

R-961

## 最 終 報 告 書

試験名：1,2,4,5-ベンゼンテトラカルボン酸のラットを用いた  
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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### 試験施設

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#### 4. 要約

1,2,4,5-ベンゼンテトラカルボン酸の0(対照群: 0.5 w/v%メチルセルロース溶液)、100、300、及び1000 mg/kgを、Sprague-Dawley系SPFラットの雄には交配前14日間及び交配期間を通して剖検前日(42日間)まで、雌には交配前14日間及び交配期間並びに妊娠期間を通して授乳4日まで(41~46日間)投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0及び1000 mg/kg投与群については42日間投与した後、14日間の回復期間を設け、毒性変化の可逆性を検討した。

##### 1) 反復投与毒性

詳細な一般状態の観察、機能検査、握力測定、自発運動量の測定、体重、摂餌量、尿検査(摂水量を含む)、血液学検査、血液化学検査、器官重量及び剖検所見に被験物質投与による影響は認められなかった。

一般状態では、1000 mg/kg投与群の雌雄で軟便がみられた。病理学検査では、投与期間終了時検査において、1000 mg/kg投与群の雄の胃で境界縁の扁平上皮に過形成がみられた。この変化には、休薬により可逆性がみられた。

##### 2) 生殖発生毒性

性周期、交尾までに要した日数、交尾率、授精率及び受胎率には被験物質投与の影響は認められなかった。更に、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数、出生率及び性比に被験物質投与の影響は認められず、授乳期間中の授乳状態にも異常が認められなかった。

出生児では、外表観察、出生時及び生後4日の体重及び生後4日剖検所見及び生存率に被験物質投与による変化は認められなかった。

これらの結果から、1,2,4,5-ベンゼンテトラカルボン酸の反復投与毒性に対する無影響量は雌雄ともに300 mg/kg/day、生殖発生毒性に対しては雌雄親動物及び児動物に対する無影響量はいずれも1000 mg/kg/dayと判断した。1000 mg/kg投与群で認められた胃の境界縁での扁平上皮の過形成には可逆性が認められた。

## 5. 緒言

厚生労働省医薬食品局審査管理課 化学物質安全対策室の委託により、1,2,4,5-ベンゼンテトラカルボン酸のラットを用いた経口投与による反復投与毒性・生殖発生毒性併合試験を実施したので、その成績を報告する。

なお、本試験は以下の基準を遵守し、ガイドライン等に準拠して、株式会社ボゾリサーチセンターで実施した。

## 6. 試験材料及び方法

### 6.1 被験物質及び媒体

#### 6.1.1 被験物質

1,2,4,5-ベンゼンテトラカルボン酸は  
以下の情報とともに供給された（添付資料 1）。

名称	:	1,2,4,5-ベンゼンテトラカルボン酸 1,2,4,5-Benzenetetracarboxylic acid
CAS 番号	:	89-05-4
構造式又は示性式	:	$C_6H_2(CO_2H)_4$
分子量	:	254.15
純度	:	99.9%
性状	:	白色粉末
安定性	:	関連試験終了後に被験物質製造者にて純度を確認した結果、安定性に問題はなかった（添付資料 2）。
入手量	:	2 kg
保存方法	:	室温（許容値：1~30°C、実測値：12~24°C）、暗所
保存場所	:	御殿場研究所 被験物質保存室及び第1研究棟2階被験物質調製室
残量の処置	:	被験物質 5 g を保存試料として御殿場研究所 被験物質保存室に保存した。分析用に小分けした残量は廃棄し、動物試験終了後の残量はすべて返却した。

#### 6.1.2 媒体

1) 名称	:	注射用水
ロット番号	:	6G00
規格	:	日本薬局方
製造者	:	株式会社大塚製薬工場
保存方法	:	室温
保存場所	:	御殿場研究所 第1研究棟2階被験物質調製室
2) 名称	:	メチルセルロース 400cP（以下 MC と略す）
ロット番号	:	ASN6984
規格	:	化学用
製造者	:	和光純薬工業株式会社
保存方法	:	室温

保存場所 : 御殿場研究所 第1研究棟2階被験物質調製室

## 6.2 被験液の調製

### 6.2.1 媒体の調製

必要量のMCを秤取し、注射用水に溶解後、メスシリンダーに移し、更に注射用水を加えて0.5w/v%MC溶液を調製した。

### 6.2.2 被験液の調製及び保存方法

濃度ごとに必要量の被験物質を秤量し、磁性乳鉢を用いて0.5w/v%MC溶液で懸濁後、メスシリンダーに移し、更に媒体を加えて所定の濃度(20、60及び200mg/mL液)を調製した。調製は8日間に1回以上の頻度で行い、使用時まで遮光容器(褐色ガラス瓶)に入れて冷暗所(冷蔵庫内、実測値:2~5°C)で保存し、使用前に室温に戻した。残液は吸水性のよいもの(新聞紙、ペーパータオル等)に吸収させて焼却処分した。

### 6.2.3 被験液の安定性

本被験物質の2及び200mg/mL液(媒体:0.5w/v%MC溶液)は、遮光容器で冷暗所(冷蔵庫内)8日間保存後、室温24時間は安定であることが株式会社ボゾリサーチセンターで確認されている(添付資料3、試験番号:A-2007)。

### 6.2.4 被験液の濃度・均一性確認

雄の投与第1週と投与最終週に用いる各濃度液について株式会社ボゾリサーチセンター御殿場研究所で吸光光度法により分析した。その結果、各濃度液とともに表示値に対する被験物質の割合は98.0~102.0%、C.V.値は3.1%以下であり、いずれも許容範囲内(濃度:表示値に対する割合;100±10%、C.V.:10%以下)であった(添付資料4、5)。

#### [測定対象標準物質]

製造者 : 三菱ガス化学株式会社  
名称 : 1,2,4,5-ベンゼンテトラカルボン酸  
ロット番号 : 6S27M  
保存方法 : 室温(許容値:1~30°C、実測値:18~24°C)、暗所  
保存場所 : 御殿場研究所 被験物質保存室及び生化学部標準物質保存場所

#### [測定実測試料の調製]

以下の表に従い、各濃度の測定試料(上、中、下層から採取)をマグネットクスターで攪拌しながら十分懸濁させた後、n=1ずつ採取した。採取した測定試料を以下の手順に従い、1次希釀は0.5w/v%MC溶液を用いて、また、2次希釀はメタノー

ルを用いて希釈して測定実測試料を調製した。なお、2次希釈時には1次希釈液をマグネチックスターラーで攪拌しながら採取した。

測定試料 (mg/mL)	1次希釈		2次希釈		希釈率
	採取量 (mL)	定容量 (mL)	採取量 (mL)	定容量 (mL)	
20	1	10	0.5	20	400
60	1	30	0.5	20	1200
200	0.5	50	0.5	20	4000

### [測定条件]

#### 吸光光度法測定条件

- 測定波長 : 291 nm  
 対照試料 : 媒体希釈液  
 セル : 1 cm 石英セル

### [測定値の算出]

標準試料溶液の吸光度を3回、測定実測試料の吸光度をそれぞれ1回ずつ測定し、以下の式により測定試料中の1,2,4,5-ベンゼンテトラカルボン酸濃度を求めた。

$$\text{測定試料中 } 1,2,4,5\text{-ベンゼンテトラカルボン酸濃度 (mg/mL)} = \frac{Qt}{Qs} \times A \times F \times \frac{1}{1000}$$

Qt : 測定実測試料の1,2,4,5-ベンゼンテトラカルボン酸の吸光度

Qs : 標準試料溶液の1,2,4,5-ベンゼンテトラカルボン酸の平均吸光度

A : 標準試料溶液中の1,2,4,5-ベンゼンテトラカルボン酸濃度 (μg/mL)

F : 希釈率

### 6.3 試験動物

Sprague-Dawley系SPFラット [Crl:CD(SD)、日本チャールス・リバー株式会社、厚木飼育センター] 雄雄各70匹を8週齢で入手<sup>注)</sup>し、14日間の検疫・馴化飼育を行った。その間、一般状態の観察（詳細な一般状態の観察を含む）、体重測定及び性周期検査（検疫期間終了後の9日間）を基に、雄は一般状態、雌は一般状態及び性周期にそれぞれ異常がなく、体重増加が良好な各58匹を選択し、10週齢で投与に使用した。投与開始時の体重範囲は雄で342 g~400 g、雌は213 g~260 gであった。

なお、群分けは群分け当日（投与開始の前日）の体重により層別化し、各群の平均体重ができるだけ均等となるよう各群に割付けた。個体の割付けはコンピュータを用いたブロック配置法及び無作為抽出法の組み合わせ（ブロック配置法で必要な群を構成し、試験群及び群内の個体番号を無作為に割当てた）で行った。群分けから除外された動物のうち、雌は無処置動物として15匹を継続飼育した。雄15匹はエーテル深

麻酔下で安楽死させた。なお、継続飼育した無処置雌動物は死亡などにより交配すべき相手がいない動物が認められなかつたため、交配期間終了後エーテル深麻酔下で安楽死させた。

注) : 試験計画書に従い、動物発注数は雌雄ともに 70 匹であったが、実際には雌雄各 73 匹が納入された。

#### 6.4 飼育条件

動物は、温度 20~26°C、相対湿度 36~60%、換気回数 1 時間 10~15 回、照明 1 日 12 時間 (07:00~19:00) の動物飼育室（飼育室番号：302 号室）でプラスチック製ケージ (W250×D350×H200 mm : 日本ケージ株式会社) で個別に、交配期間中は雌雄各 1 匹の計 2 匹を収容した。なお、妊娠 17 日から授乳 5 日までは、床敷（ホワイトフレーク : 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エコンケージ (W340×D400×H185 mm : 日本クリア株式会社) に個別に収容した。飼料は NMF 固形（滅菌：オリエンタル酵母工業株式会社、ロット番号：061214、070115）をステンレス製給餌器を用いて自由に摂取させた。飲料水は水道水（御殿場市営水道水：給水瓶使用）を自由に摂取させた。

飼料中の混入物質等については使用したロットについて、財団法人日本食品分析センターで実施した分析結果を入手し、床敷については、財団法人日本食品分析センターで定期的（年 6 回）に実施した分析結果を入手した。飲料水については、水道法に準拠した水質の分析を東芝機械環境センター株式会社に定期的（年 4 回）に依頼し、結果を入手した。これらのデータにより飼料、飲料水及び床敷中の混入物質が試験成績に影響を与える可能性のないことを確認し、分析報告書の写しを保存した。

#### 6.5 動物の識別

動物の個体識別は入荷時に小動物用耳標をつけて行った。群分け後は、飼育ケージに群ごとに色分けしたケージラベルを付け、試験番号、投与経路、投与量、性、動物番号、耳標番号、剖検予定日（主群の雄及び回復群の雌雄）、交尾成立日（主群の雌雄）及び分娩日（主群の雌）を明記した。

#### 6.6 投与経路、投与期間及び投与回数並びに回復期間とそれらの選択理由

投与経路は、OECD Guideline for Testing of Chemicals 422 に準じ、経口投与を選択した。投与期間は、主群の雄及び回復群の雌雄で交配前 14 日間、交配期間 14 日間及び交配期間終了後 14 日間の 42 日間、主群の雌で交配前 14 日間、交配期間及び妊娠期間を通して授乳 4 日までの 41~46 日間とした。

回復期間は回復群の雌雄について、投与終了後 14 日間とし、その間休薬し、観察を行った。

### 6.7 投与方法

投与方法は、げっ歯類の経口投与に際して一般的な強制経口投与とした。投与容量は5mL/kg体重とし、フレキシブル胃ゾンデを用いて強制経口投与した(07:58~12:16、ただし、投与時に分娩中であった動物は、分娩終了後の17:03~17:19に投与した)。対照群には媒体(0.5w/v%MC溶液)を同様に投与した。個体ごとの投与液量は最新の体重を基準に算出した。なお、雌の妊娠7日以降については妊娠7日の体重を基準に算出した。

### 6.8 投与量及び群構成

投与量は100、300及び1000mg/kgとし、これに対照群を加え4群構成とした。1群当たりの動物数は主群の各群で雌雄各12匹、回復群は対照群及び高用量群で雌雄各5匹とした。群構成表を表1に示した。

表1.群構成表

試験群	投与量 (mg/kg)	被験液濃度 (mg/mL)	性	主群		回復群	
				動物数	動物番号	動物数	動物番号
対照群	0	0	雄	12	1001~1012	5	1013~1017
			雌	12	1101~1112	5	1113~1117
低用量群	100	20	雄	12	2001~2012	—	—
			雌	12	2101~2112	—	—
中用量群	300	60	雄	12	3001~3012	—	—
			雌	12	3101~3112	—	—
高用量群	1000	200	雄	12	4001~4012	5	4013~4017
			雌	12	4101~4112	5	4113~4117

### 6.9 投与量の設定根拠

先に実施した「1,2,4,5-ベンゼンテトラカルボン酸のラットを用いた14日間反復経口投与毒性試験（予備試験）」（投与量：100、300及び1000mg/kg、株式会社ボゾリサーチセンター試験番号：C-R070）では、雌雄で軟便がみられたが、体重推移に影響はなく、軽度な変化であった<sup>1)</sup>。したがって、本試験では予備試験同様に1000mg/kgを高用量とし、以下公比約3で除して300及び100mg/kgの3用量を設定した。

### 6.10 観察及び検査の方法

試験日の起算は下記の通りとした。

- |                   |                 |
|-------------------|-----------------|
| 投与開始日             | : 投与第1日         |
| 交尾成立日             | : 妊娠0日          |
| 交尾までに要した日数        | : 交配開始日を0日として起算 |
| 分娩終了日             | : 授乳0日          |
| 回復開始日 (投与期間終了の翌日) | : 回復第1日         |

#### 6.10.1 一般状態の観察

全個体について、投与期間中は毎日3回（投与前、投与直後及び投与約2時間後）、回復期間中は毎日1回（午前中）、それぞれ体外表、栄養状態、姿勢、行動及び排泄物の異常などの一般状態を観察した。

#### 6.10.2 詳細な一般状態の観察、機能検査、握力及び自発運動量の測定

詳細な一般状態の観察は、投与開始前に1回、全個体について行った。また、主群の雄は投与期間中毎週1回、雌は交配前投与期間中に毎週1回、妊娠期間中及び授乳期間中は指定された日（妊娠1、7、14及び20日、授乳4日）にそれぞれ行った。なお、雌は交配5日までに全例に交尾が認められたため交配期間中の観察は実施しなかった。回復群は投与期間中及び回復期間中毎週1回行った。機能検査、握力及び自発運動量の測定は、主群の雄は投与終了週（投与第41日）に、主群の雌は授乳4日（投与第42~43日）のF1児剖検後に、回復群の雌雄は投与終了週（投与第41日）及び回復終了週（回復第10日）に1群当たり5匹について行った。上記の観察、検査及び測定は、動物をランダムに配置し、観察者に対して投与量などの情報を制限（ブラインド化）した状態で行った。なお、詳細な一般状態の観察及び機能検査の評価には実数データ項目以外はスコア化した評点法を用いた。

- 1) 詳細な一般状態の観察
  - ホームケージ内観察  
姿勢、痙攣、異常行動
  - 手に持つての観察  
ホームケージからの取り出し易さ、ハンドリングに対する反応（取り扱いやすさ、発声など）、被毛・皮膚の状態（被毛の汚れ、粗毛、外傷、皮膚の色など）、眼球（眼球突出、眼瞼の開き具合）、眼・鼻の分泌物、可視粘膜、自律神経機能（流涙、流涎、立毛、瞳孔径、呼吸）
  - オープンフィールド内観察  
覚醒状態、歩行、姿勢、振戦、痙攣、立ち上がり回数、排泄物（排糞数、排尿）、常同行動（身繕い、旋回など）、異常行動（自咬、後方突進など）
- 2) 機能検査  
聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射、空中正向反射、着地開脚幅
- 3) 握力測定  
機能検査に引き続き、CPUゲージ MODEL-9502A（アイコーエ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測定した。
- 4) 自発運動量の測定  
握力測定に引き続き、実験動物用自発運動センサーNS-AS01（株式会社ニューロサイエンス）を用いて自発運動量を測定した。測定は1時間とし、10分間隔及び0~60分の集計を行った。

#### 6.10.3 体重測定

主群の雄は投与第1、4、8、11、15、18、22、25、29、32、36、39、42日及び剖検日に、回復群の雌雄は主群の雄の測定日に加え、回復第1、4、8、11、14日及び剖検日に、主群の雌は投与第1、4、8、11、15日（未交尾動物は投与第18日にも測定）、妊娠0、4、7、11、14、17及び20日並びに授乳0及び4日に体重を測定した。なお、午後の分娩観察時に分娩の終了が確認された個体の授乳0日の体重測定(14:35~17:01)を除き 08:13~11:26 の間に行った。剖検日には相対器官重量算出のため、前日から約16時間絶食させた後の体重を測定した。

#### 6.10.4 摂餌量測定

全個体について、主群の雄は投与第1、4、8、11、15、32、36、39及び42日に、回復群の雌雄は主群の雄の測定日に加え回復第1、4、8、11及び14日に、主群の雌は投与第1、4、8、11及び15日、妊娠1、4、7、11、14、17及び20日並びに授乳2及び4日に残餌量を測定し、前日の給餌量から1匹当たりの1日摂餌量を算出した。給餌量及び残餌量の測定は08:25~11:48の間に行った。

#### 6.10.5 膀胱検査

主群の雌の全個体について、投与開始翌日から交尾が認められるまで毎日（午前中）膀胱を採取し、鏡検した。交配前投与期間中は膀胱像を発情前期、発情期、発情後期及び発情休止期に分類し、発情期像発現回数及び発情期から次の発情期までの日数（性周期）を調べ、発情前期、発情期、発情後期、休止期の周期が4~5日ごとに繰り返さない場合を性周期異常とした。交配期間中は膀胱内の精子の有無を調べた。

#### 6.10.6 交配方法

交配前投与期間終了後、主群の同一投与群の雌雄を1:1で終夜同居させ、翌朝、膀胱形成あるいは膀胱中に精子を確認したものを妊娠0日とした。交尾までに要した日数は交配開始日を0日と起算した。

#### 6.10.7 分娩及び授乳観察

##### 1) 母動物の観察

交尾確認雌動物は全例自然分娩させ、分娩状態の異常の有無を観察した。分娩終了の確認は妊娠21日から妊娠25日の午前中まで1日2回（午前、午後）を行い、妊娠期間を0.5日単位で算出した。分娩が午後5時に終了していた場合、その日を授乳0日とした。妊娠25日の午前10時までに分娩しなかった1000mg/kg投与群の1例（動物番号：4111）は、エーテル麻酔下で腹大動脈切断により放血致死させた後剖検を行い、妊娠の有無を確認した。その結果、着床痕が認められた。

分娩が終了した母動物は胎盤及び羊膜の処理の有無を観察し、分娩終了日を授乳0日とし、授乳4日まで出生児を授乳させ、児集め、営巣及び授乳を指標として授乳状

態を観察した。

分娩した母動物は授乳 4 日から一夜（約 16~20 時間）絶食させた授乳 5 日に、各群 5 匹は血液学検査及び血液化学検査のための採血後に、その他の動物はエーテル麻醉下で腹大動脈切断により放血致死させ、黄体数及び着床痕数を数えた。

## 2) 出生児の観察

出生日に出生児数、死産児数を数えた。出生児は外表異常の有無を観察<sup>注)</sup>し、性別を判定して体重を測定した後、母動物に授乳させた。出生児は生死の観察を生後 4 日まで毎日 1 回行った。なお、死産児及び死亡児は廃棄した。外表異常児はリン酸緩衝 10 vol% ホルマリン液に固定し、保存した。

生後 4 日に体重を測定した後、全例をエーテル麻醉下で放血致死させて剖検を行い、頭部・胸部・腹部を含む器官・組織の異常の有無を調べた。なお、出生児の体重は個別に体重を測定し、各腹単位で雌雄別に平均値を算出した。

<sup>注)</sup> : 頭部の陥没や裂、顔面の鼻吻や上下顎、口唇のゆがみや裂、眼瞼や耳介の大きさ、形状、左右のバランス、胸腔部のゆがみや大きさ、内部臓器の突出、尾部の長さ、形状、数、欠損、四肢部の長さ、形状、指の数、欠損及び左右のバランスに注意して観察し、正常と異なる場合を異常とした。

### 6.10.8 尿検査（摂水量測定を含む）

投与最終週（投与第 37~38 日）及び回復終了週（回復第 9~10 日）に雄の全個体について、それぞれ採尿器をセットしたケージに収容し、絶食・自由摂水下で 4 時間尿を、次いで自由摂食・自由摂水下でその後の 20 時間尿を採取した。検査項目は以下の通りである。なお、採取した最初の 4 時間尿について pH 以下沈渣までの検査と尿量を、その後に得られた 20 時間尿を用いて浸透圧及び尿量の測定を行い、尿量は 4 時間の尿量及び 20 時間の尿量を合計して算出した。摂水量は、採尿器をセットしたケージに収容した状態で前日からの 1 日の摂取量を給水瓶を用いて測定した。

検査項目	測 定 方 法
pH	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
たん白質	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
ケトン体	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
グルコース	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
潜血	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
ビリルビン	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
ウロビリノーゲン	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
色調	肉眼観察
沈渣	鏡検法
尿量（4 時間量）	目盛付スピッツ管を用いた容量測定（単位：mL）
浸透圧	冰点降下法 <sup>b)</sup> （単位：mOsm/kg）
尿量（20 時間量）	メスシリンドーを用いた容量測定（単位：mL）

摂水量（24時間量） 重量測定

#### 使用測定機器

- a) : AUTON MINI™ AM-4290 (アークレイ株式会社)
- b) : 自動浸透圧測定装置 オートアンドスタット OM-6030 (アークレイ株式会社)

#### 6.10.9 血液学検査

最終投与翌日及び回復期間終了日に、前日から一夜（約16~20時間）絶食させた各群雌雄各5匹<sup>注1)</sup>について、エーテル麻酔下に開腹し、腹大動脈からEDTA-2K加採血瓶（SB-41：シスメックス株式会社）に血液を採取し、以下の項目について測定した。なお、全例について、May-Gruenwald-Giemsa染色法による血液塗抹標本を作製した。ただし、プロトロンビン時間、活性化部分トロンボプラスチン時間及びフィブリノゲン量については、3.8%クエン酸ナトリウム溶液加試験管（血液9容に対し1容の割合）に採取した血液を遠心分離（約3,000 rpm、約1,600×g、約10分間）して得られた血漿を用いて測定した。

検査項目	測定方法	単位
赤血球数(RBC)	2角度レーザーフローサイトメトリー法 <sup>c)</sup>	10 <sup>4</sup> /μL
ヘモグロビン量(Hb)	シアノメトヘモグロビン変法 <sup>c)</sup>	g/dL
ヘマトクリット値(Ht)	赤血球数及び平均赤血球容積から算出 <sup>c)</sup>	%
平均赤血球容積(MCV)	2角度レーザーフローサイトメトリー法 <sup>c)</sup>	fL
平均赤血球血色素量(MCH)	赤血球数及びヘモグロビン量から算出 <sup>c)</sup>	pg
平均赤血球血色素濃度(MCHC)	ヘモグロビン量及びヘマトクリット値から算出 <sup>c)</sup>	g/dL
網赤血球率(Reticulocyte)	RNA染色によるレーザーフローサイトメトリー法 <sup>c)</sup>	%
血小板数(Platelet)	2角度レーザーフローサイトメトリー法 <sup>c)</sup>	10 <sup>4</sup> /μL
白血球数(WBC)	2角度レーザーフローサイトメトリー法 <sup>c)</sup>	10 <sup>2</sup> /μL
白血球百分率 <sup>注2)</sup>	ペルオキシダーゼ染色によるレーザーフローサイトメトリー法+2角度レーザーフローサイトメトリー法 <sup>c)</sup>	%
各自血球細胞の絶対数 <sup>注2)</sup>	ペルオキシダーゼ染色によるレーザーフローサイトメトリー法+2角度レーザーフローサイトメトリー法 <sup>c)</sup>	10 <sup>2</sup> /μL
プロトロンビン時間	クロット法 <sup>d)</sup>	s
活性化部分トロンボプラスチン時間	クロット法 <sup>d)</sup>	s
フィブリノゲン量	トロンボプラスチン法 <sup>d)</sup>	mg/dL

#### 使用測定機器

- c) : 総合血液学検査装置 アドヴィア 120 (Bayer Corporation, New York, USA)

d) : 血液凝固自動測定装置 ACL 100 (Instrumentation Laboratory)

注<sup>1)</sup> : 主群の検査対象各群雌雄各 5 匹は以下の例とした。

雄	雌
1001~1005	1101、1103、1105、1106、1111
2001~2005	2101、2103、2104、2105、2108
3001~3005	3101、3102、3103、3105、3107
4001~4005	4103、4104、4105、4107、4108

