BOZO RESEARCH CENTER INC.

最 終 報 告 書

2-アミノ-2-エチル-1, 3-プロパンジオール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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要　約

2-アミノ-2-エチル-1, 3-プロパンジオールの 0（対照群）、250、500、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 日間投与）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（42～48 日間投与）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 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

一般状態、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、剖検所見及び器官重量には被験物質投与による影響は認められなかった。

詳細な一般状態の観察では、オープンフィールド内観察において 1000 mg/kg 投与群の雄で投与 3、4、5 及び 6 週に立ち上がり回数の低値が認められたが、回復終了時検査には消失した。

病理組織学検査では、投与終了時検査において 1000 mg/kg 投与群の雄に前胃及び腺胃粘膜における細胞浸潤、腺胃の糜爛、腺胃における globule leukocyte 数の増加、腺胃粘膜の肥厚及び境界縁の肥厚が観察された。回復終了時検査にも腺胃における globule leukocyte 数の増加及び境界縁の肥厚は観察されたが、所見の程度は軽減し、可逆性の変化であった。

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。また、母動物の妊娠期間、出産率、黄体数、着床痕数、着床率、分娩及び哺育行動、死産児数、死産児率、出産生児数、出生率、性比、出生児の出生時観察及び生後 4 日剖検所見、体重及び生存性には被験物質投与の影響は認められなかった。

これらの結果から、本試験条件下における 2-アミノ-2-エチル-1, 3-プロパンジオールの反復投与毒性に対する無影響量は雄で 500 mg/kg/day、雌で 1000 mg/kg/day、生殖発生毒性に対する無影響量は雌雄親動物及び児動物ともに 1000 mg/kg/day と判断した。

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、2-アミノ-2-エチル-1,3-プロパンジオール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。

試験材料及び方法

1. 被験物質

2-アミノ-2-エチル-1, 3-プロパンジオールは　　から購入した(添付資料 1)。使用した被験物質のロット番号及び純度などを以下に示した。

被験物質名　：　2-アミノ-2-エチル-1, 3-プロパンジオール
1,3-Propanediol,2-amino-2-ethyl

CAS 番号　：　115-70-8

ロット番号　：

純　　度　：　99.4 %

性　　状　：　微黄色透明、粘性の液体、汚染又は可視的異物を認めなかった。

赤外吸収スペクトル
：　主な吸収波数 ; 2880.5 cm^{-1}、1591.2 cm^{-1}、1461.9 cm^{-1}及び 1043.4 cm^{-1}

安 定 性　：　動物試験終了後、株式会社ボゾリサーチセンターで分析した結果、動物試験期間中は安定であった（添付資料 2）。

保存方法　：　冷暗所（実測値：2～8℃）

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

処　　置　：　被験物質 5g 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、動物試験終了後の残量は全て焼却処分した。

2. 被験液の調製

1)　被験液の調製及び保存方法

各濃度ごとに必要量の被験物質を秤量し、注射用水（株式会社大塚製薬工場、ロット番号：1E90、1F87、3C74）で希釈して所定濃度（25、50 及び 100 mg/mL 濃度）とした。調製は 7 日間に 1 回以上の頻度で行い、使用時まで遮光容器（褐色ビン）に入れて冷蔵（実測値：3～5℃）で保存した。

2)　被験液の安定性

0.5 mg/mL 及び 200 mg/mL 濃度の水溶液は、調製後 7 日間冷蔵保存した後、更に 24 時間室温保存した時安定である（添付資料 3、試験番号：A-1483、株式会社ボゾリサーチセンター）。

3) 被験液の濃度確認

投与第 1 週と最終週の投与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で GC 法により分析した。その結果、各濃度液ともに表示値に対する割合は 98.4～105.0 %であり、いずれも許容範囲内（表示値±5 %）であった（添付資料 4、5）。

3. 試験動物

Sprague-Dawley 系 SPF ラット〔Crj:CD(SD)IGS、日本チャールス・リバー株式会社、厚木飼育センター〕雌雄各 70 匹を 8 週齢で購入（入荷匹数：雌雄各 73 匹）し、14 日間の検疫・馴化飼育を行った。その間の一般状態の観察、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、雄は一般状態に異常がなく、体重増加が良好な 58 匹を選択し、10 週齢で投与に使用した。また、雌は一般状態及び性周期に異常がなく、体重増加が良好な 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 345～403g、雌は 206～258g であった。

なお、群分けは群分け当日（投与開始の 2 日前）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り付けた。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 10 匹を継続飼育した。残りの雌雄（雄：15 匹、雌：5 匹）はマトリックス採取（試験番号：A-1562、A-1564）に用いた。なお、継続飼育した無処置雌動物 10 匹は交配成績に被験物質投与の影響が認められなかっ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。

4. 飼育条件

動物は、温度 18～25℃、相対湿度 28～58 %、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：雄は 107、雌は 108 号室）でブラケット式金属製網ケージ（W 250×D 350×H 200mm：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 4 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：日本クレア株式会社）で個別に収容した。飼料は NMF 固形（非滅菌：オリエンタル酵母工業株式会社、ロット番号：030707、0308080）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財団法人静岡県生活科学検査センターに定期的（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、分析報告書を保存した。

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（雄）、交尾日（雌）及び分娩日（雌）を明記した。

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、雄には交配前 14 日間及び交配期間を通して剖検前日（42 日間投与）まで、雌には交配前 14 日間及び交配期間及び妊娠期間を通して授乳 4 日(42～48 日間投与)までとした。

回復期間は投与終了後 14 日間とした。

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 10 mL/kg 体重とし、胃ゾンデを用いて強制経口投与した（08：27～11：48、ただし、動物番号 4105、2110 及び 3102 は午前の投与時間中に分娩が終了しなかったため、分娩終了後の 16：29～16：41 に投与した）。対照群には媒体（注射用水）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。

8. 投与量及び群構成

投与量は 250、500 及び 1000 mg/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、回復群の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	250	25	雄	12	2001～2012	−	−
			雌	12	2101～2112	−	−
中用量群	500	50	雄	12	3001～3012	−	−
			雌	12	3101～3112	−	−
高用量群	1000	100	雄	12	4001～4012	5	4013～4017
			雌	12	4101～4112	5	4113～4117

9. 投与量の設定根拠

先に実施した「2-アミノ-2-エチル-1,3-プロパンジオールのラットを用いた 14 日間反復経口投与毒性試験（予備試験）」（投与量：125、250、500 及び 1000 mg/kg、株式会社ボゾリサーチセンター試験番号：C-R010、添付資料 6）では、OECD Guideline for Testing of Chemicals 422 で投与限界量とされている 1000 mg/kg においても被験物質投与の影響は認められなかった。したがって、1000 mg/kg を高用量とし、以下公比 2 で除して 500 及び 250 mg/kg の 3 用量を設定した。

10. 観察及び検査の方法

試験日は投与開始日を投与第 1 日、交尾成立日を妊娠 0 日及び分娩終了日を授乳 0 日とした。

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 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。

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、投与期間開始前に 1 回、投与期間中及び回復期間中は毎週 1 回、全個体について行った。機能検査、握力測定及び自発運動量の測定は、主群の雄は投与終了週（投与 37 日）に、回復群の雌雄は回復終了週（回復 11 日）に、主群の雌は授乳 4 日（投与 42～43 日）の F1 児剖検後に 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、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、動物をランダムに配置した状態で行った。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（スコアの基準は添付資料 7～9）

・ ホームケージ内観察

姿勢、痙攣、異常行動

・ 手に持っての観察

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、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（スコアの基準は添付資料 10 参照）

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。

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 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 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 日の体重測定を除き 08：28～11：55 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。

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、25、29、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 日に前日の給餌量から残餌量を測定し、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 08：31～12：11 の間に行った。

5) 腟スメア検査

主群の雌の全個体について、投与開始日から交尾が認められるまで毎日腟スメアを採取し、検鏡した。交配前投与期間中は腟スメア像を発情前期、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）を調べた。交配期間中は腟スメア内の精子の有無を調べた。

6) 交配方法

交配前投与期間終了後、主群の同投与群の雌雄を 1：1 で終夜同居させ、翌朝、腟栓形成あるいは腟スメア中に精子を確認したものを交尾成立とみなした。交尾までに要した日数は交配開始日を 0 日と起算した。なお各群の交尾率、受胎率及び授精率を次式により算出した。

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

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 22 日の午後まで 1 日 2 回（午前、午後）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。妊娠期間及び出産率は次式により算出した。

妊娠期間（日）＝授乳 0 日－妊娠 0 日

出産率(%)＝（生存児出産雌数／妊娠雌数）×100

分娩が終了した母動物は出生児の喰殺、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。

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酔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、着床率を次式により算出した。

着床率(%)＝（着床痕数／黄体数）×100

(2) 出生児の観察

出生日に生存児数、死産児数を数えた。出生児は外表異常の有無を観察し、性別を判定して体重を測定した後、母動物に授乳させた。また、次式により死産児率、出生率、外表異常率及び性比を算出した。

死産児率(%)＝（死産児数／総出産児数）×100

出生率(%)＝（生存児数／総出産児数）×100

外表異常率(%)＝（外表異常児数／生存児数）×100

性比＝雄数／雄数＋雌数

死産児（死後変化の著しい場合は除く）はリン酸緩衝10 vol%ホルマリン液に固定し、保存した。

出生児は生死の観察を授乳4日まで毎日1回行い、生存率を次式により算出した。

出生児生存率(%)＝（授乳4日生存児数／授乳0日生存児数）×100

授乳4日に体重を測定した後、全例をエーテル麻酔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、出生児の体重は個体別に体重を測定し、各腹単位で雌雄別に平均値を算出した。

8) 尿検査（摂水量測定を含む）

投与最終週（投与38～39日）及び回復終了週（回復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］[a)]
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］[a)]
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］[a)]
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］[a)]
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］[a)]
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］[a)]
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］[a)]
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	氷点降下法[b)]（単位：mOsm/kg）
尿量（20 時間量）	メスシリンダ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)： AUTION 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）

