04457	6	6	0	10	10	0
F04458	7	7	0	9	9	0
F04459	12	12	0	4	4	0
F04460	9	9	0	5	5	0
F04461	9	9	0	6	6	0
F04462	Non-pregnancy					
Number of dams				11		
Total	81	81	0	75	75	0