注<sup>2)</sup> : 好中球、好酸球、好塩基球、リンパ球、単球及び大型非染色球

#### 6.10.10 血液化学検査

血液学検査用試料と同時に採取した血液を凝固促進剤入り試験管（ベノジェクト II-オートセット：テルモ株式会社）に取り、遠心分離（約 3000 rpm、約 1,600×g、約 10 分間）して得られた血清を用いて以下の項目について測定した。ただし、AST、ALT、LDH 及び  $\gamma$ -GTP については、ヘパリン加試験管（血液 1 mL 当たり約 20 単位のヘパリン）に採取した血液を遠心分離（約 3,000 rpm、約 1,600×g、約 10 分間）して得られた血漿を用いて測定した。

検査項目	測 定 方 法	単 位
AIP	Bessey-Lowry 法 <sup>e)</sup>	IU/L
総コレステロール	CEH-COD-POD 法 <sup>e)</sup>	mg/dL
トリグリセライド	LPL-GK-GPO-POD 法 <sup>e)</sup>	mg/dL
リン脂質	PLD-ChOD-POD 法 <sup>e)</sup>	mg/dL
総ビリルビン	ビリルビンオキシダーゼ法 <sup>e)</sup>	mg/dL
グルコース	グルコースデヒドログナーゼ法 <sup>e)</sup>	mg/dL
尿素窒素	Urease-LEDH 法 <sup>e)</sup>	mg/dL
クレアチニン	Creatininase-creatinase-sarcosine-oxidase-POD 法 <sup>e)</sup>	mg/dL
ナトリウム	イオン選択電極法 <sup>e)</sup>	mmol/L
カリウム	イオン選択電極法 <sup>e)</sup>	mmol/L
塩素	イオン選択電極法 <sup>e)</sup>	mmol/L
カルシウム	OCPC 法 <sup>e)</sup>	mg/dL
無機リン	モリブデン酸法 <sup>e)</sup>	mg/dL
総たん白質	Biuret 法 <sup>e)</sup>	g/dL
アルブミン	BCG 法 <sup>e)</sup>	g/dL
A/G 比	総たん白質及びアルブミンから算出	
AST(GOT)	UV-rate 法 <sup>e)</sup>	IU/L
ALT(GPT)	UV-rate 法 <sup>e)</sup>	IU/L
LDH	UV-rate 法 <sup>e)</sup>	IU/L
$\gamma$ -GTP	L- $\gamma$ -グルタミル-3-カルボキシ-4-ニトロアニリド 法 <sup>e)</sup>	IU/L

## 使用測定機器

e) : 臨床化学自動分析装置 TBA-120FR 形 (株式会社東芝)

## 6.10.11 病理学検査

## 1) 剖検及び器官重量測定

すべての生存動物について、最終投与翌日及び回復期間終了日に、血液・血液化学検査に供した動物（各群雌雄各 5 匹）は採血後に、その他の動物はエーテル麻酔下で腹大動脈切断により放血致死させた。その後、それぞれ体外表・頭部・胸部・腹部を含む全身の器官・組織の肉眼による詳細な病理解剖を行い、結果を記録した。なお、雌動物（母動物）は授乳 5 日の剖検時に黄体数及び着床痕数を数えた。次いで、血液・血液化学検査に供した各群雌雄各 5 匹について、以下に示す器官（精巣及び精巣上体は全例）の重量（絶対重量）を測定するとともに、絶対重量と剖検時の体重から体重 100 g 当たりの相対重量を算出した。なお、\*印をつけた両側性の器官については左右別々に測定し、その合計値で評価した。

脳、甲状腺\*（上皮小体を含む）、胸腺、心臓、肝臓、脾臓、腎臓\*、副腎\*、精巣\*、精巣上体\*

## 2) 病理組織学検査

全動物について、以下に示す器官・組織をリン酸緩衝 10 vol% ホルマリン液で固定、保存した（固定時に肺にはリン酸緩衝 10 vol% ホルマリン液を注入した。ただし、精巣及び精巣上体はブアン液で固定した後リン酸緩衝 10 vol% ホルマリン液で保存した）。次いで、パラフィン包埋した後、切片とし（下線を施した器官・組織は固定・保存のみとした）、ヘマトキシリン・エオジン（H・E）染色を行い、このうち対照群及び高用量群の血液・血液化学検査に供した雌雄各 5 匹並びに全動物の肉眼的異常部位について鏡検した（両側性の器官については両側を摘出し、片側を鏡検）。その結果、雌雄の胃に被験物質投与の影響が疑われたため、主群及び回復群の全例について鏡検し、正常及び異常所見の代表例を写真撮影した。

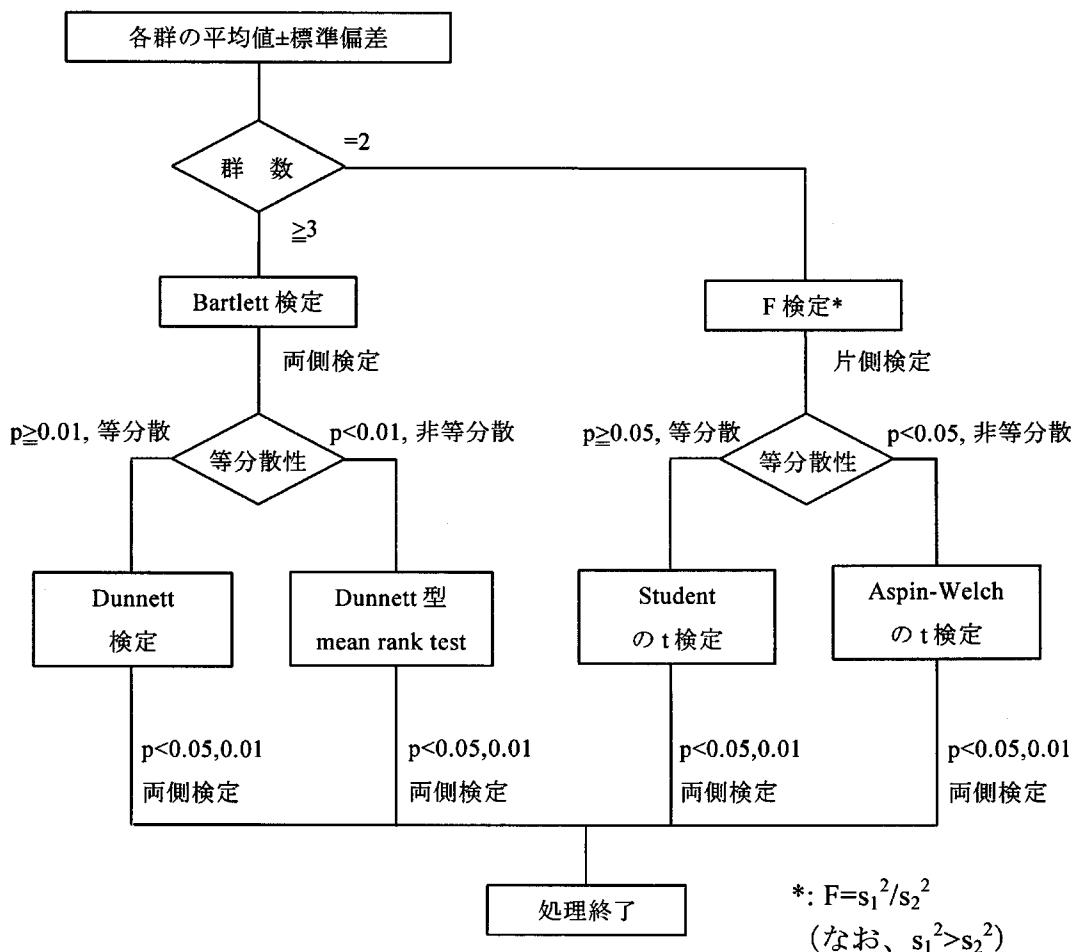
大脑、小脳、下垂体、脊髄（胸部）、坐骨神経、甲状腺、上皮小体、副腎、胸腺、脾臓、頸下リンパ節、腸間膜リンパ節、心臓、肺（気管支を含む）、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、肝臓、腎臓、膀胱、精巣、精巣上体、卵巣、子宮、精嚢、胸骨（骨髄を含む）、大腿骨（骨髄を含む）、肉眼的異常部位、個体識別部（耳介）

## 6.11 統計解析

## 1) 以下の式により各パラメータを算出した。

交尾率(%)= (交尾動物数/同居動物数) ×100  
受胎率(%)= (妊娠した雌の数/交尾した雌の数) ×100  
授精率(%)= (妊娠した雌の数/交尾した雄の数) ×100  
妊娠期間(日)= 授乳 0 日-妊娠 0 日  
出産率(%)= (出生児出産雌数/妊娠雌数) ×100  
着床率(%)= (着床痕数/黄体数) ×100  
死産児率(%)= (死産児数/総出産児数) ×100  
出生率(%)= (出生児数/総出産児数) ×100  
外表異常率(%)= (外表異常児数/出生児数) ×100  
性比= 雄数/ (雄数+雌数)  
出生児生存率(%)= (生後 4 日生存児数/生後 0 日出生児数) ×100

- 2) 体重、摂餌量、摂水量、発情期像発現回数、性周期、交尾までに要した日数、妊娠期間、黄体数、着床痕数、出生児数、オープンフィールド内観察（排糞数、立ち上がり回数）、機能検査（着地開脚幅）、握力及び自発運動量、尿検査の定量的項目、血液学検査、血液化学検査及び器官重量は次に示す模式図の方法に従つて検定した。なお、出生児体重（雌雄別）については、母動物ごとの平均値を求めた後、検定を行った<sup>2), 3)</sup>。
- 3) 着床率、死産児率、出生率、外表異常率、出生児生存率は母動物ごとに率を求めた後、Bartlett 検定により等分散性を検定し（有意水準 0.01、両側）、等分散の場合は Dunnett 検定、非等分散の場合は Dunnett 型検定を行つた（有意水準 0.05 及び 0.01、両側）<sup>2), 3)</sup>。



- 4) 交尾率、授精率、受胎率、出産率、出生児の性比、聴覚反応、接近反応、接触反応、疼痛反応、瞳孔反射、空中正向反射は、各群の交尾動物数、雌を妊娠させた雄動物数、妊娠雌動物数、生存児出産雌動物数、雄生存児数、雌生存児数、正常反射のみられた動物数の合計を求め、Yates の連続修正による  $\chi^2$  検定を行った（有意水準 0.05 及び 0.01、両側）。ただし、期待度数が 5 以下のセルがみられる場合には Fisher の直接確率計算法により検定を行った（有意水準 0.05 及び 0.01、両側）。

## 7. 試験結果

### 7.1 一般状態 (Table 1-1~1-8、Appendix 1~24)

1000 mg/kg 投与群において、軟便が主群の雄 12/12 例にほぼ継続してみられた。主群の雌では交配前投与期間から妊娠 16 日にかけて 10/12 例に断続的にみられたが、妊娠の経過に伴い発現例数は徐々に減少し、妊娠 17 日以降は消失した。回復群では投与期間中雌雄各 5/5 例にみられたが、回復期間中は回復 1 日目に雄 4/5 例と雌 1/5 例にみられたのみであった。なお、軟便は主に投与翌日に観察され、尿受けバット上で形の崩れたものを所見とした。

### 7.2 詳細な一般状態の観察、機能検査、握力測定及び自発運動量の測定

(Fig. 1~6、Table 2-1~2-105、Appendix 25~324)

#### 1) ホームケージ内観察 (Table 2-1~2-29、Appendix 25~108)

主群及び回復群のいずれの動物にも異常はみられなかった。

#### 2) 手を持っての観察 (Table 2-30~2-58、Appendix 109~192)

主群及び回復群のいずれの動物にも異常はみられなかった。

#### 3) オープンフィールド内観察 (Table 2-59~2-87、Appendix 193~276)

主群及び回復群のいずれの動物にも異常はみられなかった。また、立ち上がり回数及び排糞数にも対照群と各投与群との間に差はなかった。

#### 4) 機能検査 (Table 2-88~2-93、Appendix 277~292)

主群及び回復群のいずれの動物にも異常はみられなかった。また、着地開脚幅及び空中正向反射には対照群と各投与群との間に差はなかった。

#### 5) 握力測定 (Table 2-94~2-99、Appendix 293~308)

主群及び回復群のいずれの動物にも対照群と各投与群との間に差はなかった。

#### 6) 自発運動量の測定 (Fig. 1~6、Table 2-100~2-105、Appendix 309~324)

主群及び回復群とも対照群と各投与群との間に差はなかった。

### 7.3 体重 (Fig. 7~10、Table 3-1~3-8、Appendix 325~348)

主群及び回復群の雌雄とともに体重及び体重増加量には被験物質投与による影響は認められなかった。なお、主群の 1000 mg/kg 投与群の雄で投与 15 及び 22 日の体重が低く、その差は有意となつたが、一時的な変化であり、投与期間中の体重増加量には差がないことから生理的変動範囲内の変化と判断した。

#### 7.4 摂餌量 (Fig. 11~14、Table 4-1~4-8、Appendix 349~372)

主群及び回復群の雌雄ともに摂餌量には被験物質投与による影響は認められなかつた。

なお、100 mg/kg 投与群の雌で妊娠 1 日及び 14 日に有意な高値、300 mg/kg 投与群の雌で妊娠 14 日及び 20 日に有意な高値、1000 mg/kg 投与群の雄で交配期間中の投与 42 日に有意な高値が認められたが、一時的に有意な変動であり、関連する体重推移への影響はみられないことから生理的変動範囲内の変化と判断した。

#### 7.5 尿検査 (摂水量測定を含む) (Table 5-1~5-8、Appendix 373~390)

定性項目については、主群の投与 6 週検査時において各投与群で pH の軽度な酸性化傾向及びリン酸塩結晶の発現程度及び頻度の減少が用量に関連してみられた。他には主群及び回復群とも異常はみられなかつた。

定量項目については、主群の投与 6 週検査時において 1000 mg/kg 投与群で摂水量が増加 (33%) し、その差は有意となった。他にはいずれの検査項目においても対照群と各投与群との間に差はなかつた。

#### 7.6 血液学検査 (Table 6-1~6-8、Appendix 391~398)

##### 1) 投与期間終了時検査

いずれの検査項目においても対照群と各投与群との間に差はなかつた。

##### 2) 回復期間終了時検査

いずれの検査項目においても対照群と各投与群との間に差はなかつた。

#### 7.7 血液化学検査 (Table 7-1~7-8、Appendix 399~406)

##### 1) 投与期間終了時検査

いずれの検査項目においても対照群と各投与群との間に差はなかつた。

##### 2) 回復期間終了時検査

1000 mg/kg 投与群の雄でリン脂質の増加 (100 mg/dL) 、雌でナトリウム及び塩素の増加 (ナトリウム : 143 mmol/L、112 mmol/L) がみられ、その差は有意となつたが、背景データ [リン脂質平均値 : 78~93 mg/dL、ナトリウム平均値 : 142~145 mmol/L、塩素平均値 : 109~111 mmol/L] と同等値であり、投与期間終了時に同変動はみられていないことから、生理的変動範囲内の変化と判断した。

#### 7.8 器官重量 (Table 8-1~8-8、Appendix 407~436)

投与期間終了時検査では絶対及び相対重量の双方において、対照群と各投与群との間に差はなかつた。回復期間終了時検査においても 1000 mg/kg 投与群では絶対及び相対重量の双方において同一方向の変化 (増加又は減少) はみられなかつた。なお、以

下の器官に対照群との間に有意差がみられたが、絶対重量のみの軽度な変化であり生理的変動範囲内の変化と考えられた。

#### 回復期間終了時検査

甲状腺 : 絶対重量の有意な低値が 1000 mg/kg 投与群の雌にみられた。

#### 7.9 剖検所見 (Table 9-1, 9-2, Appendix 437~552)

##### 1) 投与期間終了時検査

以下の器官・組織に所見がみられたが、出現頻度及び病理学的性状から偶発的変化と考えられた。

腎臓 : 囊胞が 100 mg/kg 投与群の雄 1 例に、腎孟拡張が 1000 mg/kg 投与群の雄 1 例にみられた。

胃 : 腺胃の暗赤色巣が 100 mg/kg 投与群の雌 3 例、300 mg/kg 投与群の雄 1 例と雌 4 例、1000 mg/kg 投与群の雌 2 例にみられた。

精巣 : 小型化が対照群の 1 例にみられた。

甲状腺 : 小型化が 100 mg/kg 投与群の雌 1 例にみられた。

##### 2) 回復期間終了時検査

胃 : 腺胃の暗赤色巣が対照群の雌 1 例と 1000 mg/kg 投与群の雄 1 例に、境界縁の隆起巣が 1000 mg/kg 投与群の雄 1 例にみられた。

#### 7.10 病理組織学検査 (Table 10-1~10-4, Appendix 437~552)

##### 1) 投与期間終了時検査

被験物質投与によると考えられる変化が胃にみられた。

胃 : 境界縁における扁平上皮の軽微又は軽度な過形成が 1000 mg/kg 投与群の雄 3 例にみられた。

その他、以下の所見がみられたが、出現状態及び病理組織学的性状から偶発病変と考えられた。

精巣上体 : 軽微な間質細胞浸潤が対照群及び 1000 mg/kg 投与群の各 1 例にみられた。

心臓 : 軽微な限局性細胞浸潤が 1000 mg/kg 投与群の雌 1 例にみられた。

盲腸 : 粘膜の軽微な細胞浸潤が 1000 mg/kg 投与群の雄 1 例にみられた。

腎臓 : 軽微又は軽度な囊胞が 100 mg/kg 投与群の雄 1 例と

1000 mg/kg 投与群の雌 1 例に、軽度な腎孟拡張が 1000 mg/kg 投与群の雄 1 例に、軽微な尿細管再生が対照群の雄 3 例と雌 2 例、100 mg/kg 投与群の雄 1 例、1000 mg/kg 投与群の雄 4 例と雌 1 例に、軽微なヒアリン円柱形成が 100 mg/kg 投与群の雄 1 例に、軽微な髓質の鉱質沈着が対照群及び 1000 mg/kg 投与群の雌雄各 1 例に、軽微な間質細胞浸潤が 100 及び 1000 mg/kg 投与群の雄各 1 例に、軽微な限局性線維化が 1000 mg/kg 投与群の雄 1 例に、軽微な尿細管の好酸性小体が 1000 mg/kg 投与群の雄 1 例にみられた。

- 肝臓 : 軽微な微小肉芽腫が対照群の雄 5 例と雌 2 例及び 1000 mg/kg 投与群の雄 4 例と雌 2 例にみられた。
- 肺（気管支を含む） : 動脈壁の軽微な鉱質沈着が 1000 mg/kg 投与群の雄 1 例に、軽微な肺胞内泡沫細胞が対照群の雄 1 例と雌 2 例及び 1000 mg/kg 投与群の雌雄各 1 例にみられた。
- 脾臓 : 軽微又は軽度な髓外造血が対照群及び 1000 mg/kg 投与群の雌雄各 5 例にみられた。
- 胃 : 軽微又は軽度な腺胃の糜爛が 100 mg/kg 投与群の雌 3 例、300 mg/kg 投与群の雄 2 例と雌 4 例及び 1000 mg/kg 投与群の雌 3 例に、軽微な境界縁の潰瘍が対照群の雌 1 例にみられた。しかし、両所見ともに発現状況に用量との関連がないことから、被験物質投与の影響とは考えない。
- 精巣 : 精細管の中等度の萎縮が対照群の 1 例にみられた。
- 膀胱 : 粘膜又は粘膜下の軽度な水腫が対照群の雌 1 例にみられた。

## 2) 回復期間終了時検査

被験物質投与によると考えられる変化が胃にみられた。

- 胃 : 軽微な境界縁における扁平上皮の過形成が 1000 mg/kg 投与群の雄 1 例にみられ、投与期間終了時検査と比べ変化の程度は軽度となった。

その他、以下の所見がみられたが、出現状態及び病理組織学的性状から偶発病変と考えられた。

- 胃 : 軽度な上皮の囊胞が 1000 mg/kg 投与群の雄 1 例に、軽微又は軽度な腺胃の糜爛が対照群の雌 1 例と 1000 mg/kg 投与群の雄 1 例にみられた。

#### 7.11 性周期 (Table 11、Appendix 553~556)

性周期異常の動物はみられず、平均性周期日数には対照群と各投与群との間に差は認められなかつた。

#### 7.12 交配成績 (Table 12、Appendix 557~560)

交配開始後 5 日までに全ての組み合わせで交尾が認められ、全ての組み合わせで妊娠が認められた。したがつて、交尾までに要した日数、交尾率、授精率及び受胎率には対照群と各投与群との間に差は認められなかつた。

#### 7.13 分娩成績及び分娩・授乳状態 (Table 13、Appendix 561~564)

妊娠動物の分娩状態では、妊娠 21.5~22.5 日にほぼ全例が正常に分娩し、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数及び出生率には対照群と各投与群との間に差は認められなかつた。なお、1000 mg/kg 投与群で妊娠 25 日未分娩の動物が 1 例みられ、剖検の結果、着床痕(1 個)が認められた。

哺育状態では、いずれの母動物にも巣作り、児集め及び授乳行動に異常はみられなかつた。

#### 7.14 出生児の観察 (Table 14、Appendix 565~568)

出生児観察における異常は、肉眼形態学的発生異常であり先天奇形を示している。性比及び出生時体重には対照群と各投与群との間に差はなく、外表異常は曲尾が対照群で 1 例みられたのみであった。

#### 7.15 出生児の生存率 (Table 15、Appendix 569~572)

授乳期間中の死亡児は対照群で 1 例、100、300 及び 1000 mg/kg 投与群で 6、2 及び 2 例であった。生後 4 日生存率については対照群と各投与群との間に差はなかつた。

#### 7.16 出生児の体重 (Table 16、Appendix 573~576)

出生時及び生後 4 日の雌雄体重には対照群と各投与群との間に差は認められなかつた。

#### 7.17 出生児の生後 4 日剖検所見 (Table 17、Appendix 577~580)

胸腺の頸部残留が 300 mg/kg 投与群の雄 1 例にみられたが、投与用量との関連のない偶発的变化であった。その他はいずれの出生児にも異常はみられなかつた。

## 8. 考察

1,2,4,5-ベンゼンテトラカルボン酸の0（対照群：0.5 w/v% MC溶液）、100、300、及び1000 mg/kgを、Sprague-Dawley系SPFラットの雄には交配前14日間及び交配期間を通して剖検前日（42日間）まで、雌には交配前14日間及び交配期間並びに妊娠期間を通して授乳4日まで（41~46日間）投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0及び1000 mg/kg投与群については42日間投与した後、14日間の回復期間を設け、毒性変化の可逆性を検討した。

### 1) 反復投与毒性

詳細な一般状態の観察、機能検査、握力測定、自発運動量の測定、体重、摂餌量、摂水量、血液学検査、血液化学検査、器官重量及び剖検所見に被験物質投与による影響は認められなかった。

一般状態で、投与期間中1000 mg/kg投与群の雌雄に軟便がみられた。軟便は主に投与翌日に観察され、詳細な一般状態観察では認められなかつたことから、被験物質投与後に一定時間を経過した後に生じる一時的な変化と考えられた。また、体重、摂餌量に変化を及ぼさないことから、その影響は軽度なものと考えられた。

尿検査では、各投与群の雄で投与6週検査時にpHの軽度な酸性化傾向及びリン酸塩結晶の発現程度及び頻度の減少が用量に関連してみられた。これらの変化は被験液が酸性（pH：1.7、25°C飽和溶解時[水溶液]、製造者社内データ）であることから、被験物質の排泄に基づく変化と推察された。また、1000 mg/kg投与群の雄で摂水量の増加（33%）がみられたが、尿量、尿浸透圧に変化はなく、一般状態の軟便に起因する水分補給と考えられた。なお、血液・血液化学検査、尿路系の病理検査に異常はないことから、尿検査での変化はいずれも毒性学的意義のない変化と考えられた。

病理学検査では、投与期間終了時検査において、1000 mg/kg投与群の雄の胃で境界縁の扁平上皮の過形成がみられた。この変化は被験物質の刺激性を疑わせる変化であった。なお、2週間の休薬により変化の頻度及び程度が軽減したことから可逆性の変化と考えられた。

### 2) 生殖発生毒性

性周期、交尾までに要した日数、交尾率、授精率及び受胎率には被験物質投与の影響は認められなかつた。なお、1000 mg/kg投与群で妊娠25日未分婉の動物がみられ、剖検の結果、着床痕（1個）が認められたが、1例のみの発現であり、同群の他の例はすべて正常に妊娠、分娩していることから偶発的変化と判断した。更に、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数、出生率及び性比に被験物質投与の影響は認められず、授乳期間中の授乳状態にも異常が認められないことから、1000 mg/kg投与群においても雌雄動物の交尾能、授精能及び受胎能、母動物の妊娠維持、分娩及び哺育行動などの生殖機能への影響はないと考えられた。

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出生児では、外表観察、出生時及び生後 4 日の体重及び生後 4 日剖検所見及び生存率に被験物質投与による変化は認められなかった。

これらの結果から、1,2,4,5-ベンゼンテトラカルボン酸の反復投与毒性に対する無影響量は雌雄ともに 300 mg/kg/day、生殖発生毒性に対しては雌雄親動物及び児動物に対する無影響量はいずれも 1000 mg/kg/day と判断した。1000 mg/kg 投与群で認められた胃の境界縁での扁平上皮の過形成には可逆性が認められた。

## 9. 文献

- 1) 1,2,4,5-ベンゼンテトラカルボン酸のラットを用いた 14 日間反復経口投与毒性試験（予備試験）（株式会社ボゾリサーチセンター試験番号：C-R070、2007 年）
- 2) Shayne C. Gad and Carroll S. Weil (1994) : Chapter 7. Statistics for Toxicologists, In Principles and Methods of Toxicology (A. Wallace Hayes, ed.), 3rd ed., pp.221-274, Raven Press, Ltd., New York.
- 3) 佐久間昭 (1981) : 薬効評価—計画と分析-II, pp.23-27, 387-389, 東京大学出版会, 東京.