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。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ーゲン量については、3.8mg/kg 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（3,000 rpm、約 1,600×g、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	電気抵抗変化検出法[c)]	$10^4/\mu L$
ヘモグロビン量	シアンメトヘモグロビン法[c)]	g/dL
ヘマトクリット値	赤血球数及び平均赤血球容積から算出	%
平均赤血球容積	電気抵抗変化検出法[c)]	fL
平均赤血球血色素量	赤血球数及びヘモグロビン量から算出	pg
平均赤血球血色素濃度	ヘモグロビン量及びヘマトクリット値から算出	%
網赤血球率	Brecher 法	%
血小板数	電気抵抗変化検出法[c)]	$10^4/\mu L$
白血球数	電気抵抗変化検出法[c)]	$10^2/\mu L$
白血球百分率	May-Giemsa 染色による鏡検法	%
プロトロンビン時間	クロット法[d)]	s
活性化部分トロンボプラスチン時間	クロット法[d)]	s
フィブリノーゲン量	トロンボプラスチン法[d)]	mg/dL

使用測定機器

c)： コールター全自動 8 項目血球アナライザー　T890（ベックマン・コールター株式会社）

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

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-オートセップ：テルモ株式会社）に取り、遠心分離（3000 rpm、約 1,600×g、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γ-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（3,000 rpm、約 1,600×g、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
AlP	Bessey-Lowry 法[e)]	IU/L
総コレステロール	CEH-COD-POD 法[e)]	mg/dL
トリグリセライド	LPL-GK-GPO-POD 法[e)]	mg/dL
リン脂質	PLD-ChOD-POD 法[e)]	mg/dL
総ビリルビン	ビリルビンオキシダーゼ法[e)]	mg/dL
グルコース	グルコースデヒドロゲナーゼ法[e)]	mg/dL
尿素窒素	Urease-LEDH 法[e)]	mg/dL
クレアチニン	Creatininase-creatinase-sarcosine-oxidase-POD 法[e)]	mg/dL
ナトリウム	イオン選択電極法[e)]	mmol/L
カリウム	イオン選択電極法[e)]	mmol/L
塩素	イオン選択電極法[e)]	mmol/L
カルシウム	OCPC 法[e)]	mg/dL
無機リン	モリブデン酸法[e)]	mg/dL
総たん白質	Biuret 法[e)]	g/dL
アルブミン	BCG 法[e)]	g/dL
A/G 比	たん白質とアルブミンから算出	
AST(GOT)	UV-rate 法[e)]	IU/L
ALT(GPT)	UV-rate 法[e)]	IU/L
LDH	UV-rate 法[e)]	IU/L
γ-GTP	L-γ-ｸﾞﾙﾀﾐﾙ-3-ｶﾙﾎﾞｷｼ-4-ﾆﾄﾛｱﾆﾘﾄﾞ法[e)]	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）

11) 病理学検査

(1) 剖検及び器官重量測定

全ての動物について、最終投与翌日及び回復期間終了日に、血液・血液化学検査のために採血した動物（各群雌雄各 5 匹）は採血後に、その他の動物は腹大動脈切断により放血致死させた後に、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 日に黄体数及び着床痕数を数えた。次いで、血液学検査及び血液化学検査の採血

を行った各群雌雄各 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 100g 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

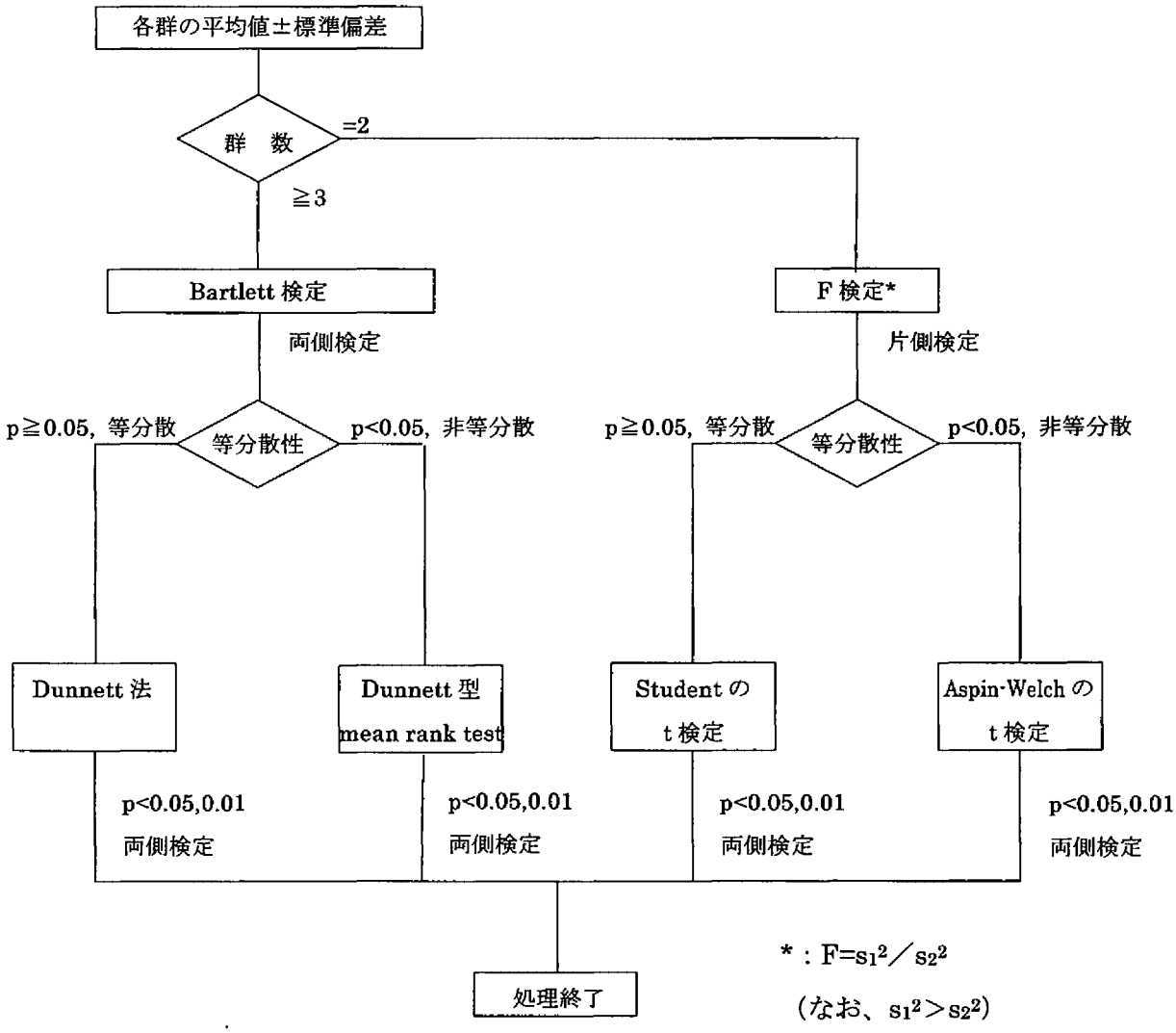
全動物について、次の器官・組織をリン酸緩衝 10vol%ホルマリン液で固定、保存した（ただし、精巣及び精巣上体はブアン液で固定した後リン酸緩衝 10vol%ホルマリン液で保存した）。次いで、下線を施した器官・組織についてパラフィン包埋した後、切片としてヘマトキシリン・エオジン（H・E）染色を行い、このうち対照群及び高用量群の血液・血液化学検査に供した雌雄各 5 匹について鏡検した（両側性の器官については両側を摘出し、片側を鏡検）。その結果、胃に被験物質投与の影響が認められたため、低及び中用量群並びに回復群についても雌雄各 5 匹を鏡検し、正常及び異常所見の代表例を撮影した。

大脳、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、顎下リンパ節、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）、個体識別部（耳介）

11. 統計解析

1) 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、生存児数、オープンフィールド内観察（立ち上がり回数、排糞数）、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 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 型検定を行った（有意水準 0.05 及び 0.01、両側）。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、Bartlett 検定により等分散性を検定し、等分散の場合は Dunnett 検定、非等分散の場合は Dunnett 型検定を行った（有意水準 0.05 及び 0.01、両側）。

2) 着床率、死産児率、出生率、外表異常率、出生児生存率は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、等分散の場合は Dunnett 検定、非等分散の場合は Dunnett 型検定を行った（有意水準 0.05 及び 0.01、両側）。



3) 交尾率、受胎率、授精率、出産率、出生児の性比、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、イェーツの連続修正による χ^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）。

試験結果

1. 一般状態（Table 1-1～1-8、Appendix 1～24）

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. 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. 1～4、Table 2-1～2-102、Appendix 25～315）

ホームケージ内観察、手に持っての観察及びオープンフィールド内観察については、投与開始前に1回、投与期間中及び回復期間中は毎週1回実施した（スコアの基準は添付資料 7～9参照）。

1) ホームケージ内観察（Table 2-1～2-30、Appendix 25～109）

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) 手に持っての観察（Table 2-31～2-60、Appendix 110～194）

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 2-61～2-90、Appendix 195～279）

主群の雄では1000 mg/kg投与群で投与3、4、5及び6週に立ち上がり回数の有意な低値が認められた。回復群の雌では1000 mg/kg投与群で投与5週に立ち上がり回数の有意な高値が認められたが、一時的であり、偶発的変化と考えられた。その他の検査項目では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、糞の個数には対照群と各被験物質投与群との間に有意差は認められなかった。

4) 機能検査（Table 2-91～2-94、Appendix 280～291）

主群の雄は投与終了週（投与6週）、雌は授乳4日に、回復群の雌雄は回復終了週に実施した（スコアの基準は添付資料 10参照）。

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、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、着地開脚幅には対照群と各被験物質投与群との間に有意差は認められなかった。