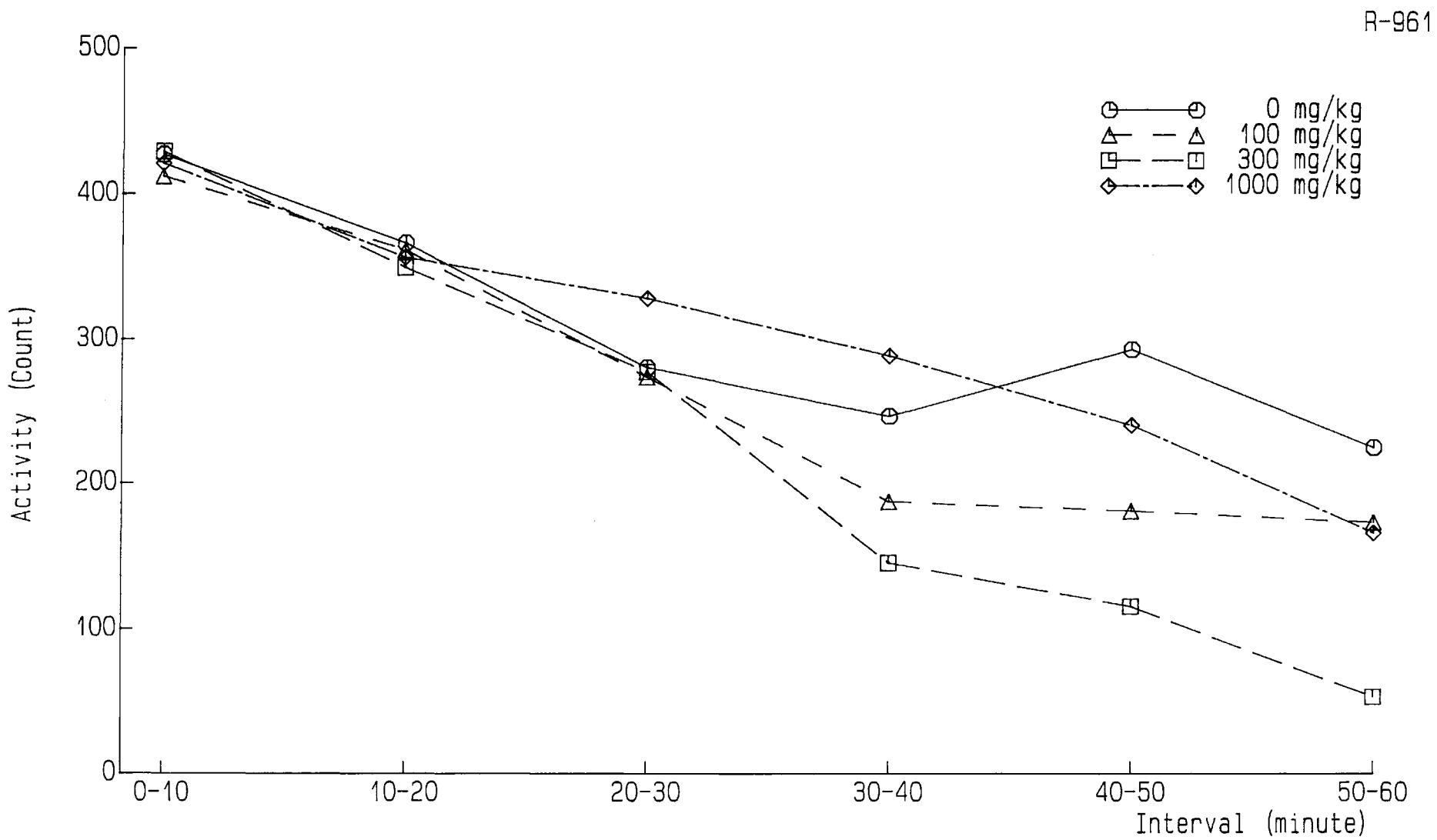


Fig.1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Motor activity of male rats (Main group, Week 6 of administration)

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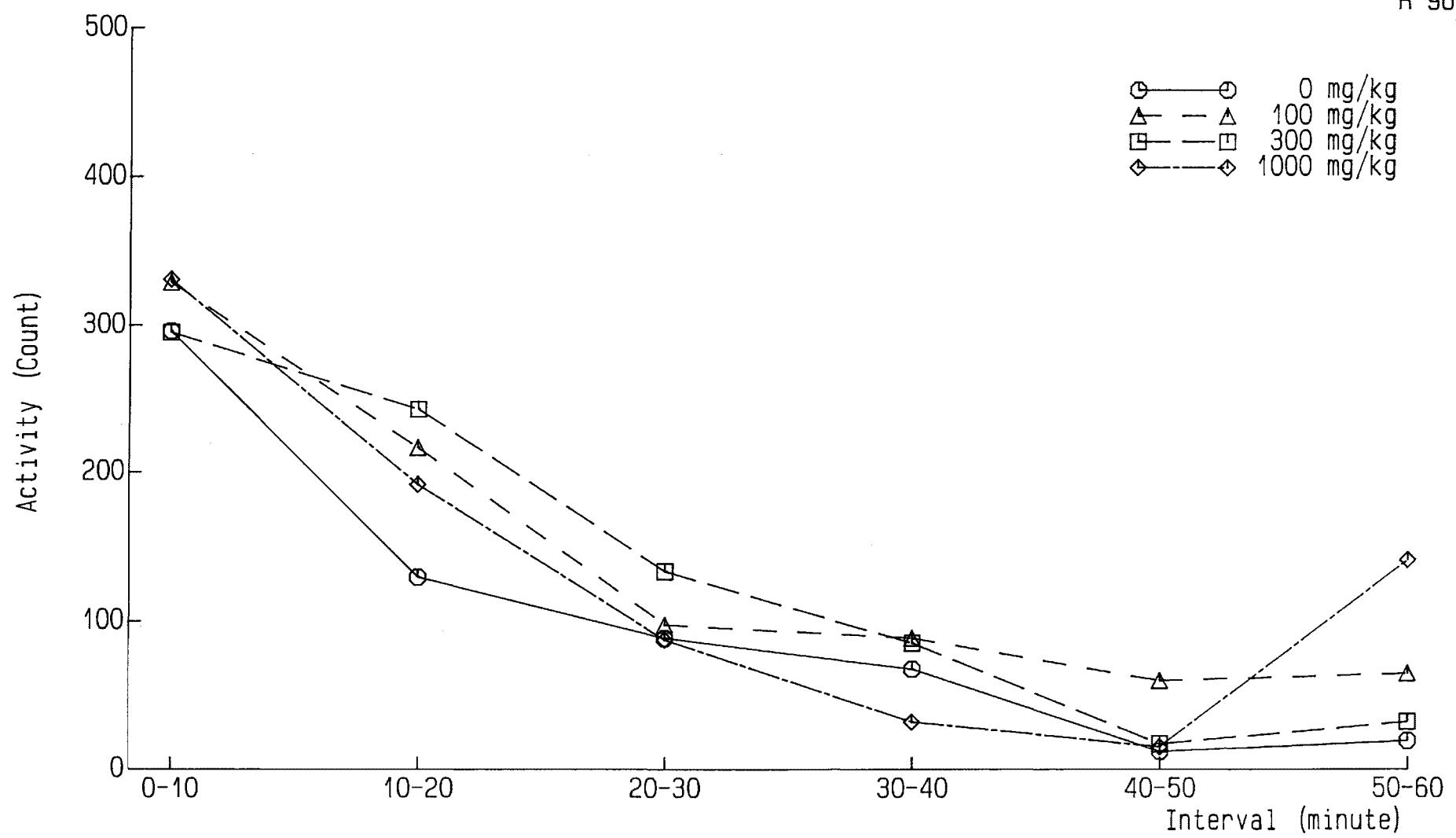


Fig.2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Motor activity of female rats (Main group, Day 4 of lactation)

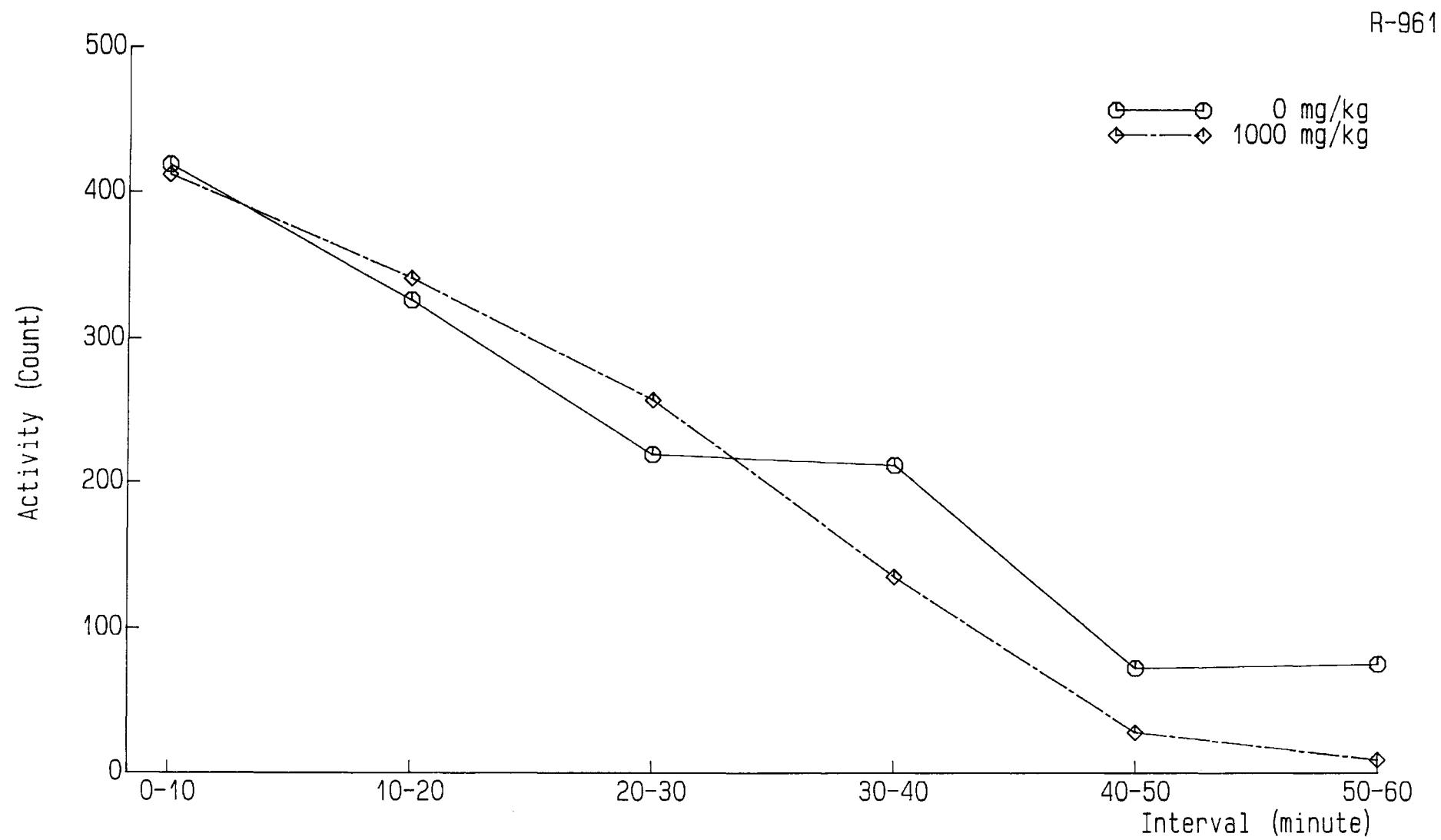


Fig.3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Motor activity of male rats (Recovery group, Week 6 of administration)

R-961

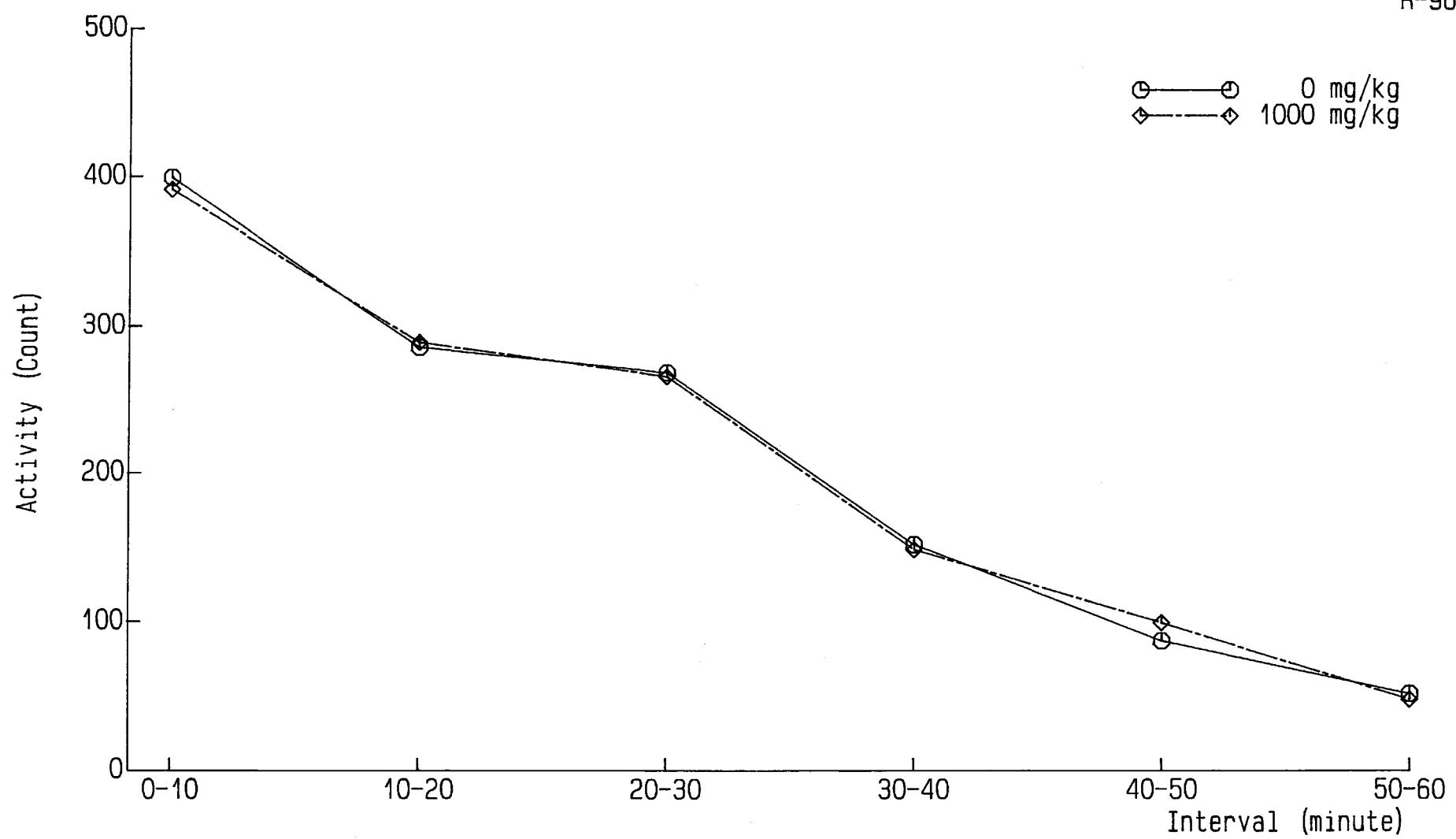


Fig.4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Motor activity of female rats (Recovery group, Week 6 of administration)

R-961

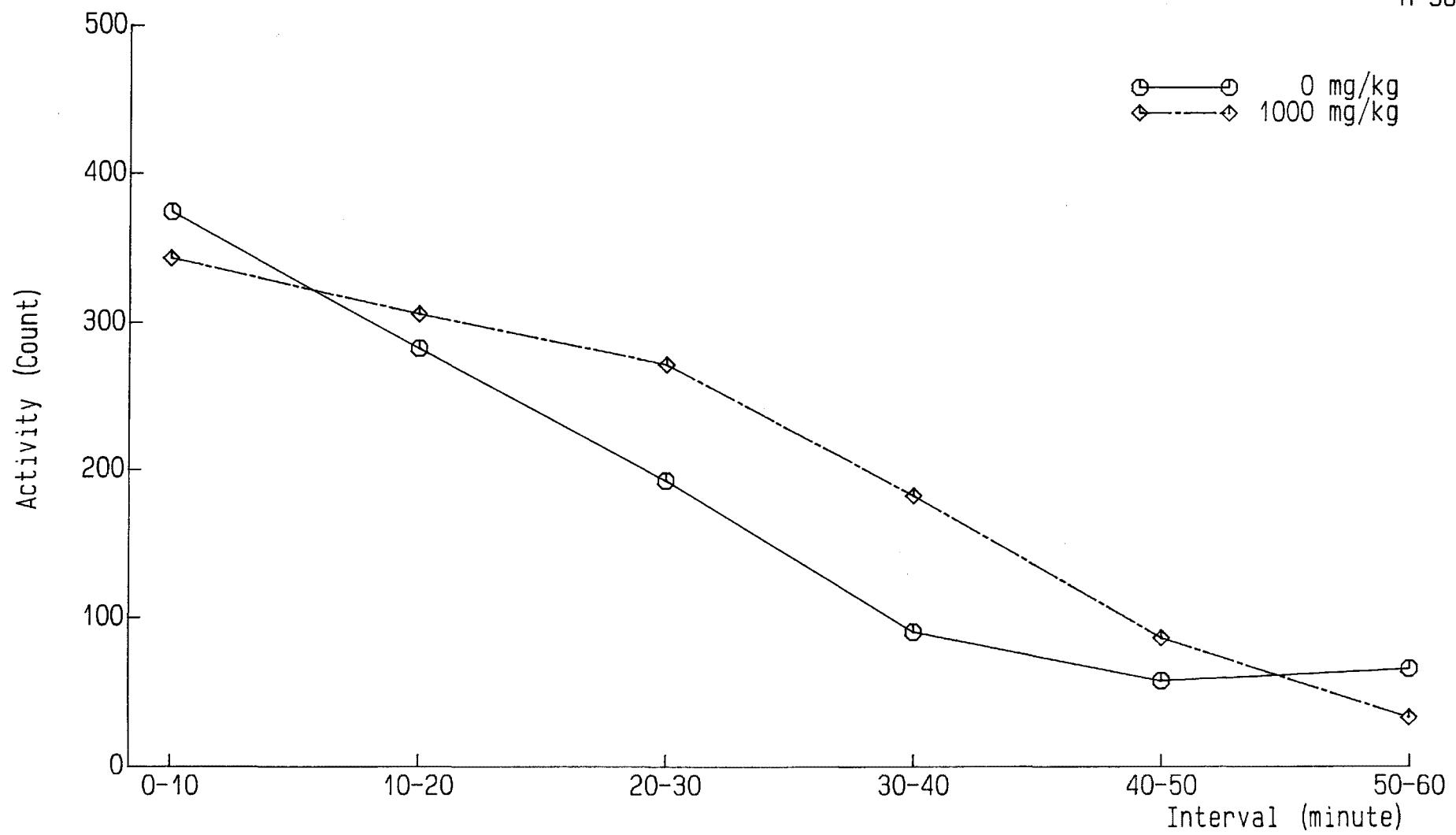


Fig.5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Motor activity of male rats (Recovery group, Week 2 of recovery)

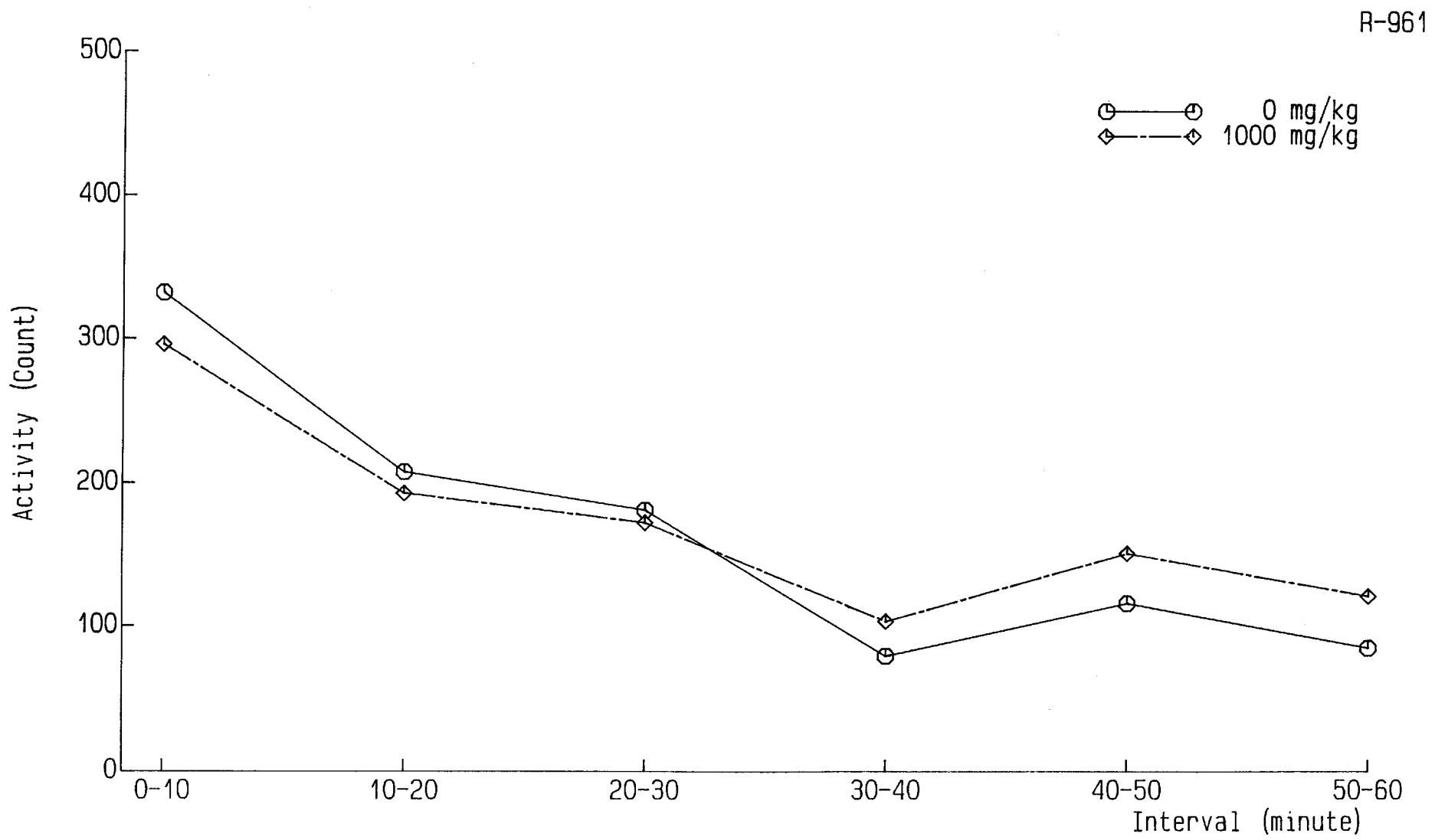


Fig.6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Motor activity of female rats (Recovery group, Week 2 of recovery)