5) 握力測定（Table 2-95～2-98、Appendix 292～303）

機能検査に引き続き、前肢及び後肢について実施した。

主群の雄及び回復群の雌雄では対照群と各被験物質投与群との間に有意差は認められなかった。主群の雌では500 mg/kg投与群で授乳4日に有意な高値が認められたが、用量との関連はなかった。

6) 自発運動量の測定（Fig. 1～4、Table 2-99～2-102、Appendix 304～315）

握力測定に引き続き、測定開始10分ごとの値と60分間合計の値で集計した。

主群の雄及び回復群の雌雄では対照群と各被験物質投与群との間に有意差は認められなかった。主群の雌では1000 mg/kg投与群で測定開始20～30分に有意な高値が認められたが、一時的であることから、変動範囲内の変化と考えられた。

3. 体重（Fig. 5～8、Table 3-1～3-8、Appendix 316～339）

主群及び回復群の雌雄ともに体重及び体重増加量には対照群と各被験物質投与群との間に有意差は認められなかった。

4. 摂餌量（Fig. 9～12、Table 4-1～4-8、Appendix 340～363）

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った。

なお、主群においては250 mg/kg投与群の雄で投与42日に有意な低値、1000 mg/kg投与群の雌で妊娠4日に有意な高値、回復群においては1000 mg/kg投与群の雌で投与25及び29日に有意な高値、同群の雌では回復11日に有意な高値が認められたが、いずれも一時的であることから変動範囲内の変化と判断した。

5. 尿検査（摂水量測定を含む）（Table 5-1～5-8、Appendix 364～381）

定量項目については、いずれの検査項目においても対照群と各被験物質投与群との間に有意差は認められなかった。

定性項目については、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。

6. 血液学検査（Table 6-1～6-8、Appendix 382～405）

1) 投与終了時検査

1000 mg/kg投与群の雄では、好酸球の有意な低値が認められたが、増加でないことから毒性学的に意義はない。また、500 mg/kg投与群の雌では、リンパ球比率の有意な高値及び分葉好中球比率の有意な低値が認められたが、用量との関連がないことから、生理的変動範囲内の変化と考えられた。

2) 回復終了時検査

1000 mg/kg投与群の雄では、赤血球数、ヘモグロビン量及びヘマトクリット値に有意な低値が認められたが、投与期間終了時にみられない変化であり、かつ投与期間終了時と

同等値であることから、生理的変動範囲内の変化と判断した。同群の雌では、網状赤血球率に有意な低値が認められたが、軽微な変化であり、他の検査項目に有意差がみられないことから、生理的変動範囲内の変化と考えられた。

7. 血液化学検査 (Table 7-1～7-8、Appendix 406～429)

1) 投与終了時検査

250 mg/kg 以上の投与群の雄では A/G 比の有意な高値、1000 mg/kg 投与群の雄でトリグリセライドの有意な高値、尿素窒素の有意な高値、塩素の有意な低値、同群の雌ではγ-GTP の有意な低値が認められた。

2) 回復終了時検査

1000 mg/kg 投与群の雌雄ともにいずれの検査項目にも有意差は認められなかった。

8. 器官重量 (Table 8-1～8-8、Appendix 430～459)

絶対及び相対重量の双方に同一方向に有意差が認められた器官・組織はなかった。

1) 投与終了時検査

脾　　臓 : 相対重量の有意な高値が 500 mg/kg 投与群の雌にみられた。

腎　　臓 : 絶対重量の有意な高値が 500 及び 1000 mg/kg 投与群の雌にみられた。

2) 回復終了時検査

甲 状 腺 : 絶対重量の有意な高値が雌にみられた。

9. 剖検所見 (Table 9、Appendix 460～575)

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。

1) 投与終了時検査

胃　　: 腺胃の暗赤色巣が 500 mg/kg 投与群の雌 2 例にみられた。

精　　巣 : 小型化が 250 mg/kg 投与群の雄 1 例にみられた。

2) 回復終了時検査

いずれの動物にも異常はみられなかった。

10. 病理組織学検査 (Table 10-1～10-3、Appendix 460～575)

被験物質投与の影響が 1000 mg/kg 投与群の雄の胃にみられた。

1) 投与終了時検査

胃　　：軽微又は軽度な前胃及び腺胃粘膜における細胞浸潤が 1000 mg/kg 投与群の雄 3 例、軽微又は軽度な腺胃の糜爛が 250 mg/kg 投与群の雌 2 例、500 mg/kg 投与群の雌 2 例及び 1000 mg/kg 投与群の雄 3 例と雌 1 例、腺胃における軽微又は軽度な globule leukocyte[1)] 数の増加が対照群の雄 1 例、500 mg/kg 投与群の雄 2 例及び 1000 mg/kg 投与群の雄 4 例と雌 1 例、軽微又は軽度な腺胃粘膜の肥厚が 1000 mg/kg 投与群の雄 3 例、軽微又は軽度な境界縁の肥厚が対照群の雄 1 例、500 mg/kg 投与群の雄 2 例及び 1000 mg/kg 投与群の雄 5 例にみられた。これら変化のうち、腺胃粘膜における細胞浸潤、腺胃の糜爛、腺胃における globule leukocyte 数の増加及び境界縁の肥厚の出現頻度が 1000 mg/kg 投与群の雄で増加し、所見の程度が増強した。

その他、以下の所見がみられたが、出現頻度及び病理学的性状から自然発生によるものと考えられた。

精巣上体　：導管内における軽微な細胞残渣が 1000 mg/kg 投与群の雄 1 例にみられた。

大腿骨（骨髄を含む）

：骨髄の軽微な線維化が対照群及び 1000 mg/kg 投与群の雌各 1 例にみられた。

心　　臓　：軽微な限局性の心筋炎が対照群の雄 2 例にみられた。

腎　　臓　：軽微な好塩基性尿細管が対照群の雄 3 例及び 1000 mg/kg 投与群の雄 1 例、尿細管における軽微又は軽度な好酸性小体が対照群の雄 1 例及び 1000 mg/kg 投与群の雄 2 例にみられた。

肝　　臓　：門脈周囲肝細胞における軽微又は軽度な空胞化が対照群の雄 3 例と雌 2 例及び 1000 mg/kg 投与群の雄 5 例と雌 3 例、軽微な髄外造血の亢進が対照群の雌 1 例及び 1000 mg/kg 投与群の雌 3 例、軽微な微小肉芽が対照群の雌雄各 4 例及び 1000 mg/kg 投与群の雌雄各 3 例にみられた。

肺（気管支を含む）

：軽微な泡沫細胞の集簇が対照群の雌雄各 1 例及び 1000 mg/kg 投与群の雌 1 例にみられた。

下 垂 体　：中間帯における偽のう胞が対照群の雄 1 例にみられた。

脾　　臓　：軽微又は軽度な髄外造血の亢進が対照群及び 1000 mg/kg 投与群の雌雄各

5 例にみられた。

胸骨（骨髄を含む）

：骨髄の軽微な線維化が対照群の雌 1 例にみられた。

精　　巣：精細管の軽度な萎縮が 1000 mg/kg 投与群 1 例にみられた。

膀　　胱：粘膜における軽微な過形成が 1000 mg/kg 投与群の雌 1 例にみられた。

2) 回復終了時検査

胃　　：軽微な腺胃の糜爛が対照群の雌 1 例、腺胃における軽微な globule leukocyte 数の増加が 1000 mg/kg 投与群の雄 3 例と雌 1 例、軽微な境界縁の肥厚が 1000 mg/kg 投与群の雄 5 例にみられ、対照群と比べ腺胃における globule leukocyte 数の増加及び境界縁の肥厚の出現頻度が 1000 mg/kg 投与群の雄で増加した。

11. 性周期（Table 11、Appendix 576～579）

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被験物質投与群との間に有意差は認められなかった。

12. 交配成績（Table 12、Appendix 580～583）

対照群の 1 組が交配開始 7 日に、他の組み合わせは交配開始後 4 日までに交尾が成立し、雌全例が妊娠した。したがって、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被験物質投与群との間に有意差は認められなかった。

13. 分娩成績及び分娩･授乳状態（Table 13、Appendix 584～587）

分娩状態では、妊娠 21.5～22.5 日に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、出産生児数及び出生率には対照群と各被験物質投与群との間に有意差は認められなかった。

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った。

14. 出生児の観察（Table 14、Appendix 588～591）

性比の有意な低値が 500 mg/kg 投与群に、出生時の雄体重の有意な高値が 250 mg/kg 投与群に認められたが、いずれも用量との関連はなかった。外表異常を有する出生児として、痕跡尾が 1000 mg/kg 投与群に 1 例みられたが、出現頻度及び外表異常の種類から自然発生

によるものと考えられた。

15. **出生児の生存率** (Table 15、Appendix 592～595)

哺育 4 日生存率には対照群と各被験物質投与群との間に有意差は認められなかった。

16. **出生児の体重** (Table 16、Appendix 596～599)

出生時の雄体重に有意な高値が 250 mg/kg 投与群に認められたが、用量との関連はなかった。哺育 4 日の体重には対照群と各被験物質投与群との間に有意差は認められなかった。

17. **出生児の授乳 4 日剖検所見** (Table 17、Appendix 600～603)

いずれの出生児にも異常はみられなかった。

考　察

2-アミノ-2-エチル-1, 3-プロパンジオールの 0（対照群）、250、500、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 日間投与）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（42～48 日間投与）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 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

一般状態、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、剖検所見及び器官重量の結果に被験物質投与による影響は認められなかった。

詳細な一般状態の観察では、オープンフィールド内観察において 1000 mg/kg 投与群の雄で投与 3、4、5 及び 6 週に立ち上がり回数の低値が認められた。しかし、他の検査項目、特に自発運動量に異常はなく、回復終了時検査に認められないことから可逆性の変化であった。

血液化学検査では、投与期間終了時検査において 250 mg/kg 以上の投与群の雄で A/G 比の高値、1000 mg/kg 投与群の雄でトリグリセライドの高値、尿素窒素の高値、塩素の低値、同群の雌ではγ-GTP の高値が認められたが、軽微な変化で関連検査項目に変動がなく、組織学的にも異常がないことから生理学的な変動範囲内の変化と判断した。

病理組織学検査では、投与終了時検査において 1000 mg/kg 投与群の雄に腺胃粘膜における細胞浸潤、腺胃の糜爛、腺胃における globule leukocyte 数の増加、腺胃粘膜の肥厚及び境界縁の肥厚が観察され、被験物質の胃への刺激性が示唆された。これら胃の変化のうち、腺胃における globule leukocyte 数の増加及び境界縁の肥厚が回復終了時検査においても観察されたが、所見の程度は軽減し、可逆性の変化であった。

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。また、母動物の出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、死産児率、出産生児数、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異常は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。

出生児では、出生時の観察及び授乳 4 日剖検所見、体重及び生存率には被験物質投与群による変化は認められないことから、1000 mg/kg 投与群においても胚・胎児の成長と形態学的変化、生後の成長・発達への影響はないと考えられた。

これらの結果から、本試験条件下における 2-アミノ-2-エチル-1, 3-プロパンジオールの反復投与毒性に対する無影響量は雄で 500 mg/kg/day、雌で 1000 mg/kg/day、生殖発生毒性に対する無影響量は雌雄親動物及び児動物ともに 1000 mg/kg/day と判断した。

文　献

1) Isao Narama, Kiyokazu Ozaki, Syuuichi Matsushima and Tetsuro Matsuura: Eosinophilic Gastroenterocolitis in Iron Lactate-Overloaded Rats, Toxicologic Pathology, vol, 27, no. 3, pp. 318-324, 1999