R-961

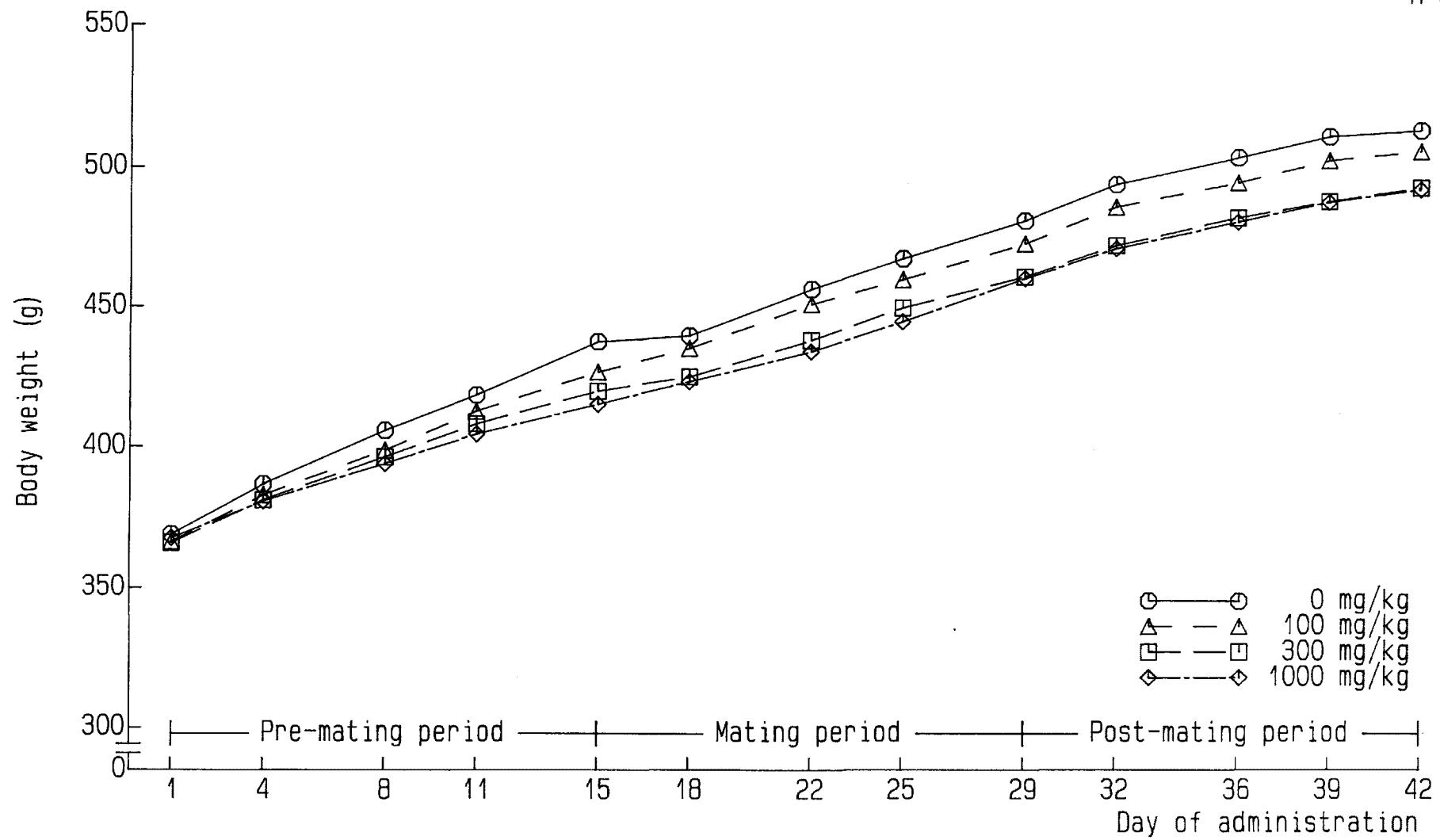


Fig.7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Body weight changes of male rats (Main group)

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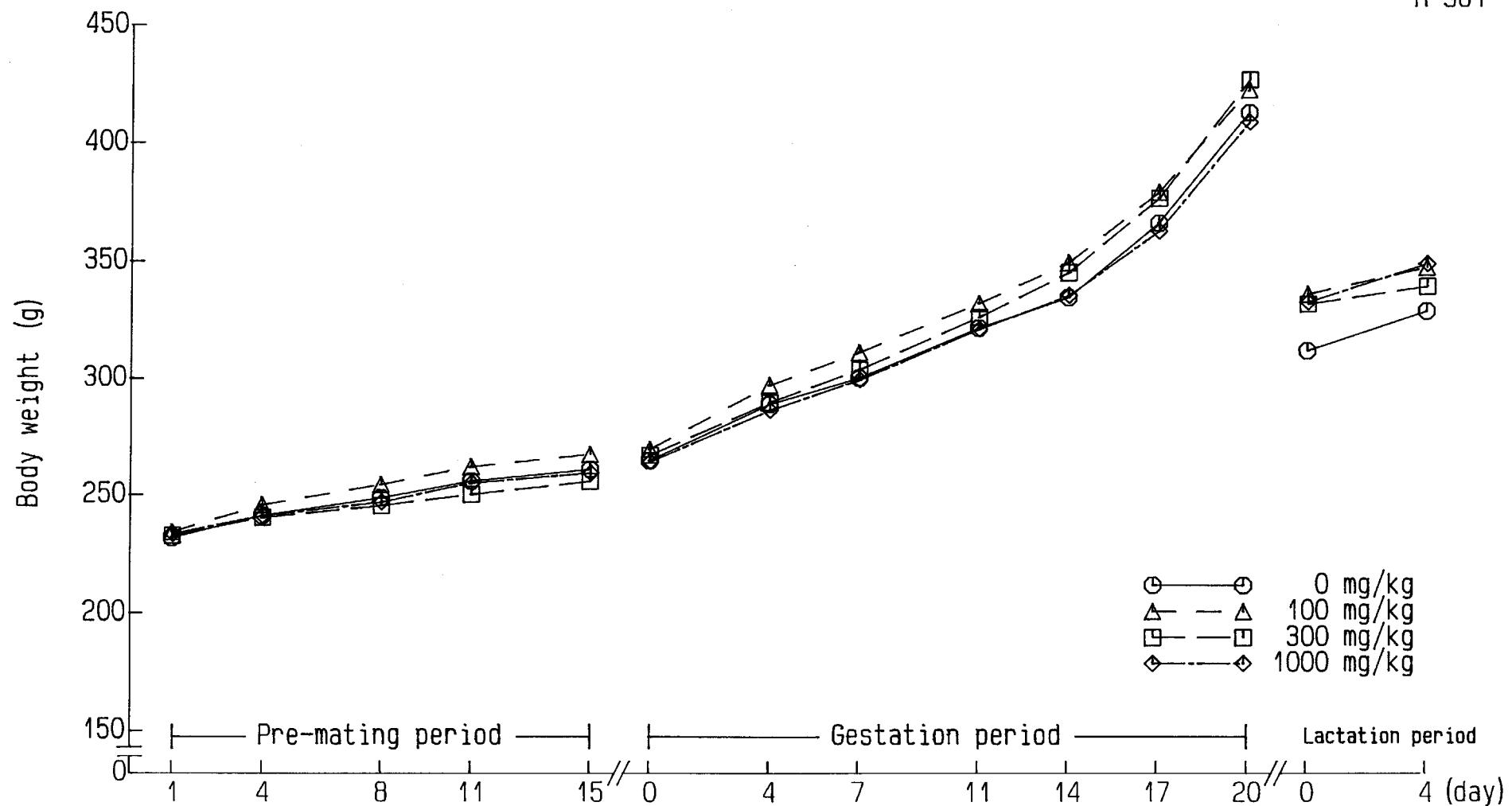


Fig.8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Body weight changes of female rats (Main group)

R-961

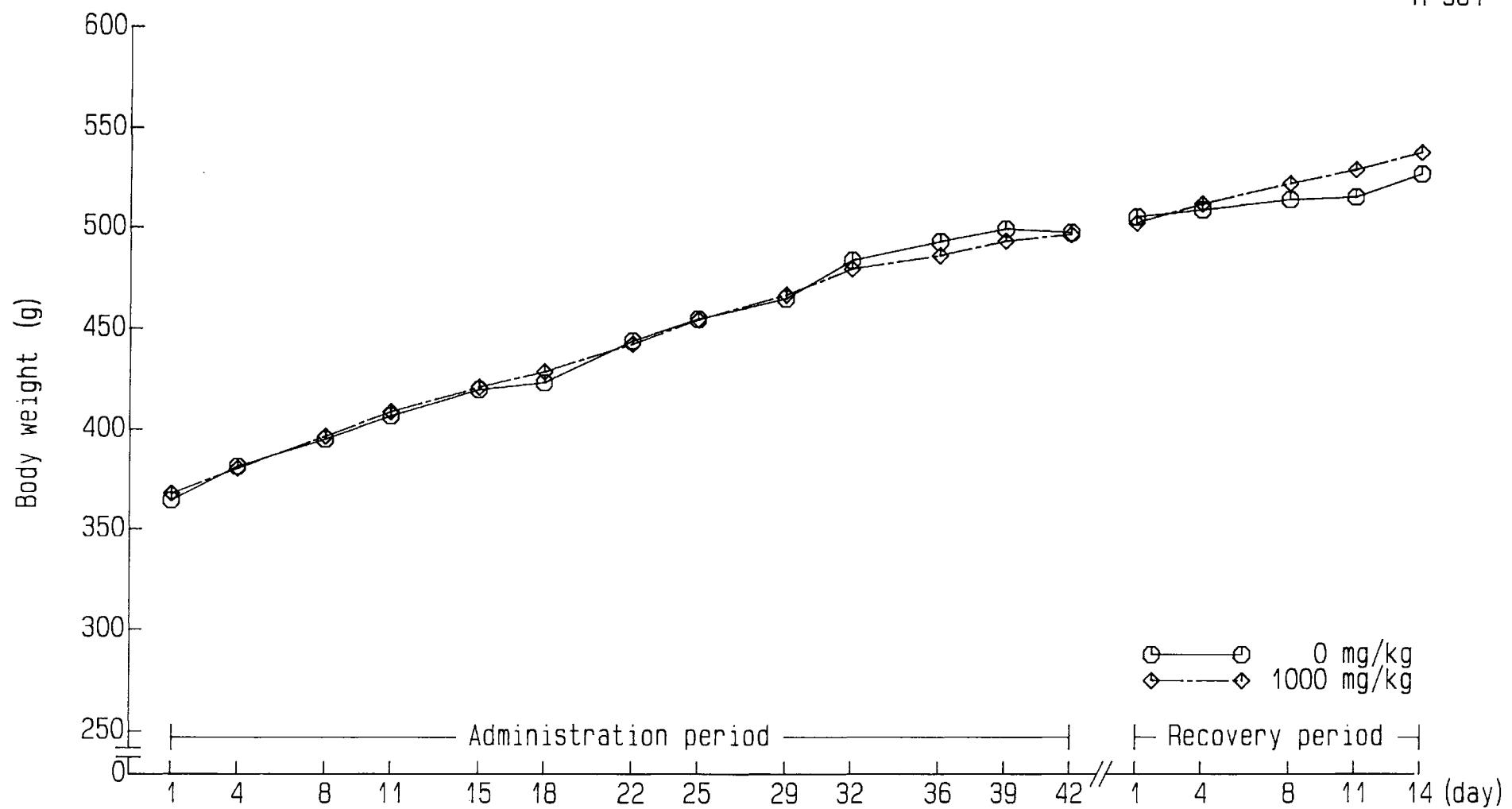


Fig.9 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Body weight changes of male rats (Recovery group)

R-961

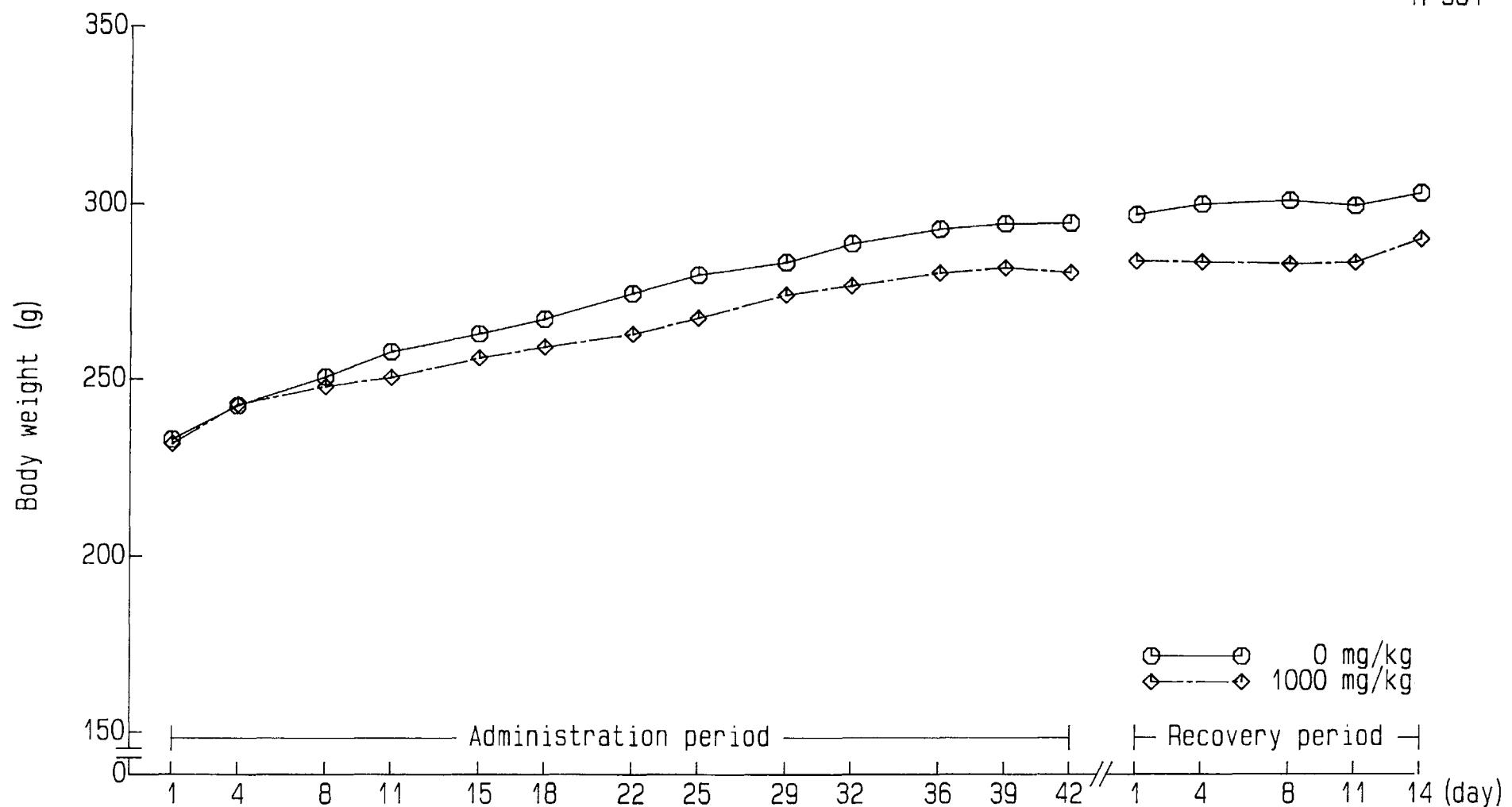


Fig.10 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Body weight changes of female rats (Recovery group)

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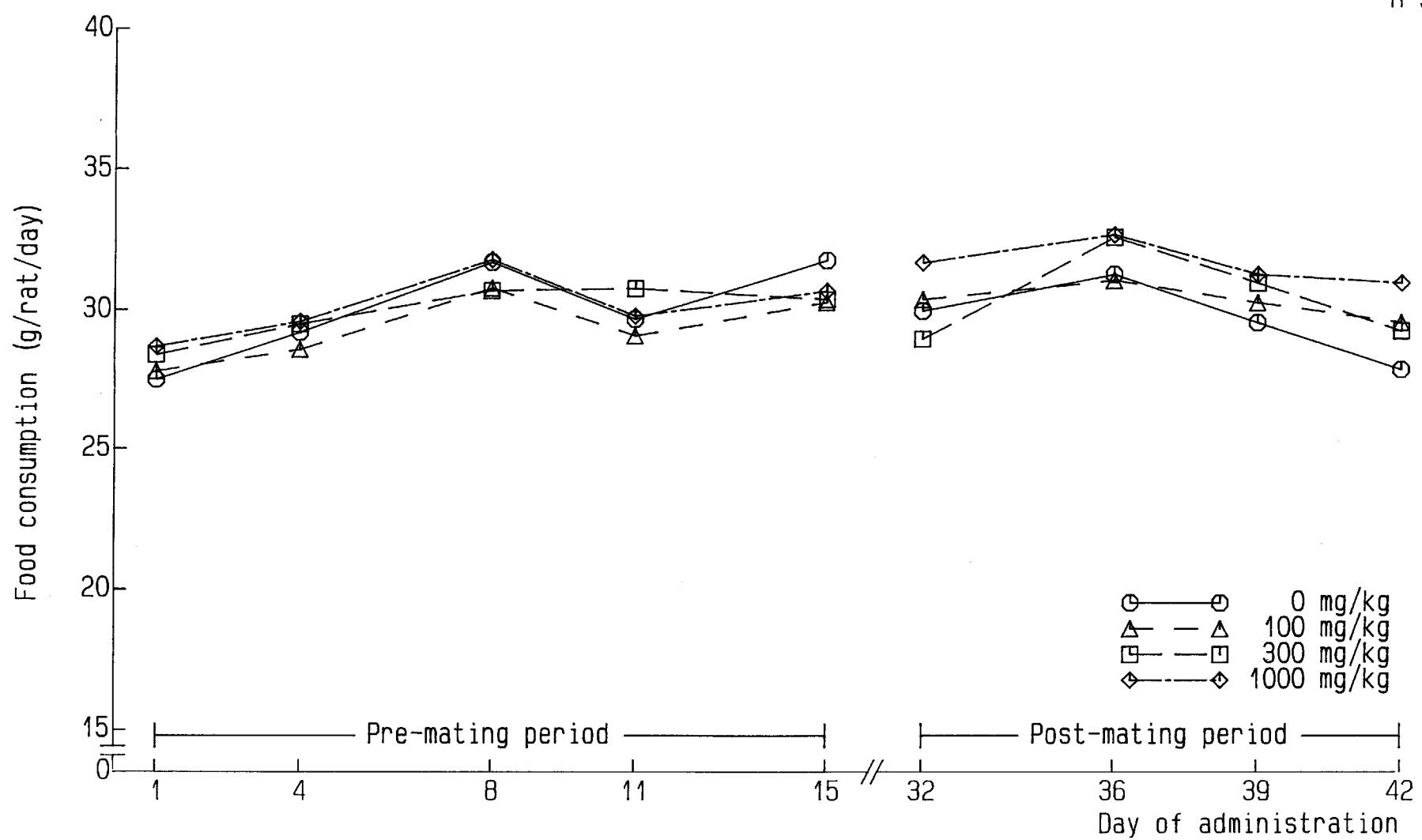


Fig.11 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Food consumption of male rats (Main group)

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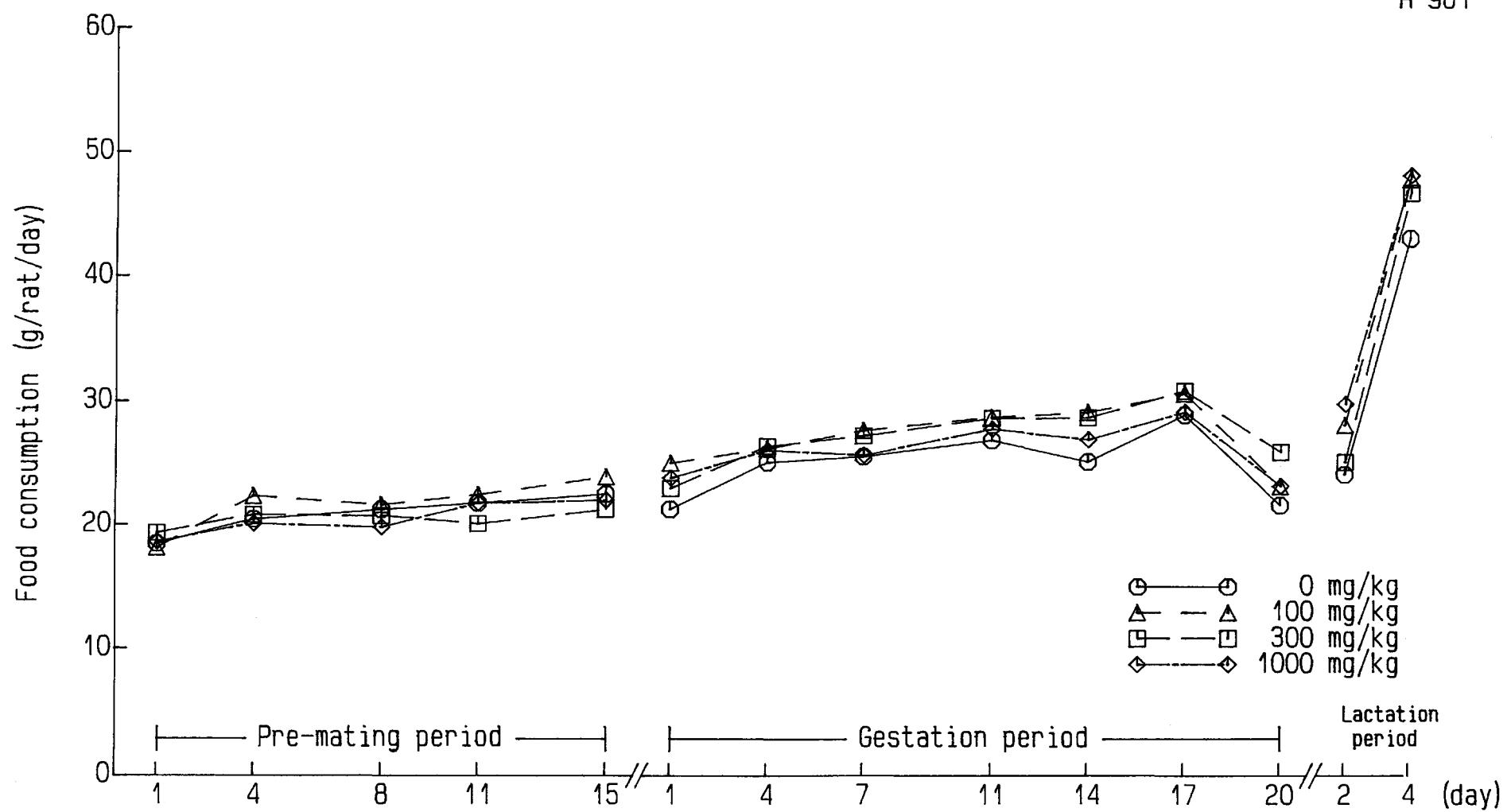


Fig.12 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Food consumption of female rats (Main group)

R-961

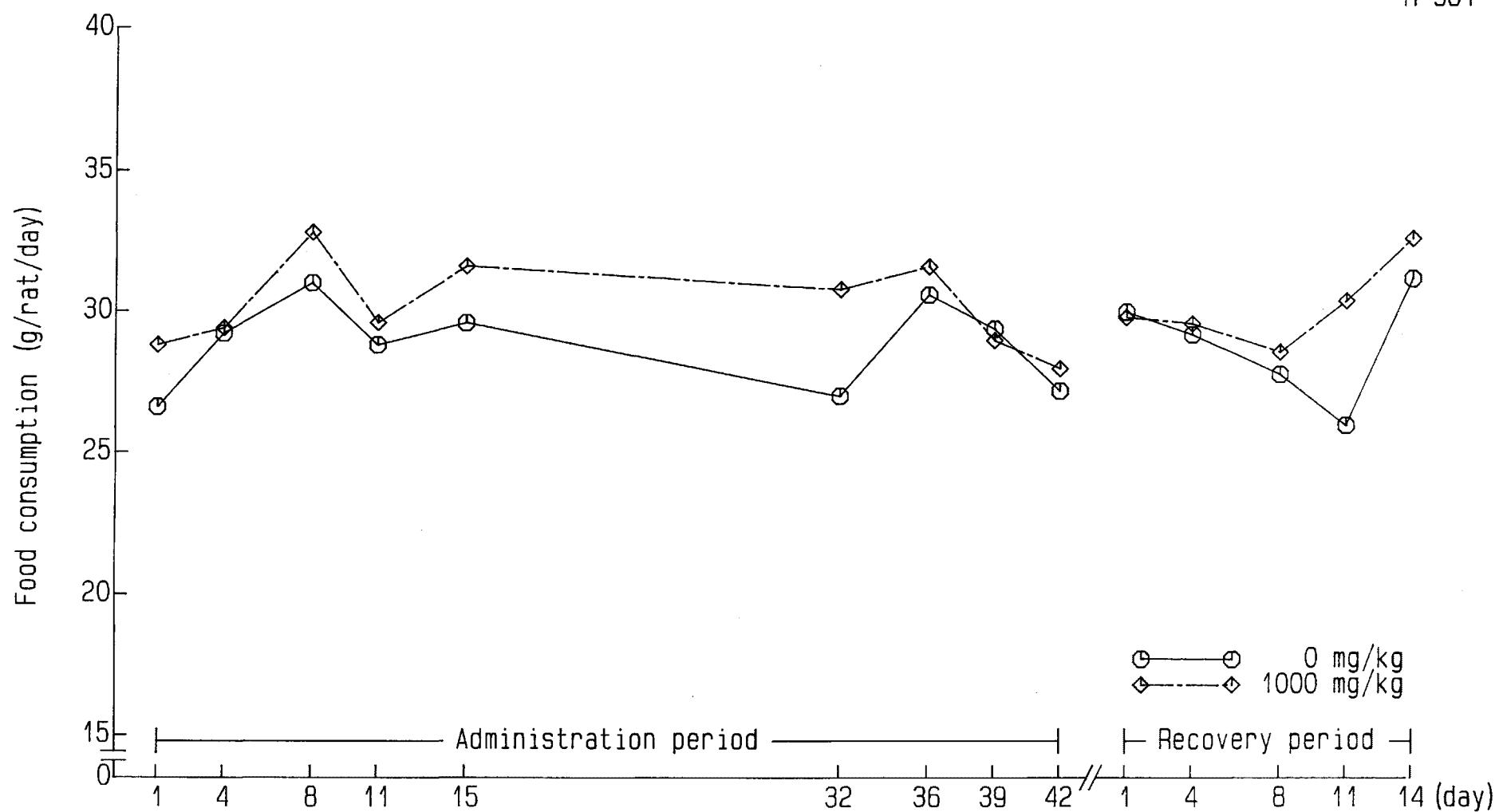


Fig.13 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Food consumption of male rats (Recovery group)