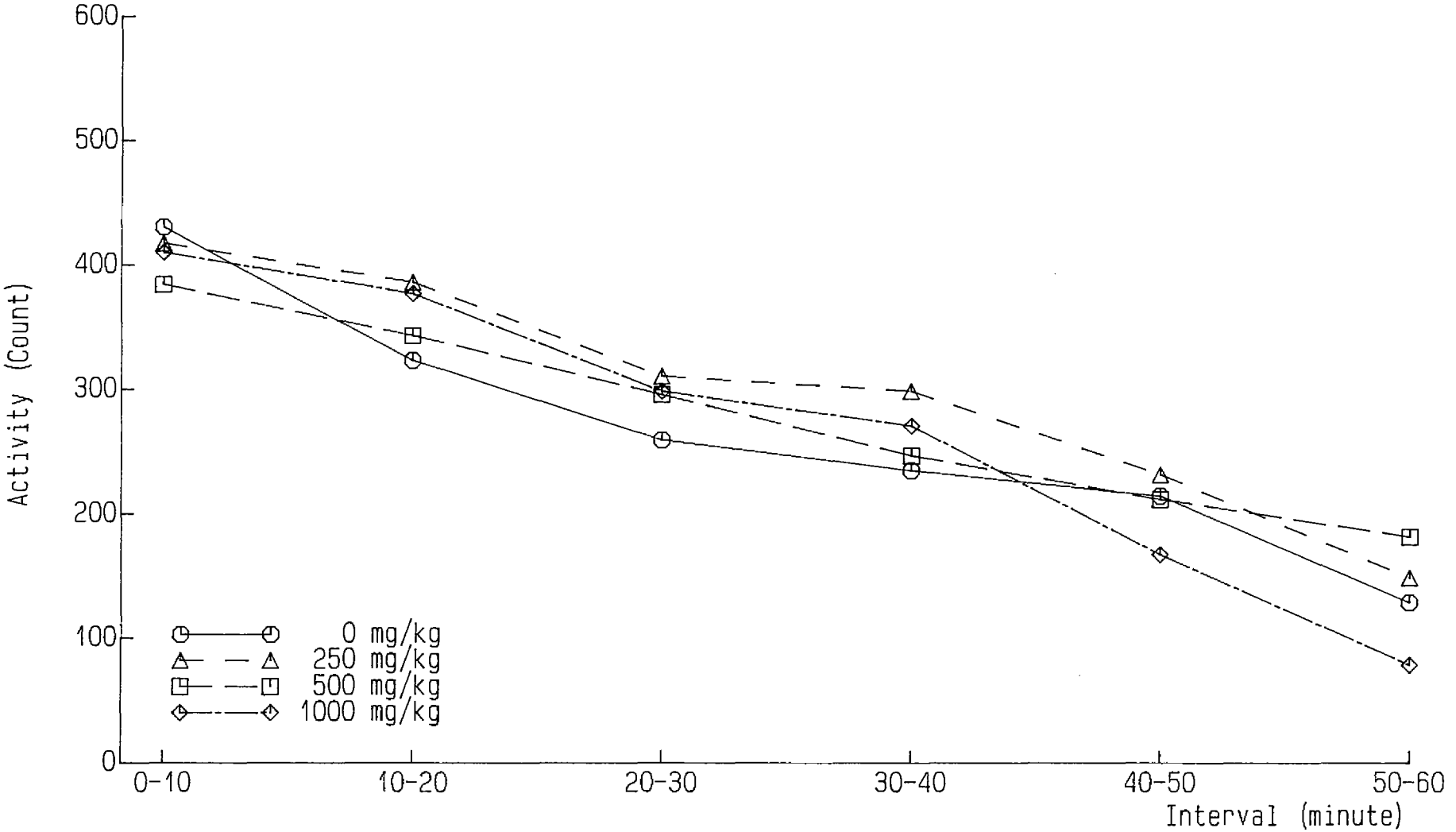


Fig.1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

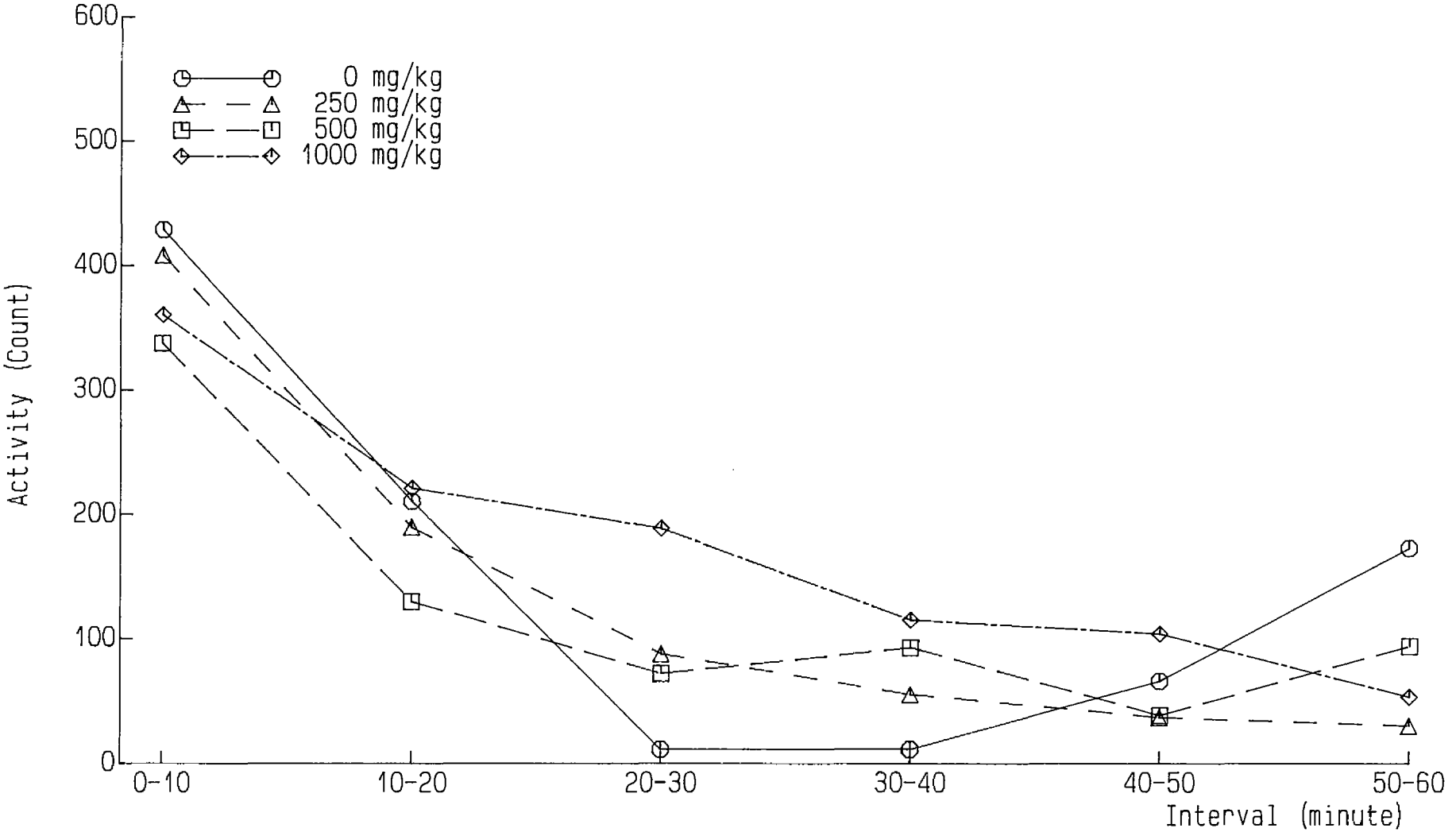


Fig.2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

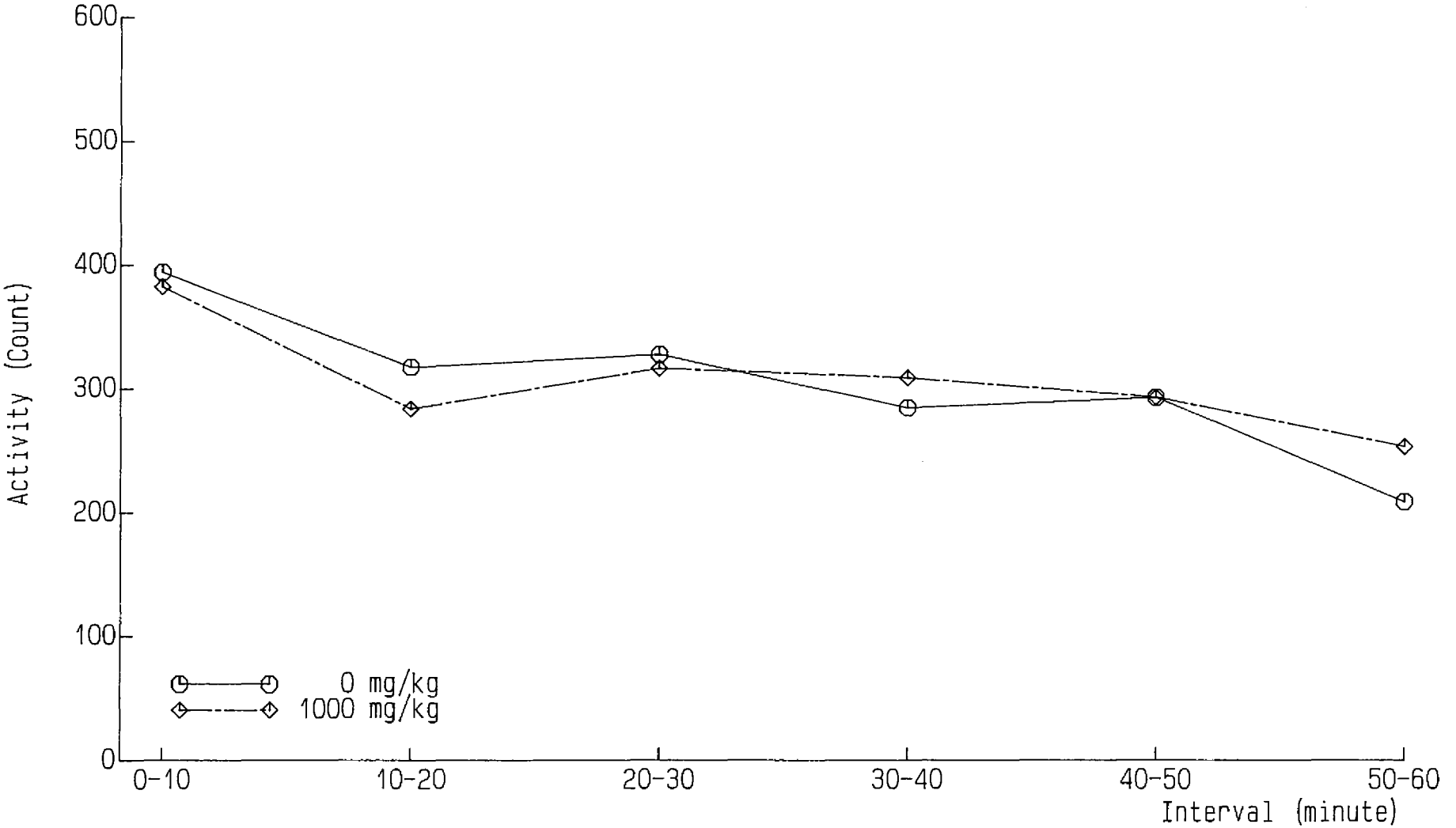


Fig.3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

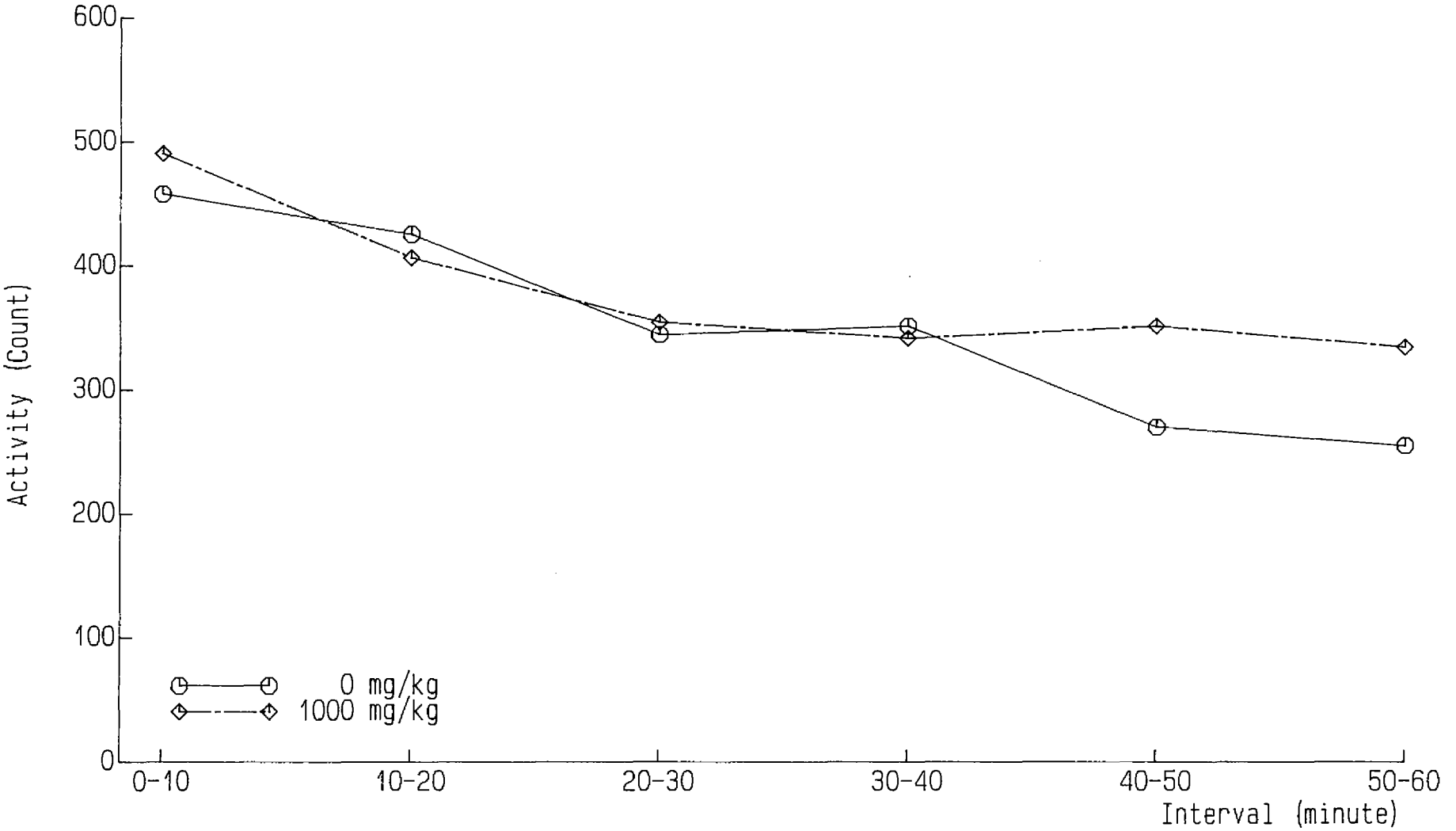


Fig.4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