R-961

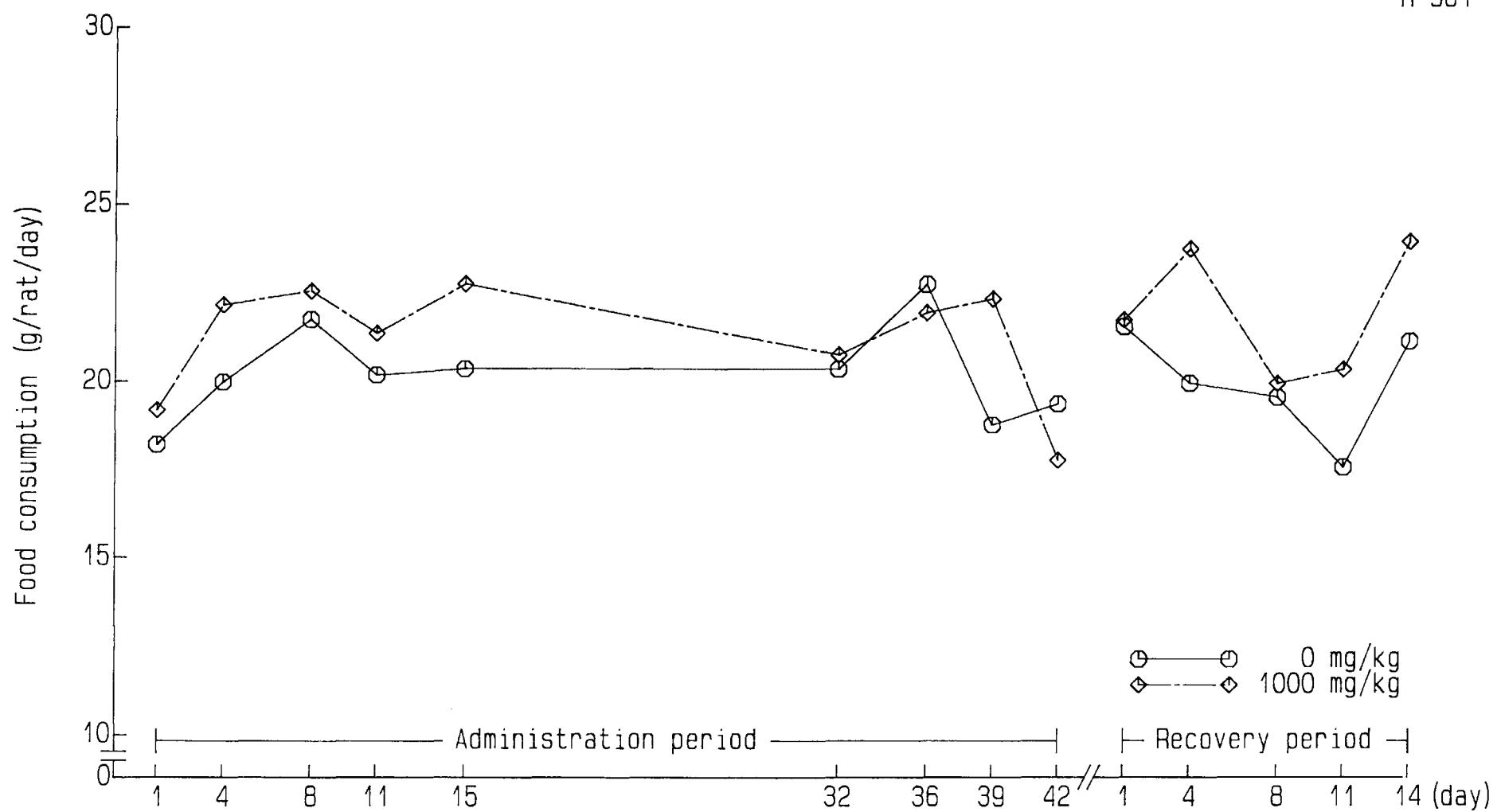


Fig.14 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 2, 4, 5-Benzenetetracarboxylic acid  
Food consumption of female rats (Recovery group)

Table 1-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Clinical signs in male rats (Main group)

Dose mg/kg	Signs	Day of administration					
		1-7	8-14	15-21	22-28	29-35	36-42
0	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0
100	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0
300	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0
1000	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	11	11	9	11	11	12
	Soft feces	11	11	9	11	11	12

Table 1-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Clinical signs in female rats during the pre-mating period (Main group)

Dose mg/kg	Signs	Day of administration														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
300	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	3	3	1	2	3	5	6	3	5	4	4	3	4
	Soft feces	0	0	3	3	1	2	3	5	6	3	5	4	4	3	4

Table 1-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Clinical signs in dams during the gestation period (Main group)

Dose mg/kg	Signs	Administration																									
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24a)	
0	No. 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	7	0	
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
100	No. 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	7	0	
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
300	No. 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	8	0	
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
1000	No. 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	10	1	1
	No. of dams with abnormal findings	0	5	3	4	3	2	2	2	2	3	1	2	2	0	1	1	2	0	0	0	0	0	0	0	0	
	Soft feces	0	5	3	4	3	2	2	2	2	3	1	2	2	0	1	1	2	0	0	0	0	0	0	0	0	

a): Day of gestation

Table 1-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Clinical signs in dams during the lactation period (Main group)

Dose mg/kg	Signs	Administration				
		0	1	2	3	4a)
0	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
100	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
300	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
1000	No. of dams	11	11	11	11	11
	No. of dams with abnormal findings	0	0	0	0	0

a): Day of lactation

Table 1-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Clinical signs in male rats (Recovery group, administration period)

Dose mg/kg	Signs	Day of administration					
		1-7	8-14	15-21	22-28	29-35	36-42
0	No. of animals	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0
1000	No. of animals	5	5	5	5	5	5
	No. of animals with abnormal findings	5	5	5	5	5	5
	Soft feces	5	5	5	5	5	5

Table 1-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Clinical signs in female rats (Recovery group, administration period)

Dose mg/kg	Signs	Day of administration					
		1-7	8-14	15-21	22-28	29-35	36-42
0	No. of animals	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0
1000	No. of animals	5	5	5	5	5	5
	No. of animals with abnormal findings	5	5	5	5	4	4
	Soft feces	5	5	5	5	4	4

Table 1-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

#### Clinical signs in male rats (Recovery group, recovery period)

Table 1-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

#### Clinical signs in female rats (Recovery group, recovery period)

Table 2-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Main group, Week 1 of administration)

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Posture Normal		12	12	12	12
Convulsion None		12	12	12	12
Abnormal behavior None		12	12	12	12

Table 2-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Main group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Main group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Main group, Week 5 of administration)

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Main group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	12	12	12	12
Posture Normal		12	12	12	12
Convulsion None		12	12	12	12
Abnormal behavior None		12	12	12	12

Table 2-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Main group, Week 2 of administration)

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-9

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Main group, Day 1 of gestation)

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-10

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Main group, Day 7 of gestation)

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-11

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Main group, Day 14 of gestation)

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-12

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Main group, Day 20 of gestation)

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-13

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Main group, Day 4 of lactation)

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	11
Posture					
Normal		12	12	12	11
Convulsion					
None		12	12	12	11
Abnormal behavior					
None		12	12	12	11

Table 2-14

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 1 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Posture				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5

Table 2-15

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 2 of administration)

Parameter	Dose (mg/kg)		
		0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-16

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 3 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Posture				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5

Table 2-17

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 4 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Posture Normal		5	5	
Convulsion None		5	5	
Abnormal behavior None		5	5	

Table 2-18

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	1000
		No. of animals	No. of animals
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-19

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	1000
		No. of animals	No. of animals
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-20

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 1 of recovery)

Parameter	Dose (mg/kg)		
		0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-21

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
		No. of animals	No. of animals
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-22

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	1000
		No. of animals	No. of animals
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-23

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	1000
		No. of animals	No. of animals
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-24

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 3 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Posture				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5

Table 2-25

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	1000
		5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-26

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 5 of administration)

Parameter	Dose (mg/kg)		
		0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-27

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	1000
		No. of animals	No. of animals
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-28

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 1 of recovery)

Parameter	Dose (mg/kg)	0	1000
		5	5
Posture			
Normal	5	5	
Convulsion			
None	5	5	
Abnormal behavior			
None	5	5	

Table 2-29

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-30

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		10	11	8	11
Soft		2	1	4	1
Reactivity to handling					
Easy		12	12	12	12

Table 2-31

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	No. of animals			
		0	100	300	1000
Ease of removal from cage					
Easy	12	11	10	10	
Some resistance/avoidance	0	1	2	2	
Fur condition					
Normal	12	12	12	12	
Skin					
Normal	12	12	12	12	
Secretions-Eye, Nose					
Absent	12	12	12	12	
Exophthalmos					
Absent	12	12	12	12	
Palpebral closure					
Normal	12	12	12	12	
Mucosal membranes					
Normal	12	12	12	12	
Lacrimation					
Normal	12	12	12	12	
Piloerection					
Absent	12	12	12	12	
Pupil size					
Normal	12	12	12	12	
Salivation					
None	12	12	12	12	
Abnormal respiration					
Absent	12	12	12	12	
Vocalization					
None	10	10	7	12	
Soft	2	2	5	0	
Reactivity to handling					
Easy	11	12	11	12	
Slightly awkward	1	0	1	0	

Table 2-32

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Ease of removal from cage					
Easy	12	12	10	12	
Some resistance/avoidance	0	0	2	0	
Fur condition					
Normal	12	12	12	12	
Skin					
Normal	12	12	12	12	
Secretions-Eye, Nose					
Absent	12	12	12	12	
Exophthalmos					
Absent	12	12	12	12	
Palpebral closure					
Normal	12	12	12	12	
Mucosal membranes					
Normal	12	12	12	12	
Lacrimation					
Normal	12	12	12	12	
Piloerection					
Absent	12	12	12	12	
Pupil size					
Normal	12	12	12	12	
Salivation					
None	12	12	12	12	
Abnormal respiration					
Absent	12	12	12	12	
Vocalization					
None	12	11	9	11	
Soft	0	1	2	1	
Moderate	0	0	1	0	
Reactivity to handling					
Easy	12	12	10	12	
Slightly awkward	0	0	2	0	

Table 2-33

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Ease of removal from cage					
Easy	11	11	11	12	
Some resistance/avoidance	1	1	1	0	
Fur condition					
Normal	12	12	12	12	
Skin					
Normal	12	12	12	12	
Secretions-Eye, Nose					
Absent	12	12	12	12	
Exophthalmos					
Absent	12	12	12	12	
Palpebral closure					
Normal	12	12	12	12	
Mucosal membranes					
Normal	12	12	12	12	
Lacrimation					
Normal	12	12	12	12	
Piloerection					
Absent	12	12	12	12	
Pupil size					
Normal	12	12	12	12	
Salivation					
None	12	12	12	12	
Abnormal respiration					
Absent	12	12	12	12	
Vocalization					
None	11	12	7	9	
Soft	1	0	5	3	
Reactivity to handling					
Easy	10	11	11	12	
Slightly awkward	2	1	1	0	

Table 2-34

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy	12	9	12	12	12
Some resistance/avoidance	0	3	0	0	0
Fur condition					
Normal	12	12	12	12	12
Skin					
Normal	12	12	12	12	12
Secretions-Eye, Nose					
Absent	12	12	12	12	12
Exophthalmos					
Absent	12	12	12	12	12
Palpebral closure					
Normal	12	12	12	12	12
Mucosal membranes					
Normal	12	12	12	12	12
Lacrimation					
Normal	12	12	12	12	12
Pilorection					
Absent	12	12	12	12	12
Pupil size					
Normal	12	12	12	12	12
Salivation					
None	12	12	12	12	12
Abnormal respiration					
Absent	12	12	12	12	12
Vocalization					
None	9	11	9	11	11
Soft	3	1	3	1	1
Reactivity to handling					
Easy	12	12	12	12	12

Table 2-35

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Ease of removal from cage					
Easy	9	11	11	11	
Some resistance/avoidance	2	1	1	1	
Difficult	1	0	0	0	
Fur condition					
Normal	12	12	12	12	
Skin					
Normal	12	12	12	12	
Secretions-Eye, Nose					
Absent	12	12	12	12	
Exophthalmos					
Absent	12	12	12	12	
Palpebral closure					
Normal	12	12	12	12	
Mucosal membranes					
Normal	12	12	12	12	
Lacrimation					
Normal	12	12	12	12	
Piloerection					
Absent	12	12	12	12	
Pupil size					
Normal	12	12	12	12	
Salivation					
None	12	12	12	12	
Abnormal respiration					
Absent	12	12	12	12	
Vocalization					
None	10	11	9	7	
Soft	1	1	2	5	
Moderate	1	0	1	0	
Reactivity to handling					
Easy	11	12	10	12	
Slightly awkward	1	0	2	0	

Table 2-36

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Ease of removal from cage					
Easy	12	12	12	12	12
Fur condition					
Normal	12	12	12	12	12
Skin					
Normal	12	12	12	12	12
Secretions-Eye, Nose					
Absent	12	12	12	12	12
Exophthalmos					
Absent	12	12	12	12	12
Palpebral closure					
Normal	12	12	12	12	12
Mucosal membranes					
Normal	12	12	12	12	12
Lacrimation					
Normal	12	12	12	12	12
Piloerection					
Absent	12	12	12	12	12
Pupil size					
Normal	12	12	12	12	12
Salivation					
None	12	12	12	12	12
Abnormal respiration					
Absent	12	12	12	12	12
Vocalization					
None	11	12	12	12	12
Soft	1	0	0	0	0
Reactivity to handling					
Easy	12	12	12	12	12

Table 2-37

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Ease of removal from cage					
Easy	12	12	12	12	12
Fur condition					
Normal	12	12	12	12	12
Skin					
Normal	12	12	12	12	12
Secretions-Eye, Nose					
Absent	12	12	12	12	12
Exophthalmos					
Absent	12	12	12	12	12
Palpebral closure					
Normal	12	12	12	12	12
Mucosal membranes					
Normal	12	12	12	12	12
Lacrimation					
Normal	12	12	12	12	12
Piloerection					
Absent	12	12	12	12	12
Pupil size					
Normal	12	12	12	12	12
Salivation					
None	12	12	12	12	12
Abnormal respiration					
Absent	12	12	12	12	12
Vocalization					
None	11	12	12	11	11
Soft	1	0	0	1	1
Reactivity to handling					
Easy	12	12	12	12	12

Table 2-38

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 1 of gestation)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Ease of removal from cage					
Easy	12	11	12	12	12
Some resistance/avoidance	0	1	0	0	0
Fur condition					
Normal	12	12	12	12	12
Skin					
Normal	12	12	12	12	12
Secretions-Eye, Nose					
Absent	12	12	12	12	12
Exophthalmos					
Absent	12	12	12	12	12
Palpebral closure					
Normal	12	12	12	12	12
Mucosal membranes					
Normal	12	12	12	12	12
Lacrimation					
Normal	12	12	12	12	12
Piloerection					
Absent	12	12	12	12	12
Pupil size					
Normal	12	12	12	12	12
Salivation					
None	12	12	12	12	12
Abnormal respiration					
Absent	12	12	12	12	12
Vocalization					
None	11	8	12	11	11
Soft	1	4	0	1	0
Reactivity to handling					
Easy	12	11	12	12	12
Slightly awkward	0	1	0	0	0

Table 2-39

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 7 of gestation)

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy	11	11	12	12	
Some resistance/avoidance	1	1	0	0	
Fur condition					
Normal	12	12	12	12	
Skin					
Normal	12	12	12	12	
Secretions-Eye, Nose					
Absent	12	12	12	12	
Exophthalmos					
Absent	12	12	12	12	
Palpebral closure					
Normal	12	12	12	12	
Mucosal membranes					
Normal	12	12	12	12	
Lacrimation					
Normal	12	12	12	12	
Piloerection					
Absent	12	12	12	12	
Pupil size					
Normal	12	12	12	12	
Salivation					
None	12	12	12	12	
Abnormal respiration					
Absent	12	12	12	12	
Vocalization					
None	12	11	12	12	
Soft	0	1	0	0	
Reactivity to handling					
Easy	11	10	12	12	
Slightly awkward	1	2	0	0	

Table 2-40

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 14 of gestation)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Ease of removal from cage					
Easy	12	12	12	12	12
Fur condition					
Normal	12	12	12	12	12
Skin					
Normal	12	12	12	12	12
Secretions-Eye, Nose					
Absent	12	12	12	12	12
Exophthalmos					
Absent	12	12	12	12	12
Palpebral closure					
Normal	12	12	12	12	12
Mucosal membranes					
Normal	12	12	12	12	12
Lacration					
Normal	12	12	12	12	12
Piloerection					
Absent	12	12	12	12	12
Pupil size					
Normal	12	12	12	12	12
Salivation					
None	12	12	12	12	12
Abnormal respiration					
Absent	12	12	12	12	12
Vocalization					
None	11	12	11	11	
Soft	1	0	1	1	
Reactivity to handling					
Easy	12	12	12	12	

Table 2-41

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 20 of gestation)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Ease of removal from cage					
Easy	12	12	12	12	12
Fur condition					
Normal	12	12	12	12	12
Skin					
Normal	12	12	12	12	12
Secretions-Eye, Nose					
Absent	12	12	12	12	12
Exophthalmos					
Absent	12	12	12	12	12
Palpebral closure					
Normal	12	12	12	12	12
Mucosal membranes					
Normal	12	12	12	12	12
Lacrimation					
Normal	12	12	12	12	12
Piloerection					
Absent	12	12	12	12	12
Pupil size					
Normal	12	12	12	12	12
Salivation					
None	12	12	12	12	12
Abnormal respiration					
Absent	12	12	12	12	12
Vocalization					
None	11	11	12	12	12
Soft	1	1	0	0	0
Reactivity to handling					
Easy	12	11	12	12	12
Slightly awkward	0	1	0	0	0

Table 2-42

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 4 of lactation)

Parameter	No. of animals	Dose (mg/kg)			
		0	100	300	1000
Ease of removal from cage					
Easy	12	12	12	12	11
Fur condition					
Normal	12	12	12	12	11
Skin					
Normal	12	12	12	12	11
Secretions-Eye, Nose					
Absent	12	12	12	12	11
Exophthalmos					
Absent	12	12	12	12	11
Palpebral closure					
Normal	12	12	12	12	11
Mucosal membranes					
Normal	12	12	12	12	11
Lacrimation					
Normal	12	12	12	12	11
Piloerection					
Absent	12	12	12	12	11
Pupil size					
Normal	12	12	12	12	11
Salivation					
None	12	12	12	12	11
Abnormal respiration					
Absent	12	12	12	12	11
Vocalization					
None	11	11	12	11	
Soft	1	1	0	0	
Reactivity to handling					
Easy	12	12	12	12	11

Table 2-43

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 1 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5	5	
Fur condition				
Normal		5	5	
Skin				
Normal		5	5	
Secretions-Eye, Nose				
Absent		5	5	
Exophthalmos				
Absent		5	5	
Palpebral closure				
Normal		5	5	
Mucosal membranes				
Normal		5	5	
Lacrimation				
Normal		5	5	
Piloerection				
Absent		5	5	
Pupil size				
Normal		5	5	
Salivation				
None		5	5	
Abnormal respiration				
Absent		5	5	
Vocalization				
None		4	4	
Soft		1	1	
Reactivity to handling				
Easy		5	5	

Table 2-44

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 2 of administration)

Parameter	Dose (mg/kg) No. of animals		
		0 5	1000 5
Ease of removal from cage			
Easy	3	5	
Some resistance/avoidance	2	0	
Fur condition			
Normal	5	5	
Skin			
Normal	5	5	
Secretions-Eye, Nose			
Absent	5	5	
Exophthalmos			
Absent	5	5	
Palpebral closure			
Normal	5	5	
Mucosal membranes			
Normal	5	5	
Lacrimation			
Normal	5	5	
Piloerection			
Absent	5	5	
Pupil size			
Normal	5	5	
Salivation			
None	5	5	
Abnormal respiration			
Absent	5	5	
Vocalization			
None	3	4	
Soft	2	1	
Reactivity to handling			
Easy	4	5	
Slightly awkward	1	0	

Table 2-45

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 3 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5	5	
Fur condition				
Normal		5	5	
Skin				
Normal		5	5	
Secretions-Eye, Nose				
Absent		5	5	
Exophthalmos				
Absent		5	5	
Palpebral closure				
Normal		5	5	
Mucosal membranes				
Normal		5	5	
Lacrimation				
Normal		5	5	
Piloerection				
Absent		5	5	
Pupil size				
Normal		5	5	
Salivation				
None		5	5	
Abnormal respiration				
Absent		5	5	
Vocalization				
None		4	5	
Soft		1	0	
Reactivity to handling				
Easy		5	5	

Table 2-46

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 4 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5		4
Some resistance/avoidance		0		1
Fur condition				
Normal		5		5
Skin				
Normal		5		5
Secretions-Eye, Nose				
Absent		5		5
Exophthalmos				
Absent		5		5
Palpebral closure				
Normal		5		5
Mucosal membranes				
Normal		5		5
Lacrimation				
Normal		5		5
Piloerection				
Absent		5		5
Pupil size				
Normal		5		5
Salivation				
None		5		5
Abnormal respiration				
Absent		5		5
Vocalization				
None		4		4
Soft		1		1
Reactivity to handling				
Easy		5		4
Slightly awkward		0		1

Table 2-47

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 5 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5	5	
Fur condition				
Normal		5	5	
Skin				
Normal		5	5	
Secretions-Eye, Nose				
Absent		5	5	
Exophthalmos				
Absent		5	5	
Palpebral closure				
Normal		5	5	
Mucosal membranes				
Normal		5	5	
Lacrimation				
Normal		5	5	
Piloerection				
Absent		5	5	
Pupil size				
Normal		5	5	
Salivation				
None		5	5	
Abnormal respiration				
Absent		5	5	
Vocalization				
None		4	5	
Soft		1	0	
Reactivity to handling				
Easy		5	5	

Table 2-48

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 6 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5	5	
Fur condition				
Normal		5	5	
Skin				
Normal		5	5	
Secretions-Eye, Nose				
Absent		5	5	
Exophthalmos				
Absent		5	5	
Palpebral closure				
Normal		5	5	
Mucosal membranes				
Normal		5	5	
Lacrimation				
Normal		5	5	
Piloerection				
Absent		5	5	
Pupil size				
Normal		5	5	
Salivation				
None		5	5	
Abnormal respiration				
Absent		5	5	
Vocalization				
None		5	5	
Reactivity to handling				
Easy		5	5	

Table 2-49

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 1 of recovery)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5		4
Some resistance/avoidance		0		1
Fur condition				
Normal		5		5
Skin				
Normal		5		5
Secretions-Eye, Nose				
Absent		5		5
Exophthalmos				
Absent		5		5
Palpebral closure				
Normal		5		5
Mucosal membranes				
Normal		5		5
Lacrimation				
Normal		5		5
Piloerection				
Absent		5		5
Pupil size				
Normal		5		5
Salivation				
None		5		5
Abnormal respiration				
Absent		5		5
Vocalization				
None		5		5
Reactivity to handling				
Easy		5		5

Table 2-50

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)		
		0	1000
	No. of animals	5	5
Ease of removal from cage			
Easy	4	5	
Some resistance/avoidance	1	0	
Fur condition			
Normal	5	5	
Skin			
Normal	5	5	
Secretions-Eye, Nose			
Absent	5	5	
Exophthalmos			
Absent	5	5	
Palpebral closure			
Normal	5	5	
Mucosal membranes			
Normal	5	5	
Lacrimation			
Normal	5	5	
Piloerection			
Absent	5	5	
Pupil size			
Normal	5	5	
Salivation			
None	5	5	
Abnormal respiration			
Absent	5	5	
Vocalization			
None	5	4	
Soft	0	1	
Reactivity to handling			
Easy	4	5	
Slightly awkward	1	0	

Table 2-51

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 1 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5	5	
Fur condition				
Normal		5	5	
Skin				
Normal		5	5	
Secretions-Eye, Nose				
Absent		5	5	
Exophthalmos				
Absent		5	5	
Palpebral closure				
Normal		5	5	
Mucosal membranes				
Normal		5	5	
Lacrimation				
Normal		5	5	
Piloerection				
Absent		5	5	
Pupil size				
Normal		5	5	
Salivation				
None		5	5	
Abnormal respiration				
Absent		5	5	
Vocalization				
None		5	5	
Reactivity to handling				
Easy		5	5	

Table 2-52

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Ease of removal from cage			
Easy		5	5
Fur condition			
Normal		5	5
Skin			
Normal		5	5
Secretions-Eye, Nose			
Absent		5	5
Exophthalmos			
Absent		5	5
Palpebral closure			
Normal		5	5
Mucosal membranes			
Normal		5	5
Lacrimation			
Normal		5	5
Piloerection			
Absent		5	5
Pupil size			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5

Table 2-53

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 3 of administration)

Parameter	No. of animals	Dose (mg/kg)	
		0	1000
Ease of removal from cage			
Easy	4	5	5
Some resistance/avoidance	1	0	0
Fur condition			
Normal	5	5	5
Skin			
Normal	5	5	5
Secretions-Eye, Nose			
Absent	5	5	5
Exophthalmos			
Absent	5	5	5
Palpebral closure			
Normal	5	5	5
Mucosal membranes			
Normal	5	5	5
Lacrimation			
Normal	5	5	5
Piloerection			
Absent	5	5	5
Pupil size			
Normal	5	5	5
Salivation			
None	5	5	5
Abnormal respiration			
Absent	5	5	5
Vocalization			
None	4	5	5
Soft	1	0	0
Reactivity to handling			
Easy	5	5	5

Table 2-54

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 4 of administration)

Parameter	Dose (mg/kg)		
		0	1000
	No. of animals	5	5
Ease of removal from cage			
Easy		5	5
Fur condition			
Normal		5	5
Skin			
Normal		5	5
Secretions-Eye, Nose			
Absent		5	5
Exophthalmos			
Absent		5	5
Palpebral closure			
Normal		5	5
Mucosal membranes			
Normal		5	5
Lacrimation			
Normal		5	5
Piloerection			
Absent		5	5
Pupil size			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5

Table 2-55

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 5 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5	5	
Fur condition				
Normal		5	5	
Skin				
Normal		5	5	
Secretions-Eye, Nose				
Absent		5	5	
Exophthalmos				
Absent		5	5	
Palpebral closure				
Normal		5	5	
Mucosal membranes				
Normal		5	5	
Lacrimation				
Normal		5	5	
Piloerection				
Absent		5	5	
Pupil size				
Normal		5	5	
Salivation				
None		5	5	
Abnormal respiration				
Absent		5	5	
Vocalization				
None		5	5	
Reactivity to handling				
Easy		5	5	

Table 2-56

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 6 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5	5	
Fur condition				
Normal		5	5	
Skin				
Normal		5	5	
Secretions-Eye, Nose				
Absent		5	5	
Exophthalmos				
Absent		5	5	
Palpebral closure				
Normal		5	5	
Mucosal membranes				
Normal		5	5	
Lacrimation				
Normal		5	5	
Piloerection				
Absent		5	5	
Pupil size				
Normal		5	5	
Salivation				
None		5	5	
Abnormal respiration				
Absent		5	5	
Vocalization				
None		5	5	
Reactivity to handling				
Easy		5	5	

Table 2-57

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 1 of recovery)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5	4	
Some resistance/avoidance		0	1	
Fur condition				
Normal		5	5	
Skin				
Normal		5	5	
Secretions-Eye, Nose				
Absent		5	5	
Exophthalmos				
Absent		5	5	
Palpebral closure				
Normal		5	5	
Mucosal membranes				
Normal		5	5	
Lacrimation				
Normal		5	5	
Piloerection				
Absent		5	5	
Pupil size				
Normal		5	5	
Salivation				
None		5	5	
Abnormal respiration				
Absent		5	5	
Vocalization				
None		5	4	
Soft		0	1	
Reactivity to handling				
Easy		5	5	

Table 2-58

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 2 of recovery)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Ease of removal from cage				
Easy		5		4
Some resistance/avoidance		0		1
Fur condition				
Normal		5		5
Skin				
Normal		5		5
Secretions-Eye, Nose				
Absent		5		5
Exophthalmos				
Absent		5		5
Palpebral closure				
Normal		5		5
Mucosal membranes				
Normal		5		5
Lacrimation				
Normal		5		5
Piloerection				
Absent		5		5
Pupil size				
Normal		5		5
Salivation				
None		5		5
Abnormal respiration				
Absent		5		5
Vocalization				
None		5		5
Reactivity to handling				
Easy		5		5

Table 2-59

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)		4 $\pm$ 2	4 $\pm$ 2	4 $\pm$ 2	4 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		1 $\pm$ 2	0 $\pm$ 0	0 $\pm$ 1	0 $\pm$ 0
Urination					
None		12	12	10	11
Small amount		0	0	2	1

No significant difference in any treated groups from control group.

Table 2-60

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean+S.D.)	4± 2	4± 2	4± 3	5± 3	
Defecation count (Mean+S.D.)	0± 0	0± 0	0± 1	0± 1	
Urination					
None	11	8	11	11	
Small amount	1	4	1	1	

No significant difference in any treated groups from control group.

Table 2-61

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Main group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)	4 $\pm$ 1	3 $\pm$ 2	4 $\pm$ 3	3 $\pm$ 2	
Defecation count (Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 1	0 $\pm$ 0	
Urination					
None	12	9	11	10	
Small amount	0	3	1	2	

No significant difference in any treated groups from control group.

Table 2-62

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Main group, Week 4 of administration)

Parameter	No. of animals	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)		5 $\pm$ 2	5 $\pm$ 2	4 $\pm$ 2	5 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 1	0 $\pm$ 0
Urination					
None		11	11	10	12
Small amount		1	1	2	0

No significant difference in any treated groups from control group.

Table 2-63

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Main group, Week 5 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	100	300	1000
			12	12	12	12
Arousal						
Normal		12	12	12	12	12
Convulsion						
None		12	12	12	12	12
Abnormal behavior						
None		12	12	12	12	12
Stereotypy						
None		12	12	12	12	12
Gait						
No/minimal location		1	0	0	0	0
Normal		11	12	12	12	12
Posture						
Normal		12	12	12	12	12
Grooming						
None		12	12	12	12	12
Rearing (Mean+S.D.)		4± 2	4± 2	4± 2	4± 1	
Defecation count (Mean+S.D.)		0± 0	0± 0	0± 1	0± 0	
Urination						
None		11	11	10	12	
Small amount		1	0	2	0	
Moderate amount		0	1	0	0	

No significant difference in any treated groups from control group.

Table 2-64

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Main group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean+S.D.)		5± 2	4± 2	5± 1	4± 2
Defecation count (Mean+S.D.)		0± 0	0± 0	0± 1	0± 0
Urination					
None		12	10	9	12
Small amount		0	1	1	0
Moderate amount		0	1	2	0

No significant difference in any treated groups from control group.

Table 2-65

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Main group, Week 1 of administration)

Parameter	No. of animals	Dose (mg/kg)			
		0	100	300	1000
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		6± 2	7± 2	7± 2	8± 3
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	11	12	12
Small amount		0	1	0	0

No significant difference in any treated groups from control group.

Table 2-66

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Main group, Week 2 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	100	300	1000
			12	12	12	12
Arousal						
Normal		12	12	12	12	12
Convulsion						
None		12	12	12	12	12
Abnormal behavior						
None		12	12	12	12	12
Stereotypy						
None		12	12	12	12	12
Gait						
Normal		12	12	12	12	12
Posture						
Normal		12	12	12	12	12
Grooming						
None		12	12	12	12	12
Rearing (Mean±S.D.)		7± 2	8± 3	8± 3	8± 3	
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0	
Urination						
None		12	12	12	12	

No significant difference in any treated groups from control group.

Table 2-67

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Main group, Day 1 of gestation)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean+S.D.)		7± 1	8± 2	8± 2	7± 2
Defecation count (Mean+S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	12	12	12

No significant difference in any treated groups from control group.

Table 2-68

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Main group, Day 7 of gestation)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean+S.D.)		6± 1	7± 2	7± 2	7± 1
Defecation count (Mean+S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	12	12	12

No significant difference in any treated groups from control group.

Table 2-69

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Main group, Day 14 of gestation)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)	5 $\pm$ 2	6 $\pm$ 2	6 $\pm$ 1	6 $\pm$ 3	
Defecation count (Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	
Urination					
None		12	12	12	12

No significant difference in any treated groups from control group.

Table 2-70

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Main group, Day 20 of gestation)

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)		5 $\pm$ 1	5 $\pm$ 2	4 $\pm$ 2	6 $\pm$ 1
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		12	12	12	12

No significant difference in any treated groups from control group.

Table 2-71

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Main group, Day 4 of lactation)

Parameter	No. of animals	0	100	300	1000
		12	12	12	11
Arousal					
Normal		12	12	12	11
Convulsion					
None		12	12	12	11
Abnormal behavior					
None		12	12	12	11
Stereotypy					
None		12	12	12	11
Gait					
Normal		12	12	12	11
Posture					
Normal		12	12	12	11
Grooming					
None		12	12	12	11
Rearing (Mean $\pm$ S.D.)		6 $\pm$ 2	7 $\pm$ 2	6 $\pm$ 1	7 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		11	12	12	10
Small amount		1	0	0	1

No significant difference in any treated groups from control group.

Table 2-72

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Recovery group, Week 1 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean $\pm$ S.D.)		3 $\pm$ 2		4 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0		0 $\pm$ 0
Urination				
None		4		5
Small amount		1		0

No significant difference between treated group and control group.

Table 2-73

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Recovery group, Week 2 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
No/minimal location			2	0
Normal			3	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean $\pm$ S.D.)			3 $\pm$ 4	3 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)			0 $\pm$ 0	0 $\pm$ 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-74

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Recovery group, Week 3 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
No/minimal location			1	0
Normal			4	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean $\pm$ S.D.)			2 $\pm$ 2	3 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)			0 $\pm$ 0	0 $\pm$ 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-75

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Recovery group, Week 4 of administration)

Parameter	Dose (mg/kg)		
		0	1000
	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean+S.D.)		4± 2	4± 2
Defecation count (Mean+S.D.)		0± 0	0± 1
Urination			
None		4	5
Small amount		1	0

No significant difference between treated group and control group.

Table 2-76

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Recovery group, Week 5 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean $\pm$ S.D.)			4 $\pm$ 2	3 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)			0 $\pm$ 0	0 $\pm$ 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-77

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Recovery group, Week 6 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean $\pm$ S.D.)			5 $\pm$ 1	5 $\pm$ 4
Defecation count (Mean $\pm$ S.D.)			0 $\pm$ 0	0 $\pm$ 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-78

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Recovery group, Week 1 of recovery)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean $\pm$ S.D.)			3 $\pm$ 1	3 $\pm$ 1
Defecation count (Mean $\pm$ S.D.)			0 $\pm$ 0	0 $\pm$ 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-79

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in male rats: open field observation (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)		
		0	1000
	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
No/minimal location		0	1
Normal		5	4
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean $\pm$ S.D.)		6 $\pm$ 2	3 $\pm$ 3
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Urination			
None		3	4
Small amount		2	1

No significant difference between treated group and control group.

Table 2-80

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Recovery group, Week 1 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean+S.D.)			6± 2	7± 1
Defecation count (Mean+S.D.)			0± 0	0± 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-81

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Recovery group, Week 2 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean+S.D.)			7± 2	9± 3
Defecation count (Mean+S.D.)			0± 0	0± 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-82

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Recovery group, Week 3 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean+S.D.)			8± 1	7± 2
Defecation count (Mean+S.D.)			0± 0	0± 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-83

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Recovery group, Week 4 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal		5	5	
Convulsion				
None		5	5	
Abnormal behavior				
None		5	5	
Stereotypy				
None		5	5	
Gait				
Normal		5	5	
Posture				
Normal		5	5	
Grooming				
None		5	5	
Rearing (Mean $\pm$ S.D.)		6 $\pm$ 2	7 $\pm$ 2	
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	
Urination				
None		5	5	

No significant difference between treated group and control group.

Table 2-84

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Recovery group, Week 5 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean $\pm$ S.D.)			8 $\pm$ 2	7 $\pm$ 3
Defecation count (Mean $\pm$ S.D.)			0 $\pm$ 0	0 $\pm$ 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-85

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Recovery group, Week 6 of administration)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal			5	5
Convulsion				
None			5	5
Abnormal behavior				
None			5	5
Stereotypy				
None			5	5
Gait				
Normal			5	5
Posture				
Normal			5	5
Grooming				
None			5	5
Rearing (Mean+S.D.)			8± 1	8± 2
Defecation count (Mean+S.D.)			0± 0	0± 0
Urination				
None			5	5

No significant difference between treated group and control group.

Table 2-86

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Recovery group, Week 1 of recovery)

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal		5	5	
Convulsion				
None		5	5	
Abnormal behavior				
None		5	5	
Stereotypy				
None		5	5	
Gait				
Normal		5	5	
Posture				
Normal		5	5	
Grooming				
None		5	5	
Rearing (Mean $\pm$ S.D.)		7 $\pm$ 2	6 $\pm$ 2	
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	
Urination				
None		5	5	

No significant difference between treated group and control group.

Table 2-87

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Detailed clinical signs in female rats: open field observation (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)		
		0	1000
	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean+S.D.)		8± 2	10± 1
Defecation count (Mean+S.D.)		0± 0	0± 0
Urination			
None		3	4
Small amount		2	1

No significant difference between treated group and control group.

Table 2-88

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Manipulative test of male rats (Main group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	5	5	5	5
Auditory response Normal		5	5	5	5
Approach response Normal		5	5	5	5
Touch response Normal		5	5	5	5
Tail pinch response Normal		5	5	5	5
Pupillary reflex Pass, both		5	5	5	5
Aerial righting reflex (Total score: Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	
Landing foot splay (mm: Mean $\pm$ S.D.)	69 $\pm$ 16	70 $\pm$ 14	86 $\pm$ 22	66 $\pm$ 13	

No significant difference in any treated groups from control group.

Table 2-89

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Manipulative test of female rats (Main group, Day 4 of lactation)

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	5	5	5	5
Auditory response					
Normal	5	5	5	5	5
Approach response					
Normal	5	5	5	5	5
Touch response					
Normal	5	5	5	5	5
Tail pinch response					
Normal	5	5	5	5	5
Pupillary reflex					
Pass, both	5	5	5	5	5
Aerial righting reflex					
(Total score: Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	
Landing foot splay (mm: Mean $\pm$ S.D.)	75 $\pm$ 16	69 $\pm$ 18	65 $\pm$ 15	82 $\pm$ 19	

No significant difference in any treated groups from control group.

Table 2-90

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Manipulative test of male rats (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Landing foot splay (mm: Mean $\pm$ S.D.)		78 $\pm$ 29	75 $\pm$ 22

No significant difference between treated group and control group.

Table 2-91

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Manipulative test of female rats (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	
Landing foot splay (mm: Mean $\pm$ S.D.)	65 $\pm$ 21	68 $\pm$ 22	

No significant difference between treated group and control group.

Table 2-92

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Manipulative test of male rats (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	
Landing foot splay (mm: Mean $\pm$ S.D.)	90 $\pm$ 19	81 $\pm$ 18	

No significant difference between treated group and control group.

Table 2-93

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Manipulative test of female rats (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	
Landing foot splay (mm: Mean $\pm$ S.D.)	63 $\pm$ 8	62 $\pm$ 7	

No significant difference between treated group and control group.

Table 2-94

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Grip strength of male rats (Main group, Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1223	868
	S.D.	140	111
100	No.	5	5
	Mean	1347	900
	S.D.	84	89
300	No.	5	5
	Mean	1341	884
	S.D.	216	169
1000	No.	5	5
	Mean	1275	863
	S.D.	97	224

No significant difference in any treated groups from control group.

Table 2-95

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Grip strength of female rats (Main group, Day 4 of lactation)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1174	882
	S.D.	89	172
100	No.	5	5
	Mean	1137	853
	S.D.	190	97
300	No.	5	5
	Mean	1088	676
	S.D.	157	45
1000	No.	5	5
	Mean	1213	947
	S.D.	134	187

No significant difference in any treated groups from control group.

Table 2-96

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Grip strength of male rats (Recovery group, Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1222	823
	S.D.	113	100
1000	No.	5	5
	Mean	1273	898
	S.D.	165	112

No significant difference between treated group and control group.

Table 2-97

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Grip strength of female rats (Recovery group, Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	953	772
	S.D.	111	146
1000	No.	5	5
	Mean	842	663
	S.D.	114	100

No significant difference between treated group and control group.

Table 2-98

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Grip strength of male rats (Recovery group, Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1751	952
	S.D.	84	176
1000	No.	5	5
	Mean	1662	899
	S.D.	212	164

No significant difference between treated group and control group.

Table 2-99

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Grip strength of female rats (Recovery group, Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1041	819
	S.D.	276	147
1000	No.	5	5
	Mean	1012	731
	S.D.	165	135

No significant difference between treated group and control group.

Table 2-100

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Motor activity of male rats (Main group, Week 6 of administration)

Dose mg/kg	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No. Mean S.D.	5 427 33	5 367 36	5 281 97	5 247 40	5 294 35	5 226 72
100	No. Mean S.D.	5 412 28	5 362 33	5 274 83	5 188 88	5 182 131	5 174 158
300	No. Mean S.D.	5 429 26	5 350 81	5 278 70	5 146 128	5 116 106	5 53 43
1000	No. Mean S.D.	5 421 15	5 357 43	5 329 39	5 289 140	5 241 137	5 167 128

No significant difference in any treated groups from control group.

Table 2-101

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Motor activity of female rats (Main group, Day 4 of lactation)

Dose mg/kg	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No. Mean S.D.	5 296 128	5 130 158	5 89 120	5 68 110	5 12 14	5 19 20
100	No. Mean S.D.	5 329 63	5 217 103	5 98 116	5 89 109	5 60 92	5 65 111
300	No. Mean S.D.	5 295 63	5 243 109	5 134 108	5 86 126	5 17 12	5 32 18
1000	No. Mean S.D.	5 331 69	5 192 95	5 88 69	5 32 43	5 15 5	5 142 123
							799 179

No significant difference in any treated groups from control group.

Table 2-102

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Motor activity of male rats (Recovery group, Week 6 of administration)

Dose mg/kg	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5
	Mean	419	327	220	213	73	1327
	S.D.	29	97	163	172	110	495
1000	No.	5	5	5	5	5	5
	Mean	412	342	258	136	28	1186
	S.D.	48	41	146	111	40	306

No significant difference between treated group and control group.

Table 2-103

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Motor activity of female rats (Recovery group, Week 6 of administration)

Dose mg/kg	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5
	Mean	399	286	269	153	88	1248
	S.D.	46	110	94	137	131	370
1000	No.	5	5	5	5	5	5
	Mean	391	289	266	149	100	1242
	S.D.	40	119	93	91	153	337

No significant difference between treated group and control group.

Table 2-104

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Motor activity of male rats (Recovery group, Week 2 of recovery)

Dose mg/kg	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No. Mean S.D.	5 374 18	5 283 78	5 193 95	5 91 73	5 58 63	5 66 77
1000	No. Mean S.D.	5 343 58	5 306 28	5 272 44	5 183 97	5 87 108	5 33 38
							1064 172
							1224 196

No significant difference between treated group and control group.

Table 2-105

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Motor activity of female rats (Recovery group, Week 2 of recovery)

Dose mg/kg	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No. 5	5	5	5	5	5	5
	Mean 332	208	182	80	117	86	1006
	S.D. 67	100	96	83	145	117	322
1000	No. 5	5	5	5	5	5	5
	Mean 296	193	173	104	152	122	1040
	S.D. 46	43	139	84	100	121	126

No significant difference between treated group and control group.

Table 3-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Body weight of male rats (Main group)

Dose mg/kg	Pre-mating period					Mating period				Post-mating period				Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42a)	
0	No.	12	12	12	12	12	12	12	12	12	12	12	12	12
0	Mean	369.0	386.8	405.8	418.3	437.7	439.7	456.5	467.3	480.8	493.9	503.5	510.8	513.0
0	S.D.	15.1	17.4	19.7	21.5	20.5	22.4	23.4	22.7	23.0	24.0	24.6	24.3	27.2
100	No.	12	12	12	12	12	12	12	12	12	12	12	12	12
100	Mean	366.5	382.8	398.8	412.5	426.8	435.3	451.0	459.8	472.7	485.7	494.5	502.3	505.6
100	S.D.	14.7	16.2	17.0	18.9	18.8	17.9	17.0	20.3	19.9	20.5	21.0	22.2	19.7
300	No.	12	12	12	12	12	12	12	12	12	12	12	12	12
300	Mean	366.0	381.2	396.3	408.2	419.9	425.0	438.3	449.8	460.8	472.1	481.8	487.5	492.5
300	S.D.	14.4	16.6	19.2	21.8	23.2	19.7	25.3	25.2	24.7	25.9	27.4	27.6	28.8
1000	No.	12	12	12	12	12	12	12	12	12	12	12	12	12
1000	Mean	367.8	380.8	394.1	404.5	415.2*	423.2	434.1*	444.9	460.3	471.0	480.4	487.3	491.9
1000	S.D.	18.6	13.5	14.8	15.2	19.6D	20.1	23.5D	23.9	27.0	26.8	28.1	28.4	31.3

Unit: g

No.: No. of animals

a): Day of administration

\*: p&lt;0.05 (Significant difference from control group)

D: Dunnett's test

Table 3-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Body weight of female rats during the pre-mating period (Main group)

Dose mg/kg	Day of administration					Gain 1-15	
	1	4	8	11	15		
0	No. Mean S.D.	12 231.8 10.8	12 241.2 11.6	12 249.0 12.8	12 256.1 14.6	12 261.4 16.6	29.6 7.6
100	No. Mean S.D.	12 234.3 9.8	12 245.9 11.8	12 254.5 13.7	12 262.4 12.1	12 267.8 12.4	33.6 5.7
300	No. Mean S.D.	12 232.8 12.5	12 240.6 11.8	12 245.6 14.2	12 250.4 13.9	12 256.2 14.7	23.4 7.8
1000	No. Mean S.D.	12 233.6 10.6	12 241.3 11.6	12 247.2 13.4	12 255.3 16.7	12 259.7 19.8	26.1 11.8

Unit: g

No.: No. of animals

No significant difference in any treated groups from control group.

Table 3-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Body weight of dams during the gestation period (Main group)

Dose mg/kg	Administration							Gain 0-20	
	0	4	7	11	14	17	20a)		
0	No. Mean S.D.	12 265.0 18.3	12 289.6 19.5	12 300.7 21.4	12 322.4 24.0	12 385.3 25.9	12 366.6 29.6	12 413.8 32.7	12 148.8 18.8
100	No. Mean S.D.	12 270.1 14.6	12 297.7 12.5	12 311.7 13.0	12 332.9 13.4	12 349.9 13.1	12 379.8 15.9	12 423.7 19.0	12 153.6 15.1
300	No. Mean S.D.	12 267.4 18.1	12 290.3 16.8	12 304.4 18.7	12 327.0 18.7	12 345.9 20.6	12 377.1 23.4	12 428.0 27.8	12 160.6 14.8
1000	No. Mean S.D.	12 264.7 19.0	12 286.8 21.2	12 300.0 23.2	12 321.8 27.4	12 336.2 27.9	12 363.3 33.5	12 409.8 46.7	12 145.2 35.9

Unit: g

No.: No. of dams

a): Day of gestation

No significant difference in any treated groups from control group.

Table 3-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Body weight of dams during the lactation period (Main group)

Dose mg/kg	Administration			Gain 0-4
	0	4a)		
0	No.	12	12	12
	Mean	312.8	329.7	16.9
	S.D.	23.7	24.8	17.7
100	No.	12	12	12
	Mean	336.9	348.3	11.3
	S.D.	21.8	23.8	15.1
300	No.	12	12	12
	Mean	332.9	340.2	7.3
	S.D.	29.0	22.2	14.3
1000	No.	11	11	11
	Mean	333.7	349.8	16.1
	S.D.	28.1	29.4	15.9

Unit: g

No.: No. of dams

a): Day of lactation

No significant difference in any treated groups from control group.