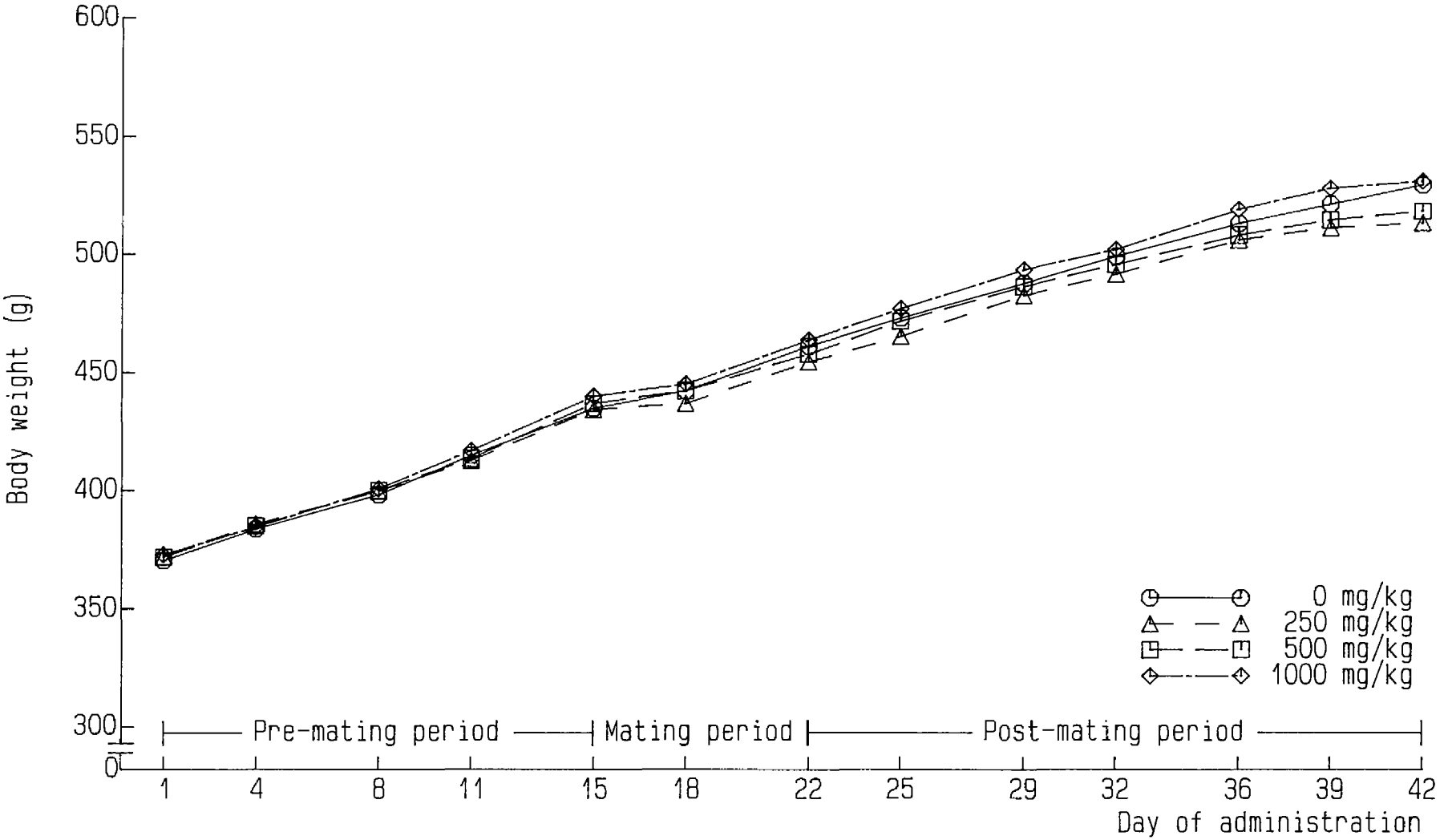


Fig.5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Body weight changes of male rats (Main group)

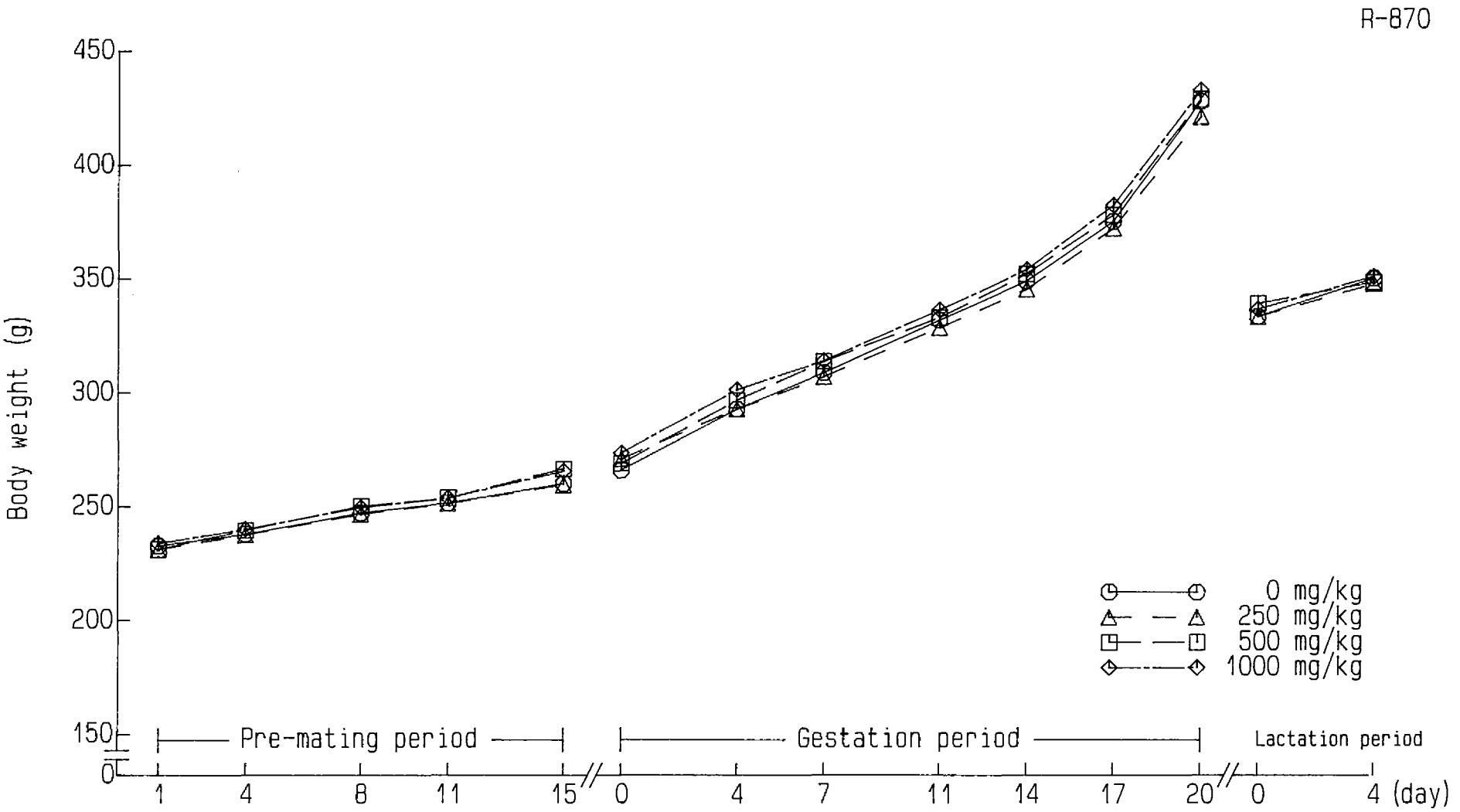


Fig.6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Body weight changes of female rats (Main group)

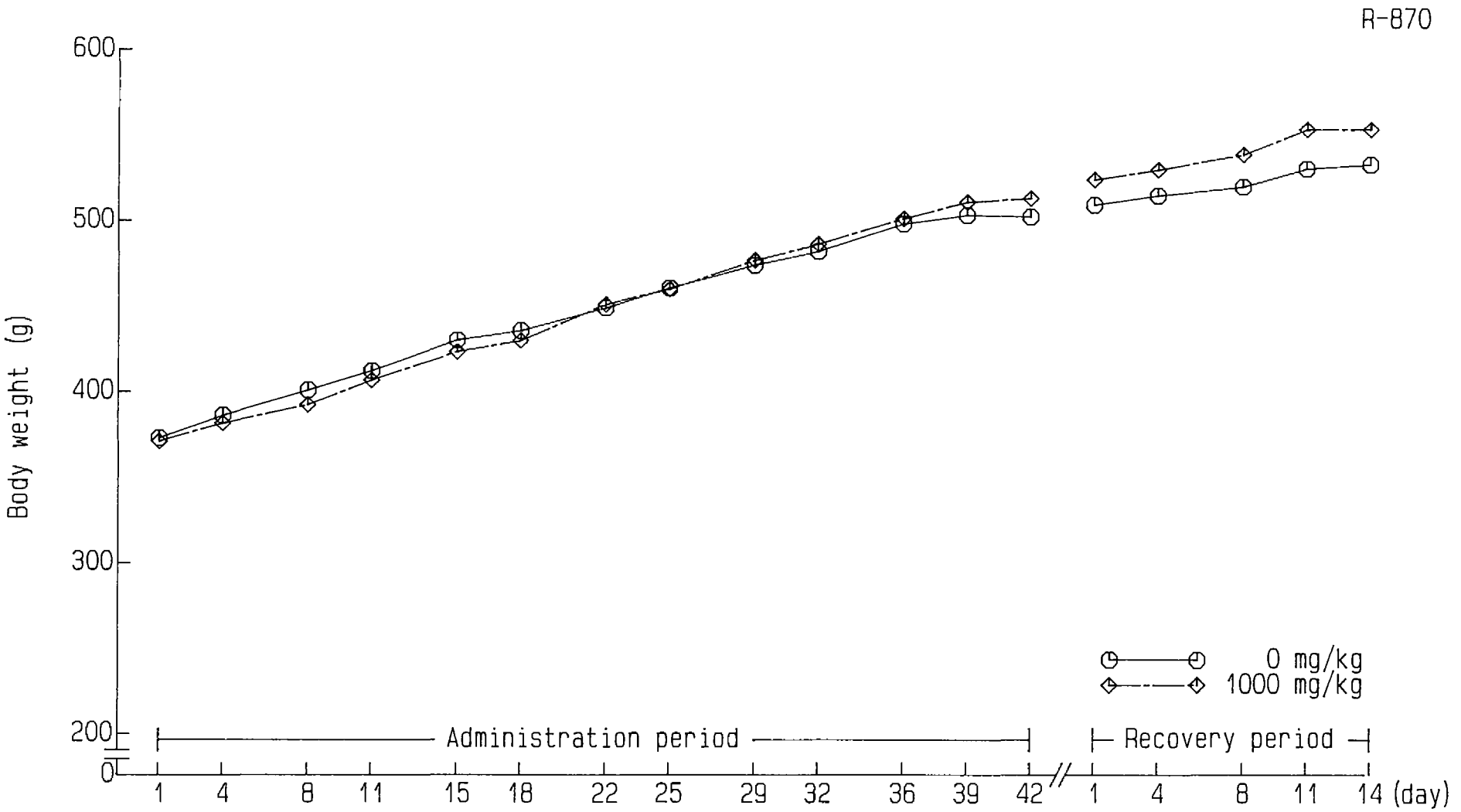


Fig.7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Body weight changes of male rats (Recovery group)