Table 3-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Body weight of male rats during the administration period (Recovery group)

Dose mg/kg	Day of administration													Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42	
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5
0	Mean	364.4	381.4	395.0	406.8	419.8	423.4	444.2	455.0	465.2	483.8	493.2	499.4	497.6
0	S.D.	18.1	18.3	19.3	21.6	24.4	25.1	27.5	32.7	35.1	42.0	46.6	50.6	52.1
1000	No.	5	5	5	5	5	5	5	5	5	5	5	5	5
1000	Mean	368.0	380.4	396.6	408.8	421.2	429.0	442.6	454.6	467.0	479.6	486.4	493.4	496.8
1000	S.D.	21.0	22.9	28.1	33.4	38.5	42.4	48.2	50.6	53.3	53.6	58.3	60.8	68.3

Unit: g

No.: No. of animals

No significant difference between treated group and control group.

Table 3-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Body weight of female rats during the administration period (Recovery group)

Dose mg/kg	Day of administration													Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42	
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5
0	Mean	233.0	242.6	250.8	258.0	263.2	267.4	274.8	280.0	283.6	289.0	293.0	294.6	294.8
0	S.D.	11.4	12.6	13.9	11.1	14.7	17.8	17.9	22.4	21.4	24.0	23.9	23.4	27.2
1000	No.	5	5	5	5	5	5	5	5	5	5	5	5	5
1000	Mean	231.8	243.0	248.2	250.6	256.4	259.4	263.2	267.8	274.4	277.0	280.6	282.2	280.8
1000	S.D.	10.2	9.2	11.4	13.7	15.0	10.1	11.4	13.9	15.7	17.4	18.8	12.2	10.9

Unit: g

No.: No. of animals

No significant difference between treated group and control group.

Table 3-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Body weight of male rats during the recovery period (Recovery group)

Dose mg/kg	Day of recovery					Gain 1-14
	1	4	8	11	14	
0	No.	5	5	5	5	5
	Mean	505.6	509.0	514.2	515.4	527.0
	S.D.	52.6	56.5	63.0	64.6	65.3
1000	No.	5	5	5	5	5
	Mean	502.6	512.0	522.2	529.0	537.8
	S.D.	66.0	67.5	71.9	75.5	72.0

Unit: g

No.: No. of animals

No significant difference between treated group and control group.

Table 3-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Body weight of female rats during the recovery period (Recovery group)

Dose mg/kg	Day of recovery					Gain 1-14
	1	4	8	11	14	
0	No.	5	5	5	5	5
0	Mean	297.2	300.2	301.2	299.8	303.4
0	S.D.	23.9	27.3	29.3	28.9	26.7
1000	No.	5	5	5	5	5
1000	Mean	284.0	283.8	283.4	283.6	290.4
1000	S.D.	14.4	11.8	14.4	18.7	19.3

Unit: g

No.: No. of animals

No significant difference between treated group and control group.

Table 4-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Food consumption of male rats (Main group)

Dose mg/kg	Pre-mating period					Post-mating period			
	1	4	8	11	15	32	36	39	42a)
0	No.	12	12	12	12	12	12	12	12
0	Mean	27.5	29.2	31.7	29.7	31.8	30.0	31.3	29.6
0	S.D.	2.6	2.1	2.8	2.2	2.0	2.4	3.8	3.1
100	No.	12	12	12	12	12	12	12	12
100	Mean	27.8	28.6	30.8	29.1	30.3	30.4	31.1	30.3
100	S.D.	2.2	1.9	2.8	2.2	1.9	2.6	2.4	2.6
300	No.	12	12	12	12	12	12	12	12
300	Mean	28.4	29.5	30.7	30.8	30.4	29.0	32.6	31.0
300	S.D.	2.6	2.8	2.8	2.1	2.4	1.8	3.0	2.7
1000	No.	12	12	12	12	12	12	12	12
1000	Mean	28.7	29.6	31.8	29.8	30.7	31.7	32.7	31.3
1000	S.D.	2.4	1.9	2.1	2.9	2.8	3.0	2.8	2.4
									31.0*
									2.5D

Unit: g/rat/day

No.: No. of animals

a): Day of administration

\*: p&lt;0.05 (Significant difference from control group)

D: Dunnett's test

Table 4-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Food consumption of female rats during the pre-mating period (Main group)

Dose mg/kg	Day of administration					
	1	4	8	11	15	
0	No. Mean S.D.	12 18.5 3.8	12 20.5 2.8	12 21.3 3.5	12 21.8 2.3	12 22.6 2.4
100	No. Mean S.D.	12 18.2 2.9	12 22.4 1.7	12 21.7 4.0	12 22.5 2.8	12 24.0 2.5
300	No. Mean S.D.	12 19.4 3.1	12 20.9 1.9	12 20.8 2.8	12 20.2 3.2	12 21.4 2.6
1000	No. Mean S.D.	12 18.7 3.5	12 20.2 3.5	12 19.9 3.0	12 21.8 2.6	12 22.1 3.8

Unit: g/rat/day

No.: No. of animals

No significant difference in any treated groups from control group.

Table 4-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Food consumption of dams during the gestation period (Main group)

Dose mg/kg	Administration						
	1	4	7	11	14	17	20a)
0	No. Mean S.D.	12 21.4 2.3	12 25.2 3.0	12 25.7 3.0	12 27.0 3.1	12 25.3 2.6	12 29.1 3.2
100	No. Mean S.D.	12 25.1* 4.4D	12 26.3 2.2	12 27.8 1.7	12 28.9 2.7	12 29.3** 2.5D	12 30.8 1.9
300	No. Mean S.D.	12 23.1 3.1	12 26.5 3.4	12 27.4 2.4	12 28.8 3.3	12 28.9** 2.3D	12 31.0 1.9
1000	No. Mean S.D.	12 23.9 3.6	12 26.2 3.1	12 25.8 3.5	12 27.9 4.7	12 27.1 3.6	12 29.3 4.1

Unit: g/rat/day

No.: No. of dams

a): Day of gestation

\*: p<0.05; \*\*: p<0.01 (Significant difference from control group)

D: Dunnett's test

Table 4-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Food consumption of dams during the lactation period (Main group)

Dose mg/kg	Administration		
		2	4a)
0	No.	12	12
0	Mean	24.3	43.2
0	S.D.	8.8	8.3
100	No.	12	12
100	Mean	28.3	48.0
100	S.D.	6.4	4.4
300	No.	12	12
300	Mean	25.3	46.9
300	S.D.	6.7	7.8
1000	No.	11	11
1000	Mean	30.0	48.3
1000	S.D.	8.6	8.6

Unit: g/rat/day

No.: No. of dams

a): Day of lactation

No significant difference in any treated groups from control group.

Table 4-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Food consumption of male rats during the administration period (Recovery group)

Dose mg/kg	Day of administration								
	1	4	8	11	15	32	36	39	42
0	No.	5	5	5	5	5	5	5	5
0	Mean	26.6	29.2	31.0	28.8	29.6	27.0	30.6	29.4
0	S.D.	3.2	1.8	2.1	2.3	3.2	9.1	3.3	2.8
1000	No.	5	5	5	5	5	5	5	5
1000	Mean	28.8	29.4	32.8	29.6	31.6	30.8	31.6	29.0
1000	S.D.	3.1	3.4	3.6	2.9	2.1	3.1	2.6	2.9

Unit: g/rat/day

No.: No. of animals

No significant difference between treated group and control group.

Table 4-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Food consumption of female rats during the administration period (Recovery group)

Dose mg/kg	Day of administration								
	1	4	8	11	15	32	36	39	42
0	No.	5	5	5	5	5	5	5	5
0	Mean	18.2	20.0	21.8	20.2	20.4	20.4	22.8	18.8
0	S.D.	4.4	3.9	3.7	4.2	6.6	3.6	3.2	3.0
1000	No.	5	5	5	5	5	5	5	5
1000	Mean	19.2	22.2	22.6	21.4	22.8	20.8	22.0	22.4
1000	S.D.	3.3	3.7	3.4	3.6	3.3	4.3	5.2	2.1
									17.8

Unit: g/rat/day

No.: No. of animals

No significant difference between treated group and control group.

Table 4-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Food consumption of male rats during the recovery period (Recovery group)

Dose mg/kg	Day of recovery				
	1	4	8	11	14
0	No.	5	5	5	5
	Mean	30.0	29.2	27.8	26.0
	S.D.	2.7	2.9	5.0	4.6
1000	No.	5	5	5	5
	Mean	29.8	29.6	28.6	30.4
	S.D.	3.0	2.1	3.4	6.2

Unit: g/rat/day

No.: No. of animals

No significant difference between treated group and control group.

Table 4-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Food consumption of female rats during the recovery period (Recovery group)

Dose mg/kg	Day of recovery					
	1	4	8	11	14	
0	No. Mean S.D.	5 21.6 2.3	5 20.0 3.1	5 19.6 4.7	5 17.6 2.1	5 21.2 3.6
1000	No. Mean S.D.	5 21.8 4.1	5 23.8 3.6	5 20.0 2.0	5 20.4 4.3	5 24.0 3.0

Unit: g/rat/day

No.: No. of animals

No significant difference between treated group and control group.

Table 5-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	pH									1) Protein					2) Ketone body					3) Glucose							
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++
0	17	0	0	0	0	1	2	10	4	0	4	5	8	0	0	0	9	8	0	0	0	0	17	0	0	0	0	0
100	12	0	0	0	1	3	7	0	1	0	0	5	6	1	0	0	5	2	5	0	0	0	12	0	0	0	0	0
300	12	0	0	2	9	1	0	0	0	0	0	9	3	0	0	0	9	2	1	0	0	0	12	0	0	0	0	0
1000	17	0	1	4	12	0	0	0	0	0	1	15	1	0	0	0	17	0	0	0	0	0	17	0	0	0	0	0

1) - : &lt;10 mg/dL

+- : 10 - 25 mg/dL

+ : 26 - 85 mg/dL

++ : 86 - 250 mg/dL

+++ : 251 - 600 mg/dL

++++ : &gt;600 mg/dL

2) - : &lt;5 mg/dL

+- : 5 - 7.5 mg/dL

+ : 7.6 - 30 mg/dL

++ : 31 - 70 mg/dL

+++ : 71 - 125 mg/dL

++++ : &gt;125 mg/dL

3) - : &lt;30 mg/dL

+- : 30 - 60 mg/dL

+ : 61 - 125 mg/dL

++ : 126 - 250 mg/dL

+++ : 251 - 750 mg/dL

++++ : &gt;750 mg/dL

Table 5-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	4) Occult blood					5) Bilirubin					6) Urobilinogen					7) Color		
		-	+-	+	++	+++	-	+	++	+++	++++	-	+	++	+++	++++	LY	Y	DY
0	17	14	3	0	0	0	17	0	0	0	0	17	0	0	0	0	0	17	0
100	12	11	1	0	0	0	12	0	0	0	0	10	2	0	0	0	0	12	0
300	12	9	1	0	1	1	12	0	0	0	0	12	0	0	0	0	0	12	0
1000	17	16	1	0	0	0	17	0	0	0	0	17	0	0	0	0	0	17	0

4) - : <0.03 mg/dL      +- : 0.03 - 0.05 mg/dL      + : 0.06 - 0.15 mg/dL      ++ : 0.16 - 0.75 mg/dL      +++ : >0.75 mg/dL

5) - : <0.5 mg/dL      + : 0.5 - 1.5 mg/dL      ++ : 1.6 - 5.0 mg/dL      +++ : 5.1 - 10.0 mg/dL      +++++ : >10.0 mg/dL

6) +- : <2.0 mg/dL      + : 2.0 - 3.5 mg/dL      ++ : 3.6 - 7.0 mg/dL      +++ : 7.1 - 12.0 mg/dL      +++++ : >12.0 mg/dL

7) LY : Light yellow      Y : Yellow      DY : Dark yellow

Table 5-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

#### Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	URINE SEDIMENT												CRYSTALLIZATION																
		RBC				WBC				SEC				SREC				Cast			PS			CO						
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++	
0	17	17	0	0	0	0	17	0	0	0	0	0	17	0	0	0	0	17	0	0	4	12	1	0	0	17	0	0	0	0
100	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	0	12	0	0	1	10	0	1	0	12	0	0	0	0
300	12	9	2	1	0	0	12	0	0	0	0	0	12	0	0	0	0	12	0	0	6	6	0	0	0	12	0	0	0	0
1000	17	17	0	0	0	0	16	1	0	0	0	0	16	1	0	0	0	17	0	0	9	8	0	0	0	17	0	0	0	0

SEC	Squamous Epithelial Cell	-	Negative
SREC	Small Round Epithelial Cell	+-	Slight
PS	Phosphate Salts	+	Mild
CO	Calcium Oxalate	++	Moderate
		+++	Severe

Table 5-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Water intake and urinalysis (Week 6 of administration)

Male

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
0	17	Mean	45	22.7	1809
		S.D.	7	6.7	364
100	12	Mean	45	21.5	1868
		S.D.	8	6.8	354
300	12	Mean	50	18.8	2005
		S.D.	9	5.6	326
1000	17	Mean	60**	20.2	1951
		S.D.	11D	7.3	342

\*\* : p<0.01 (Significant difference from control group)

D : Dunnett's test

Table 5-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

### Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	pH									1) Protein					2) Ketone body					3) Glucose							
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++
0	5	0	0	0	0	1	0	3	1	0	0	2	3	0	0	0	2	2	1	0	0	0	5	0	0	0	0	0
1000	5	0	0	0	0	1	0	1	3	0	0	0	5	0	0	0	0	3	2	0	0	0	5	0	0	0	0	0

Table 5-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	4) Occult blood					5) Bilirubin					6) Urobilinogen					7) Color			
		-	+	--	+	++	+++	----	+	++	+++	-	+	++	+++	++++	LY	Y	DY	
0	5	5	0	0	0	0	0	5	0	0	0	0	4	1	0	0	0	0	5	0
1000	5	5	0	0	0	0	0	5	0	0	0	0	4	1	0	0	0	0	5	0

4) - : &lt;0.03 mg/dL

-- : 0.03 - 0.05 mg/dL + : 0.06 - 0.15 mg/dL ++ : 0.16 - 0.75 mg/dL +++ : &gt;0.75 mg/dL

5) - : &lt;0.5 mg/dL

+ : 0.5 - 1.5 mg/dL ++ : 1.6 - 5.0 mg/dL +++ : 5.1 - 10.0 mg/dL ++++ : &gt;10.0 mg/dL

6) +- : &lt;2.0 mg/dL

+ : 2.0 - 3.5 mg/dL ++ : 3.6 - 7.0 mg/dL +++ : 7.1 - 12.0 mg/dL ++++ : &gt;12.0 mg/dL

7) LY : Light yellow

Y : Yellow DY : Dark yellow

Table 5-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

#### Urinalysis of male rats (Week 2 of recovery)

URINE SEDIMENT																								
Dose mg/kg	No.	RBC				WBC				SEC				SREC				Cast		CRYSTALLIZATION				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	5	0	0	0
1000	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	1	4	0	0	0

SEC	Squamous Epithelial Cell	-	Negative
SREC	Small Round Epithelial Cell	+-	Slight
PS	Phosphate Salts	+	Mild
CO	Calcium Oxalate	++	Moderate
		+++	Severe

Table 5-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Water intake and urinalysis (Week 2 of recovery)

Male

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
0	5	Mean	40	17.7	1918
		S.D.	6	7.8	433
1000	5	Mean	39	17.6	2172
		S.D.	8	6.9	349

No significant difference between treated group and control group.

Table 6-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Hematology (Week 6 of administration)

Male

Dose mg/kg	No.	RBC X10 <sup>6</sup> /μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let X10 <sup>3</sup> /μL	PT s	APTT s	Fibri- nogen mg/dL
0	5	Mean 903	17.4	44.0	48.7	19.3	39.7	2.0	119.6	14.3	21.7	303
		S.D. 24	0.3	1.7	1.8	0.6	1.0	0.3	8.5	0.9	1.5	7
100	5	Mean 910	17.3	44.2	48.6	19.0	39.2	1.8	116.2	14.1	20.4	304
		S.D. 27	0.5	1.2	1.4	0.4	0.6	0.4	10.5	1.3	1.4	29
300	5	Mean 904	17.3	43.8	48.4	19.1	39.4	1.9	111.5	15.0	23.7	313
		S.D. 50	1.2	2.9	0.7	0.4	0.5	0.2	9.7	1.0	2.8	37
1000	5	Mean 914	17.4	43.6	47.7	19.0	39.8	1.7	114.5	14.1	20.6	315
		S.D. 53	0.7	2.1	0.8	0.4	0.4	0.3	12.1	1.0	3.4	8

No significant difference in any treated groups from control group.

Table 6-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Hematology (Week 6 of administration)

Male

Dose mg/kg	No.	WBC X10 <sup>3</sup> /μL	Differential leukocyte counts (%)					Differential leukocyte counts (X10 <sup>3</sup> /μL)							
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	
0	5	Mean	116.1	77.7	17.8	1.4	0.4	2.1	0.7	90.1	20.7	1.6	0.5	2.4	0.8
		S.D.	56.8	3.3	3.2	0.2	0.1	0.5	0.2	42.8	11.7	0.6	0.4	1.6	0.5
100	5	Mean	97.5	79.5	16.3	1.5	0.3	1.8	0.6	77.9	15.5	1.5	0.3	1.7	0.6
		S.D.	13.7	8.8	8.1	0.7	0.1	0.5	0.2	16.8	7.6	0.6	0.2	0.3	0.3
300	5	Mean	91.7	71.2	23.6	1.9	0.3	2.4	0.5	66.2	20.9	1.5	0.3	2.3	0.6
		S.D.	29.8	6.2	6.3	1.0	0.1	0.3	0.2	24.6	7.1	0.4	0.2	0.9	0.4
1000	5	Mean	117.9	80.9	15.4	0.8	0.4	1.9	0.7	96.2	17.3	0.9	0.5	2.2	0.8
		S.D.	40.8	5.3	4.7	0.2	0.1	0.3	0.3	37.9	4.5	0.3	0.3	0.7	0.3

LUC : Large unstained cells

No significant difference in any treated groups from control group.

Table 6-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Hematology (Day 4 of lactation)

Female

Dose mg/kg	No.	RBC X10 <sup>4</sup> /μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let X10 <sup>4</sup> /μL	PT s	APTT s	Fibri- nogen mg/dL
0	5	Mean 742	14.4	38.3	51.8	19.4	37.5	5.8	141.9	12.3	16.7	298
		S.D. 69	0.6	1.4	3.1	1.2	0.9	1.5	17.1	0.7	2.9	28
100	5	Mean 770	15.2	40.2	52.2	19.8	37.8	5.2	142.7	12.6	15.5	276
		S.D. 72	1.3	3.2	2.0	0.7	0.2	1.7	26.8	0.4	2.2	30
300	5	Mean 725	14.5	38.5	53.1	20.0	37.6	4.8	135.8	12.2	16.9	317
		S.D. 40	0.8	2.1	1.3	0.5	0.4	0.8	20.1	0.8	2.1	30
1000	5	Mean 751	15.1	39.6	52.7	20.2	38.3	5.0	144.5	12.3	14.8	332
		S.D. 25	0.5	1.0	1.5	0.3	0.6	0.7	25.7	0.7	2.3	46

No significant difference in any treated groups from control group.

Table 6-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Hematology (Day 4 of lactation)

Female

Dose mg/kg	No.	WBC ×10 <sup>3</sup> /μL	Differential leukocyte counts (%)					Differential leukocyte counts (×10 <sup>2</sup> /μL)							
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	
0	5	Mean	127.7	60.7	35.4	0.7	0.2	2.4	0.5	77.0	45.8	1.0	0.3	3.1	0.6
		S.D.	25.3	6.4	6.6	0.2	0.1	0.7	0.2	13.8	15.7	0.4	0.0	0.8	0.3
100	5	Mean	127.6	62.2	34.1	0.8	0.3	2.2	0.5	79.0	43.8	1.0	0.3	2.8	0.7
		S.D.	27.4	7.5	7.6	0.3	0.1	0.4	0.2	16.3	15.6	0.4	0.1	0.9	0.4
300	5	Mean	121.4	55.2	40.6	0.6	0.2	2.9	0.4	65.0	51.1	0.7	0.3	3.7	0.5
		S.D.	38.0	15.4	15.8	0.3	0.1	1.1	0.2	22.7	24.6	0.1	0.2	2.4	0.3
1000	5	Mean	156.7	57.9	38.0	0.7	0.3	2.4	0.6	90.7	59.7	1.1	0.5	3.9	1.0
		S.D.	31.0	8.2	8.4	0.2	0.1	0.6	0.2	21.1	16.4	0.3	0.2	1.8	0.4

LUC : Large unstained cells

No significant difference in any treated groups from control group.

Table 6-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Hematology (Day 14 of recovery)

Male

Dose mg/kg	No.	RBC X10 <sup>6</sup> /μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let X10 <sup>3</sup> /μL	PT s	APTT s	Fibri- nogen mg/dL
0	5	Mean 922	16.5	43.4	47.1	17.9	38.0	2.0	120.1	14.5	23.5	309
		S.D. 28	0.3	0.7	1.5	0.8	0.6	0.5	21.1	1.0	2.0	16
1000	5	Mean 927	16.6	43.3	46.7	17.9	38.2	1.9	109.4	13.7	21.1	314
		S.D. 33	0.8	2.0	0.9	0.3	0.3	0.4	8.5	1.5	4.3	23

No significant difference between treated group and control group.

Table 6-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Hematology (Day 14 of recovery)

Male

Dose mg/kg	No.	WBC ×10 <sup>3</sup> /μL	Differential leukocyte counts (%)					Differential leukocyte counts (×10 <sup>3</sup> /μL)							
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	
0	5	Mean	113.9	81.7	14.8	0.9	0.5	1.8	0.3	93.4	16.5	1.0	0.6	2.0	0.4
		S.D.	34.6	2.9	2.5	0.2	0.1	0.4	0.1	29.9	4.0	0.4	0.3	0.7	0.2
1000	5	Mean	99.1	79.2	16.8	1.1	0.4	2.2	0.4	79.2	15.8	1.1	0.4	2.1	0.4
		S.D.	19.2	7.2	7.0	0.4	0.2	0.4	0.2	21.0	4.5	0.5	0.3	0.2	0.2

LUC : Large unstained cells

No significant difference between treated group and control group.

Table 6-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Hematology (Day 14 of recovery)

Female

Dose mg/kg	No.	RBC X10 <sup>6</sup> /μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let X10 <sup>3</sup> /μL	PT s	APTT s	Fibri- nogen mg/dL
0	5	Mean 855	16.1	41.6	48.7	18.9	38.8	1.4	117.9	11.6	18.0	234
		S.D. 45	0.6	1.4	1.2	0.5	0.5	0.4	8.0	0.8	1.9	31
1000	5	Mean 852	16.3	42.1	49.5	19.2	38.8	1.6	122.4	11.8	19.5	230
		S.D. 40	0.3	0.8	1.6	0.7	0.5	0.3	7.8	0.2	1.3	10

No significant difference between treated group and control group.

Table 6-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Hematology (Day 14 of recovery)

## Female

Dose mg/kg	No.	WBC ×10 <sup>3</sup> /μL	Differential leukocyte counts (%)					Differential leukocyte counts (×10 <sup>2</sup> /μL)							
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	
0	5	Mean	63.3	74.6	21.0	1.8	0.3	2.0	0.4	47.2	13.2	1.1	0.2	1.3	0.2
		S.D.	5.3	3.6	3.6	0.2	0.1	0.2	0.2	5.5	1.8	0.3	0.1	0.2	0.1
1000	5	Mean	55.5	75.4	20.1	1.7	0.3	2.1	0.5	41.7	11.3	0.9	0.2	1.1	0.2
		S.D.	14.9	5.4	5.3	0.3	0.1	0.4	0.1	11.6	4.0	0.3	0.1	0.3	0.1

LUC : Large unstained cells

No significant difference between treated group and control group.

Table 7-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Blood chemistry (Week 6 of administration)

Male

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	5	Mean	71	36	48	1	403	48	43	83	0.1	148
		S.D.	17	6	10	0	26	6	28	13	0.0	14
100	5	Mean	71	35	52	1	450	45	22	75	0.1	145
		S.D.	7	10	10	1	85	6	5	9	0.1	10
300	5	Mean	65	36	51	1	438	43	24	76	0.1	139
		S.D.	6	8	10	0	73	7	15	12	0.1	12
1000	5	Mean	72	36	47	1	481	39	33	73	0.1	138
		S.D.	7	6	8	0	46	8	14	6	0.0	11

No significant difference in any treated groups from control group.