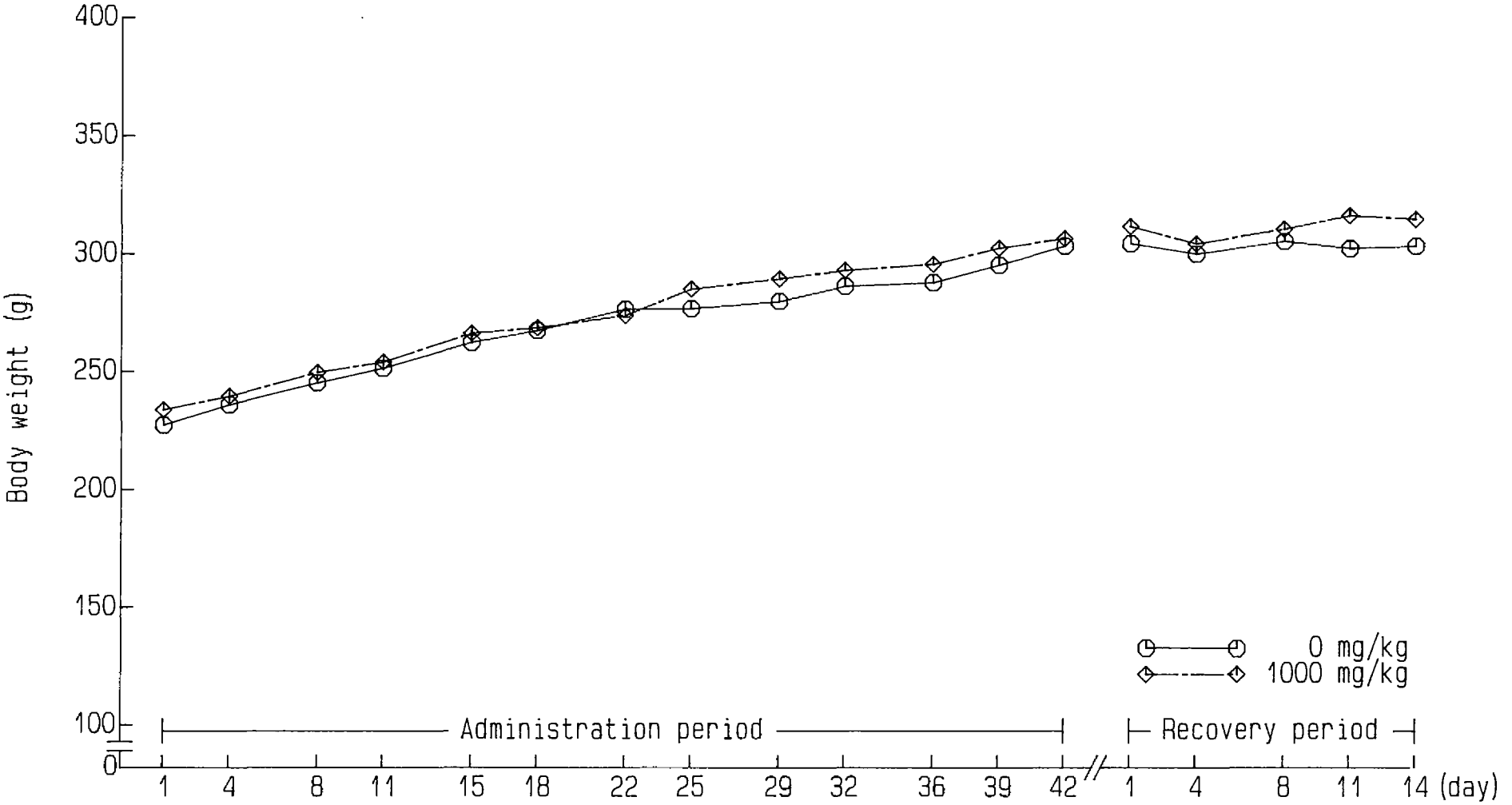


Fig.8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Body weight changes of female rats (Recovery group)

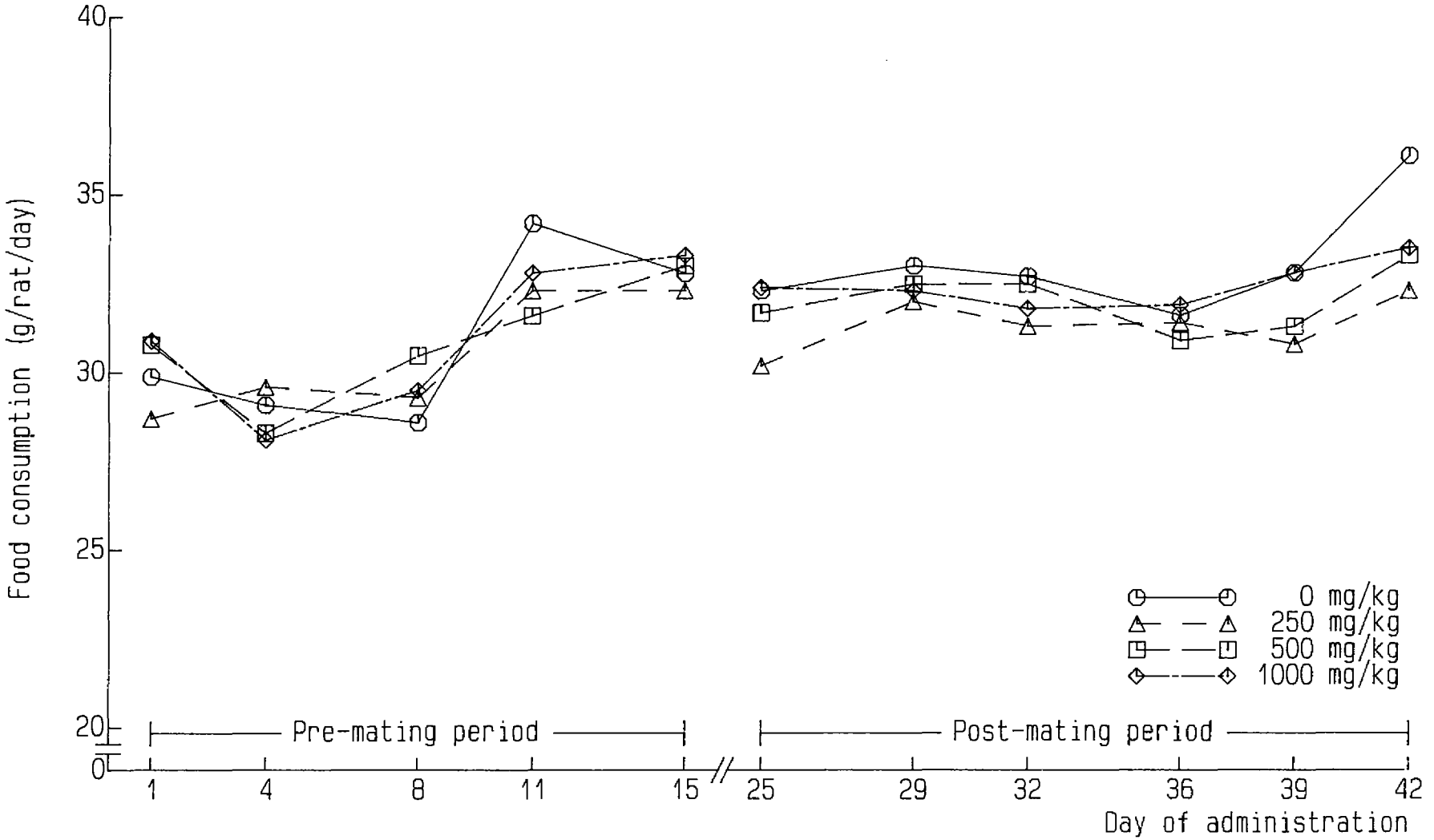


Fig.9 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Food consumption of male rats (Main group)

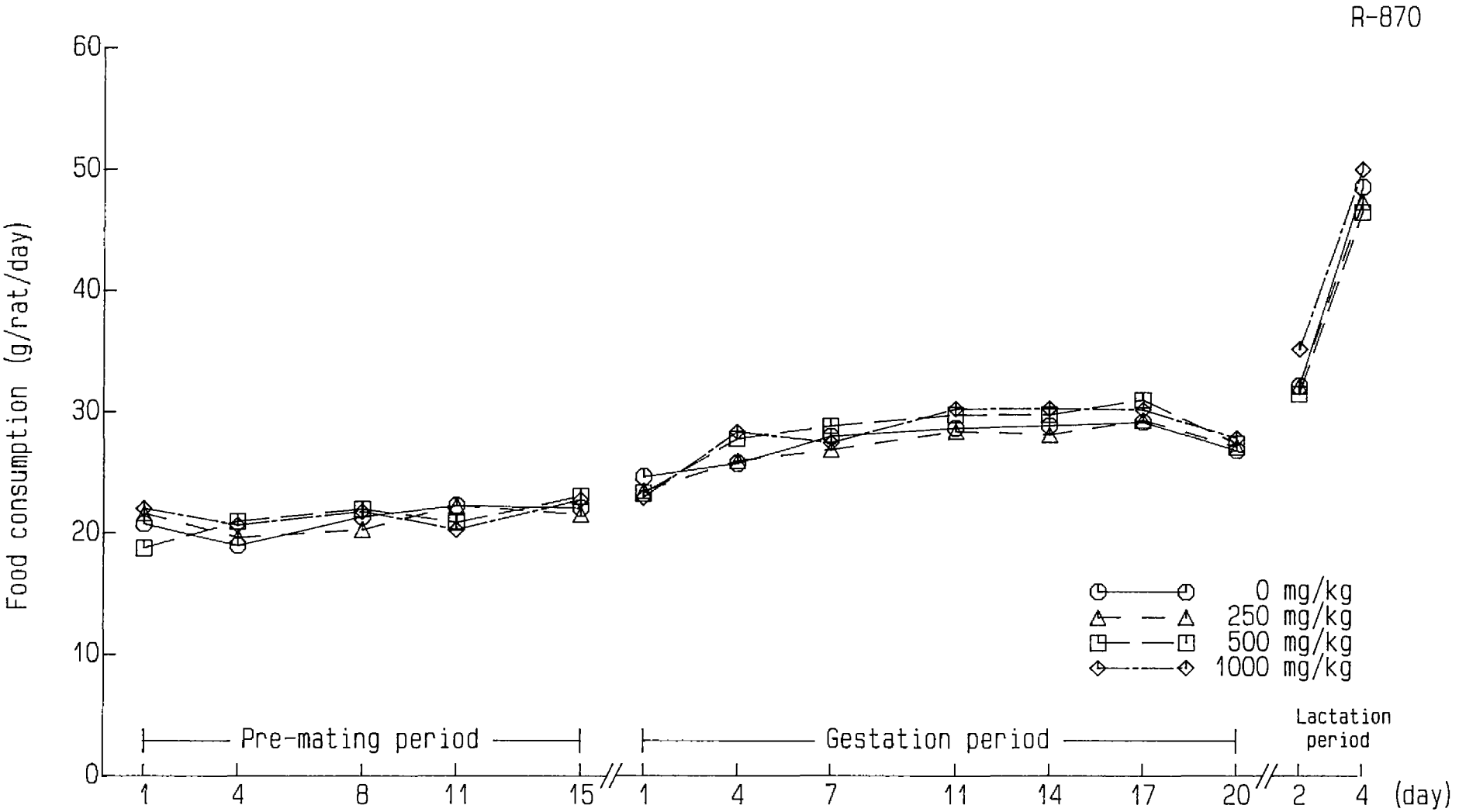


Fig.10 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Food consumption of female rats (Main group)