Table 7-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

## Blood chemistry (Week 6 of administration)

Male

Dose mg/kg	No.		BUN mg/dL	Crea- tinine mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	15	0.26	143	5.0	108	9.5	6.1	6.2	2.8	0.84
		S.D.	2	0.05	2	0.2	2	0.1	0.5	0.2	0.1	0.02
100	5	Mean	16	0.26	143	4.8	107	9.5	6.3	6.1	2.8	0.86
		S.D.	2	0.03	2	0.1	1	0.1	0.4	0.2	0.0	0.04
300	5	Mean	14	0.24	143	4.8	107	9.6	6.3	6.1	2.8	0.83
		S.D.	1	0.04	2	0.5	2	0.2	0.4	0.2	0.1	0.04
1000	5	Mean	14	0.27	143	5.0	106	9.4	6.3	5.9	2.8	0.87
		S.D.	2	0.02	1	0.1	1	0.3	0.3	0.3	0.1	0.08

No significant difference in any treated groups from control group.

Table 7-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Blood chemistry (Day 4 of lactation)

Female

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	5	Mean	86	59	42	1	191	52	26	99	0.0	143
		S.D.	8	10	6	0	10	13	12	20	0.1	18
100	5	Mean	95	51	55	1	258	48	22	95	0.0	138
		S.D.	21	10	15	0	41	14	13	28	0.1	19
300	5	Mean	88	51	55	1	284	57	42	108	0.0	142
		S.D.	40	9	25	0	87	19	32	29	0.1	13
1000	5	Mean	81	52	50	1	306	53	28	105	0.1	143
		S.D.	11	12	11	0	145	12	13	24	0.0	17

No significant difference in any treated groups from control group.

Table 7-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Blood chemistry (Day 4 of lactation)

Female

Dose mg/kg	No.		BUN mg/dL	Crea- tinine mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	15	0.31	141	4.8	110	10.0	6.7	6.2	3.0	0.93
		S.D.	2	0.04	1	0.5	1	0.3	0.4	0.3	0.1	0.03
100	5	Mean	14	0.29	142	4.4	109	9.9	7.1	6.2	2.9	0.90
		S.D.	1	0.04	1	0.6	1	0.3	1.2	0.3	0.2	0.07
300	5	Mean	14	0.28	142	4.1	108	9.9	7.0	6.0	2.9	0.90
		S.D.	2	0.04	2	0.2	2	0.4	1.1	0.4	0.2	0.02
1000	5	Mean	13	0.27	141	4.4	106	10.1	7.4	6.2	2.9	0.90
		S.D.	1	0.04	2	0.6	4	0.4	1.0	0.3	0.2	0.02

No significant difference in any treated groups from control group.

Table 7-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Blood chemistry (Day 14 of recovery)

Male

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	5	Mean	65	32	64	1	367	45	36	77	0.1	162
		S.D.	7	5	22	0	60	11	16	13	0.0	20
1000	5	Mean	59	33	58	1	403	59	48	100** 6T	0.1 0.0	156 19
		S.D.	5	7	14	0	88	10	8			

\*\* : p&lt;0.01 (Significant difference from control group)

T : Student's t-test

Table 7-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Blood chemistry (Day 14 of recovery)

Male

Dose mg/kg	No.	BUN mg/dL	Crea- tinine mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean 16	0.27	144	4.6	107	9.6	6.1	6.1	2.7	0.82
		S.D. 2	0.03	1	0.4	2	0.4	0.4	0.2	0.1	0.05
1000	5	Mean 16	0.24	143	4.3	106	9.7	6.4	6.3	2.8	0.82
		S.D. 1	0.02	1	0.3	2	0.3	0.4	0.3	0.1	0.04

No significant difference between treated group and control group.

Table 7-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Blood chemistry (Day 14 of recovery)

Female

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	5	Mean	86	49	63	1	188	67	14	123	0.1	139
		S.D.	17	15	14	1	92	10	4	19	0.0	14
1000	5	Mean	76	41	57	2	182	60	10	110	0.1	139
		S.D.	20	9	20	1	6	11	6	21	0.0	21

No significant difference between treated group and control group.

Table 7-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Blood chemistry (Day 14 of recovery)

Female

Dose mg/kg	No.		BUN mg/dL	Crea- tinine mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	18	0.31	141	4.0	109	9.6	4.4	6.4	3.1	0.95
		S.D.	4	0.04	1	0.3	1	0.4	0.8	0.5	0.3	0.06
1000	5	Mean	18	0.32	143**	4.1	112**	9.6	4.6	6.5	3.1	0.91
		S.D.	3	0.03	1T	0.2	1T	0.1	0.9	0.3	0.2	0.04

\*\* : p<0.01 (Significant difference from control group)

T : Student's t-test

Table 8-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Organ weight of male rats (Main group)

		Dose mg/kg	Body weight g	Brain g(g/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
		0	No. Mean S.D.	5 486 36	5 2.13 0.09	5 23.8 5.9	5 332 100	5 1.44 0.10
Absolute	100		No. Mean S.D.	5 472 25	5 2.12 0.10	5 27.2 2.9	5 337 59	5 1.40 0.10
	300		No. Mean S.D.	5 476 25	5 2.10 0.05	5 23.7 2.9	5 252 59	5 1.45 0.10
	1000		No. Mean S.D.	5 456 40	5 2.08 0.10	5 23.9 6.0	5 290 68	5 1.39 0.12
	0		No. Mean S.D.	5 0.44 0.02	5 4.9 1.1	5 68 18	5 0.30 0.03	5 2.59 0.14
Relative	100		No. Mean S.D.	5 0.45 0.02	5 5.8 0.4	5 72 13	5 0.30 0.02	5 2.53 0.13
	300		No. Mean S.D.	5 0.44 0.02	5 5.0 0.5	5 53 12	5 0.30 0.02	5 2.62 0.29
	1000		No. Mean S.D.	5 0.46 0.03	5 5.2 1.1	5 63 13	5 0.31 0.02	5 2.58 0.15

No significant difference in any treated groups from control group.

Table 8-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Organ weight of male rats (Main group)

	Dose mg/kg	Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Body weight g	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)
	0	No. Mean S.D.	5 0.82 0.14	5 3.31 0.13	5 71 13	12 484 26	12 3.31 0.37
Absolute	100	No. Mean S.D.	5 0.76 0.10	5 3.20 0.18	5 71 18	12 476 22	12 3.40 0.22
	300	No. Mean S.D.	5 0.76 0.10	5 3.38 0.26	5 65 14	12 466 30	12 3.30 0.29
	1000	No. Mean S.D.	5 0.71 0.21	5 3.22 0.16	5 69 9	12 459 29	12 3.43 0.28
	0	No. Mean S.D.	5 0.17 0.02	5 0.68 0.03	5 15 3	12 0.69 0.08	12 266 24
Relative	100	No. Mean S.D.	5 0.16 0.02	5 0.68 0.03	5 15 4	12 0.71 0.05	12 282 25
	300	No. Mean S.D.	5 0.16 0.03	5 0.71 0.04	5 14 3	12 0.71 0.08	12 274 30
	1000	No. Mean S.D.	5 0.16 0.03	5 0.71 0.04	5 15 2	12 0.75 0.06	12 288 34

No significant difference in any treated groups from control group.

Table 8-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Organ weight of female rats (Main group)

		Dose mg/kg	Body weight g	Brain g(g/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
		0	No. Mean S.D.	5 300 23	5 1.98 0.04	5 19.3 3.2	5 202 85	5 0.95 0.07
Absolute	100		No. Mean S.D.	5 307 23	5 2.00 0.05	5 17.7 1.1	5 230 80	5 1.02 0.08
	300		No. Mean S.D.	5 296 18	5 1.96 0.07	5 19.1 1.4	5 206 87	5 0.98 0.07
	1000		No. Mean S.D.	5 321 31	5 2.00 0.11	5 16.6 1.6	5 264 82	5 1.04 0.13
	0		No. Mean S.D.	5 0.66 0.05	5 6.4 0.9	5 66 25	5 0.32 0.02	5 3.30 0.21
Relative	100		No. Mean S.D.	5 0.65 0.06	5 5.8 0.6	5 74 24	5 0.33 0.03	5 3.17 0.14
	300		No. Mean S.D.	5 0.66 0.04	5 6.5 0.6	5 69 27	5 0.33 0.03	5 3.50 0.14
	1000		No. Mean S.D.	5 0.63 0.04	5 5.2 0.8	5 82 24	5 0.32 0.02	5 3.40 0.15

No significant difference in any treated groups from control group.

Table 8-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Organ weight of female rats (Main group)

		Dose mg/kg	Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)
Absolute	0	No.	5	5	5
		Mean	0.64	2.08	100
		S.D.	0.08	0.15	12
	100	No.	5	5	5
		Mean	0.62	2.03	92
		S.D.	0.05	0.17	11
	300	No.	5	5	5
		Mean	0.59	2.07	102
		S.D.	0.03	0.16	9
	1000	No.	5	5	5
		Mean	0.72	2.17	95
		S.D.	0.09	0.20	10
Relative	0	No.	5	5	5
		Mean	0.21	0.69	33
		S.D.	0.02	0.03	3
	100	No.	5	5	5
		Mean	0.20	0.67	30
		S.D.	0.01	0.07	5
	300	No.	5	5	5
		Mean	0.20	0.70	34
		S.D.	0.02	0.04	4
	1000	No.	5	5	5
		Mean	0.22	0.68	30
		S.D.	0.02	0.05	1

No significant difference in any treated groups from control group.

Table 8-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Organ weight of male rats (Recovery group)

Dose mg/kg	No. of animals		Body weight	Brain	Thyroid (R+L)	Thymus	Heart	Liver
			g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	0	5	Mean	494	2.13	21.3	277	1.32
			S.D.	64	0.14	2.4	84	0.17
	1000	5	Mean	504	2.14	19.9	294	1.35
			S.D.	70	0.06	2.9	72	0.14
Relative	0	5	Mean		0.44	4.3	55	0.27
			S.D.		0.03	0.3	11	0.01
	1000	5	Mean		0.43	4.1	58	0.27
			S.D.		0.05	1.0	9	0.02

No significant difference between treated group and control group.

Table 8-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Organ weight of male rats (Recovery group)

Dose mg/kg	No. of animals	Spleen		Kidney (R+L)	Adrenal (R+L)	Testis (R+L)	Epididymis (R+L)
		g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)	mg(mg/100g BW)	
Absolute	0	5	Mean S.D.	0.86 0.22	3.18 0.32	61 7	3.22 0.24
	1000	5	Mean S.D.	0.77 0.12	3.14 0.28	72 12	3.35 0.18
Relative	0	5	Mean S.D.	0.17 0.02	0.64 0.03	12 1	0.66 0.04
	1000	5	Mean S.D.	0.15 0.01	0.63 0.04	14 3	0.67 0.07

No significant difference between treated group and control group.

Table 8-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Organ weight of female rats (Recovery group)

	Dose mg/kg	No. of animals		Body weight g	Brain g(g/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	5	Mean	285	1.98	19.2	238	0.91	7.26
			S.D.	25	0.05	2.6	65	0.07	0.57
	1000	5	Mean	270	1.96	15.6*	241	0.89	6.90
			S.D.	14	0.05	1.9T	42	0.05	0.60
Relative	0	5	Mean		0.70	6.8	83	0.32	2.56
			S.D.		0.05	1.4	16	0.02	0.21
	1000	5	Mean		0.73	5.8	89	0.33	2.55
			S.D.		0.03	0.9	11	0.02	0.18

\*: p<0.05 (Significant difference from control group)

T: Student's t-test

Table 8-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Organ weight of female rats (Recovery group)

Dose mg/kg	No. of animals	Spleen		Kidney (R+L)	Adrenal (R+L)
			g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)
Absolute	0	5	Mean	0.56	79
			S.D.	0.08	11
1000	5	Mean	0.46	1.82	73
		S.D.	0.07	0.10	6
Relative	0	5	Mean	0.20	28
			S.D.	0.01	3
1000	5	Mean	0.17	0.68	27
		S.D.	0.03	0.03	3

No significant difference between treated group and control group.

Table 9-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Gross pathological findings (Main group)

Organs Findings	Sex: Number:	M 0 12	M 100 12	M 300 12	M 1000 12	F 0 12	F 100 12	F 300 12	F 1000 12
Kidney									
Cyst		0	1	0	0	0	0	0	0
Dilatation,pelvic		0	0	0	1	0	0	0	0
Stomach									
Focus,dark red,glandular stomach		0	0	1	0	0	3	4	2
Testis									
Small		1	0	0	0	-	-	-	-
Thyroid									
Small		0	0	0	0	0	1	0	0

-: Not applicable

Table 9-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Gross pathological findings (Recovery group)

Organs Findings	Sex: Dose(mg/kg): Number:	M 0 5	M 1000 5	F 0 5	F 1000 5
<b>Stomach</b>					
Focus,dark red,glandular stomach		0	1	1	0
Focus,raised,limiting ridge		0	1	0	0

Table 10-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Histopathological findings (Main group)

Organs Findings	Sex: Dose (mg/kg): Number:	M 0 12	M 100 12	M 300 12	M 1000 12	F 0 12	F 100 12	F 300 12	F 1000 12
Adrenal									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Cerebellum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Cerebrum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Epididymis									
Number examined		5	0	0	5	-	-	-	-
Not remarkable		4	0	0	4	-	-	-	-
Cell infiltration, interstitial		1	0	0	1	-	-	-	-
minimal		1	0	0	1	-	-	-	-
Femur+Marrow									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Heart									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Cell infiltration, focal		0	0	0	0	0	0	0	1
minimal		0	0	0	0	0	0	0	1
Intestine, duodenum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Intestine, jejunum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Intestine, ileum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Intestine, cecum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	4	5	0	0	5
Cell infiltration, mucosal		0	0	0	1	0	0	0	0
minimal		0	0	0	1	0	0	0	0
Intestine, colon									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Intestine, rectum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Kidney									
Number examined		5	1	0	6	5	0	0	5
Not remarkable		1	0	0	1	3	0	0	2
Cyst		0	1	0	0	0	0	0	1
minimal		0	0	0	0	0	0	0	0
mild		0	1	0	0	0	0	0	0
Dilatation, pelvic		0	0	0	1	0	0	0	0
mild		0	0	0	1	0	0	0	0
Regeneration, tubular		3	1	0	4	2	0	0	1

- : Not applicable

Table 10-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Histopathological findings (Main group)

Organs Findings	Sex: Dose(mg/kg): Number:	M 0 12	M 100 12	M 300 12	M 1000 12	F 0 12	F 100 12	F 300 12	F 1000 12
<b>Kidney (continued)</b>									
Regeneration,tubular (continued)									
minimal	3	1	0	4	2	0	0	0	1
Urinary cast,hyaline	0	1	0	0	0	0	0	0	0
minimal	0	1	0	0	0	0	0	0	0
Mineralization,medullary	1	0	0	1	1	0	0	0	1
minimal	1	0	0	1	1	0	0	0	1
Cell infiltration,interstitial	0	1	0	1	0	0	0	0	0
minimal	0	1	0	1	0	0	0	0	0
Fibrosis,focal	0	0	0	1	0	0	0	0	0
minimal	0	0	0	1	0	0	0	0	0
Eosinophilic body,tubular	0	0	0	1	0	0	0	0	0
minimal	0	0	0	1	0	0	0	0	0
<b>Liver</b>									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	1	3	0	0	0	3
Microgranuloma	5	0	0	4	2	0	0	0	2
minimal	5	0	0	4	2	0	0	0	2
<b>Lung(bronchus)</b>									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	4	0	0	3	3	0	0	0	4
Mineralization,arterial wall	0	0	0	1	0	0	0	0	0
minimal	0	0	0	1	0	0	0	0	0
Alveolar macrophage	1	0	0	1	2	0	0	0	1
minimal	1	0	0	1	2	0	0	0	1
<b>Lymph node,mesenteric</b>									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
<b>Lymph node,submandibular</b>									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
<b>Parathyroid</b>									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
<b>Pituitary</b>									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
<b>Sciatic nerve</b>									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
<b>Seminal vesicle</b>									
Number examined	5	0	0	5	-	-	-	-	-
Not remarkable	5	0	0	5	-	-	-	-	-
<b>Spinal cord(thoracic)</b>									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
<b>Spleen</b>									
Number examined	5	0	0	5	5	0	0	0	5
Hematopoiesis,extramedullary	5	0	0	5	5	0	0	0	5
minimal	2	0	0	4	1	0	0	0	1
mild	3	0	0	1	4	0	0	0	4

-: Not applicable

Table 10-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Histopathological findings (Main group)

Organs Findings	Sex: Dose(mg/kg): Number:	M 0 12	M 100 12	M 300 12	M 1000 12	F 0 12	F 100 12	F 300 12	F 1000 12
Sternum+Marrow									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
Stomach									
Number examined	12	12	12	12	12	12	12	12	12
Not remarkable	12	12	10	9	11	9	8	9	9
Erosion,glandular stomach	0	0	2	0	0	3	4	3	3
minimal	0	0	1	0	0	2	1	3	3
mild	0	0	1	0	0	1	3	0	0
Hyperplasia,squamous,limiting ridge	0	0	0	3	0	0	0	0	0
minimal	0	0	0	1	0	0	0	0	0
mild	0	0	0	2	0	0	0	0	0
Ulcer,limiting ridge	0	0	0	0	1	0	0	0	0
minimal	0	0	0	0	1	0	0	0	0
Testis									
Number examined	6	0	0	5	-	-	-	-	-
Not remarkable	5	0	0	5	-	-	-	-	-
Atrophy,seminiferous tubular	1	0	0	0	-	-	-	-	-
moderate	1	0	0	0	-	-	-	-	-
Thymus									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
Thyroid									
Number examined	5	0	0	5	5	1	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
Urinary bladder									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	4	0	0	0	5
Edema,submucosal/mucosal	0	0	0	0	1	0	0	0	0
mild	0	0	0	0	1	0	0	0	0
Uterus									
Number examined	-	-	-	-	5	0	0	0	5
Not remarkable	-	-	-	-	5	0	0	0	5

-: Not applicable

Table 10-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Histopathological findings (Recovery group)

Organs Findings	Sex: Dose(mg/kg): Number:	M 0 5	M 1000 5	F 0 5	F 1000 5
Stomach					
Number examined		5	5	5	5
Not remarkable		5	2	4	5
Cyst, epidermal		0	1	0	0
mild		0	1	0	0
Erosion, glandular stomach		0	1	1	0
minimal		0	1	0	0
mild		0	0	1	0
Hyperplasia, squamous, limiting ridge		0	1	0	0
minimal		0	1	0	0

Table 11

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1,2,4,5-Benzenetetracarboxylic acid

Estrous cycle in female rats during the pre-mating period (Main group)

Dose mg/kg	No. of animals	Count of estrus						Mean duration of cycles Mean±S.D.
		0	1	2	3	4	Mean±S.D.	
0	12	0	0	0	8	4	3.3±0.5	4.2±0.4
100	12	0	0	0	9	3	3.3±0.5	4.1±0.3
300	12	0	0	0	8	4	3.3±0.5	4.2±0.3
1000	12	0	0	0	9	3	3.3±0.5	4.2±0.4

No significant difference in any treated groups from control group.

Table 12

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Mating and fertility of animals

Dose mg/kg	No. of males	Male			Female			
		Days until copulation Mean±S.D.	Copulation index (%) a)	Insemination index (%) b)	No. of females	Days until copulation Mean±S.D.	Copulation index (%) a)	Fertility index (%) c)
0	12	2.7±0.9	12/12(100.0)	12/12(100.0)	12	2.7±0.9	12/12(100.0)	12/12(100.0)
100	12	2.5±1.1	12/12(100.0)	12/12(100.0)	12	2.5±1.1	12/12(100.0)	12/12(100.0)
300	12	2.8±1.0	12/12(100.0)	12/12(100.0)	12	2.8±1.0	12/12(100.0)	12/12(100.0)
1000	12	2.7±1.3	12/12(100.0)	12/12(100.0)	12	2.7±1.3	12/12(100.0)	12/12(100.0)

a): (No. of copulated animals / No. of mated animals) × 100

b): (No. of males which inseminated females / No. of copulated males) × 100

c): (No. of pregnant animals / No. of copulated females) × 100

No significant difference in any treated groups from control group.

Table 13

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Delivery data on dams

Dose mg/kg		No. of pregnant females	No. of females with live pups	Delivery index % a)	Gestation period	No. of corpora lutea	No. of implan- tation sites	Implan- tation index % b)	No. of stillborn pups (%c)	No. of liveborn pups	Live birth index % d)
0	Total	12	12	100.0	21.8 0.3	198	184	93.4 4.7	4	175	97.7 3.4
	Mean					16.5	15.3		( 2.3)	14.6	
	S.D.					2.6	1.9		( 3.4)	2.2	
100	Total	12	12	100.0	21.9 0.4	189	177	93.0 13.5	1	165	99.4 1.9
	Mean					15.8	14.8		( 0.6)	13.8	
	S.D.					1.7	3.0		( 1.9)	2.6	
300	Total	12	12	100.0	22.0 0.4	193	187	96.9 3.3	1	174	99.5 1.7
	Mean					16.1	15.6		( 0.5)	14.5	
	S.D.					1.3	1.4		( 1.7)	1.8	
1000	Total	12e)	11	91.7	22.0 0.4	174	167	96.1 6.1	1	149	99.4 2.0
	Mean					15.8	15.2		( 0.6)	13.5	
	S.D.					1.7	1.7		( 2.0)	2.7	

a): (No. of females which delivered live pups / No. of pregnant females) × 100

b): (No. of implantation sites / No. of corpora lutea) × 100

c): (No. of stillborn pups / No. of stillborn and liveborn pups) × 100

d): (No. of liveborn pups / No. of stillborn and liveborn pups) × 100

e): One dam was not delivered.

No significant difference in any treated groups from control group.

Table 14

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

External examination of liveborn pups

Dose mg/kg	No. of dams	No. of males	No. of females	Sex ratio a)	Body weight(g)		External b) abnor- malities(%)c)
					Male	Female	
0	12	Total	84	91	0.48		1d)
		Mean	7.0	7.6		6.3	( 0.6)
		S.D.	2.0	2.5		0.5	( 1.9)
100	12	Total	76	89	0.46		0
		Mean	6.3	7.4		6.5	( 0.0)
		S.D.	1.8	2.4		0.6	( 0.0)
300	12	Total	83	91	0.48		0
		Mean	6.9	7.6		6.5	( 0.0)
		S.D.	1.9	2.4		0.4	( 0.0)
1000	11	Total	59	90	0.40		0
		Mean	5.4	8.2		6.8	( 0.0)
		S.D.	1.6	2.5		0.6	( 0.0)

a): No. of males / No. of liveborn pups

b): No. of liveborn pups with external abnormalities

c): (No. of liveborn pups with external abnormalities / No. of liveborn pups) × 100

d): Convoluted tail

No significant difference in any treated groups from control group.

Table 15

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Viability index of pups

Dose mg/kg	No. of dams	No. of live pups		Viability index on day 4 after birth % a)	
		Day 0	Day 4		
0	Total	12	174 <sup>b)</sup>	173	
	Mean		14.5	14.4	
	S.D.		2.2	2.0	99.6
					1.5
100	Total	12	165	159	
	Mean		13.8	13.3	
	S.D.		2.6	2.5	96.6
					5.4
300	Total	12	174	172	
	Mean		14.5	14.3	
	S.D.		1.8	1.7	99.0
					2.4
1000	Total	11	149	147	
	Mean		13.5	13.4	
	S.D.		2.7	2.7	98.8
					2.7

a): (No. of live pups on day 4 / No. of liveborn pups on day 0) × 100

b): One pup with external malformation was excluded.

No significant difference in any treated groups from control group.

Table 16

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

## Body weight of pups

Dose mg/kg	Male		Female	
	0	4	0	4a)
0	No.	12	12	12
0	Mean	6.3	9.4	5.9
0	S.D.	0.5	1.0	0.5
100	No.	12	12	12
100	Mean	6.5	10.2	6.1
100	S.D.	0.6	1.5	0.6
300	No.	12	12	12
300	Mean	6.5	10.0	6.2
300	S.D.	0.4	1.2	0.4
1000	No.	11	11	11
1000	Mean	6.8	10.6	6.3
1000	S.D.	0.6	1.3	0.5

Unit: g

No.: No. of dams

a): Day after birth

No significant difference in any treated groups from control group.

Table 17

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with 1,2,4,5-Benzenetetracarboxylic acid

Gross pathological findings in pups on day 4 after birth

	Dose (mg/kg)	0	100	300	1000
<b>Male</b>					
No. of pups examined	82	73	83	59	
No. of pups with abnormal findings	0	0	1	0	
Thymic remnant in neck	0	0	1	0	
<b>Female</b>					
No. of pups examined	91	86	89	88	
No. of pups with abnormal findings	0	0	0	0	