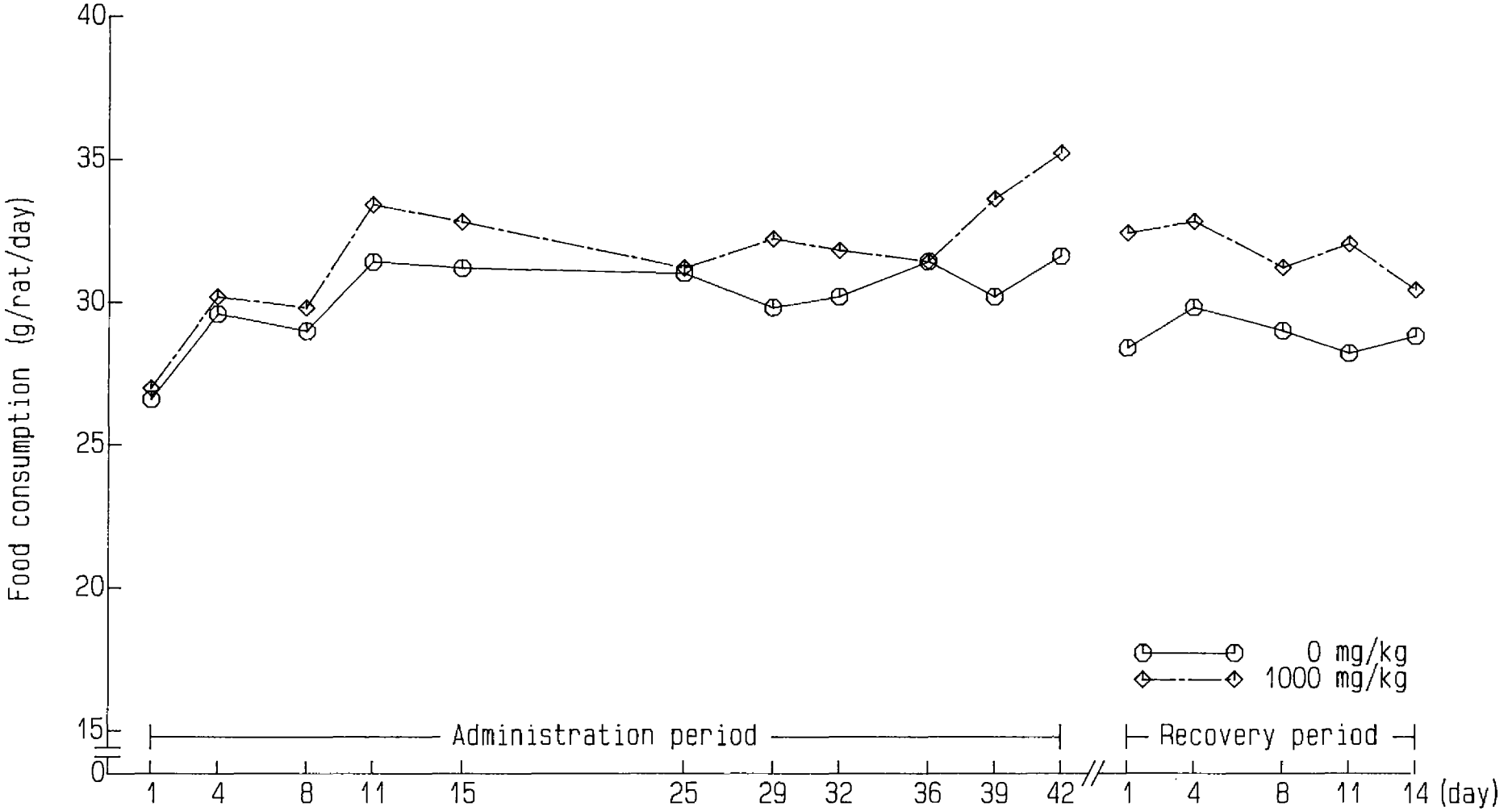


Fig.11 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Food consumption of male rats (Recovery group)

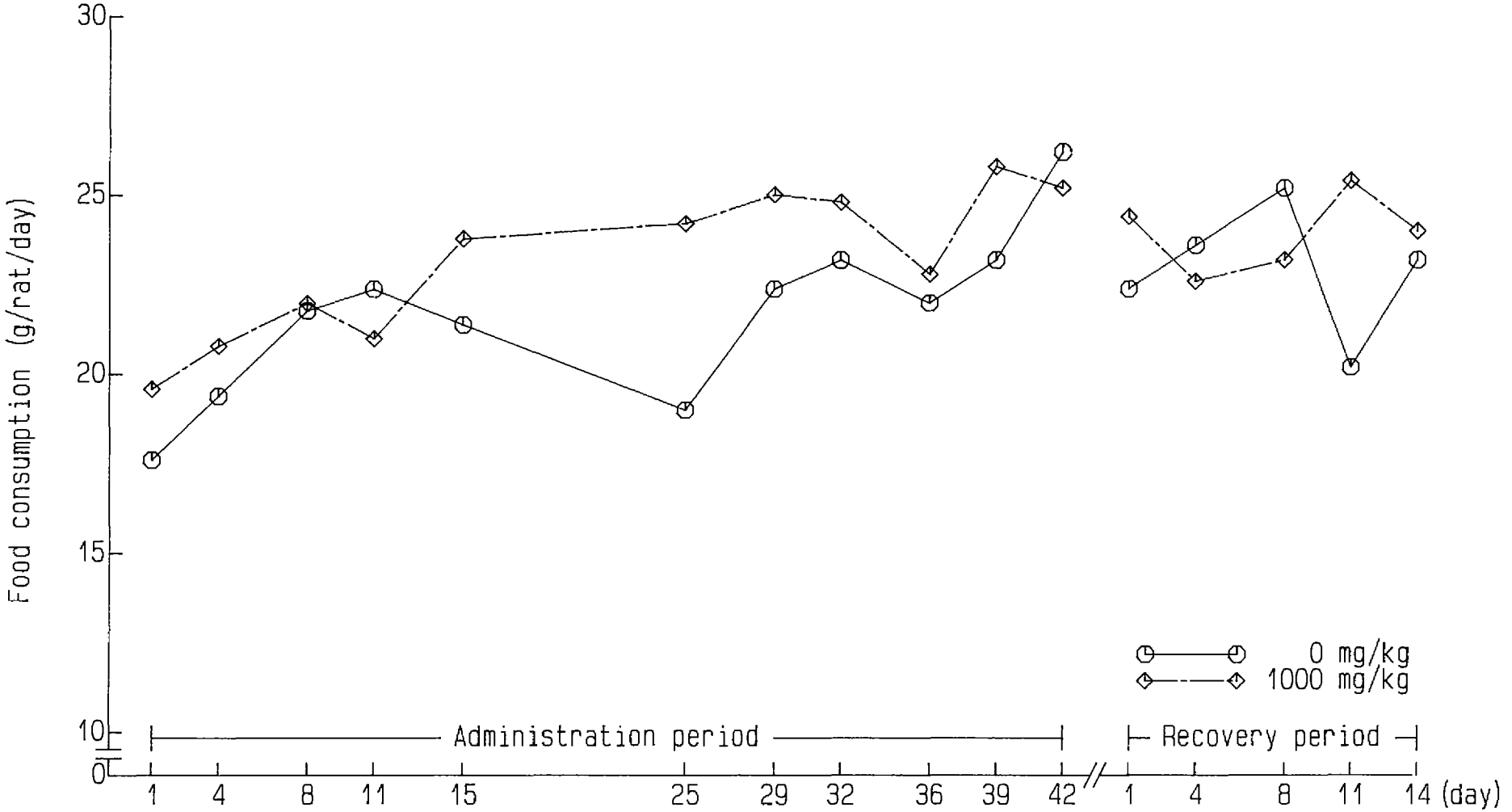


Fig.12 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Food consumption of female rats (Recovery group)

Table 1-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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
250	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0
500	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	0	0	0	0	0	0

Table 1-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg	Signs	Administration														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
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
250	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
500	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	0	0	0	0	0	0	0	0	0	0	0	0	0

a): Day of administration

Table 1-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	22a)
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	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	
250	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	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	
500	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	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	
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	10	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	

a): Day of gestation

Table 1-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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
250	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
500	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
1000	No. of dams	12	12	12	12	12
	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, 3-Propanediol, 2-amino-2-ethyl

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	0	0	0	0	0	0

Table 1-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	0	0	0	0	0	0

Table 1-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg	Signs	Day of recovery 1-7	Day of recovery 8-14
0	No. of animals	5	5
	No. of animals with abnormal findings	0	0
1000	No. of animals	5	5
	No. of animals with abnormal findings	0	0

Table 1-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg	Signs	Day of recovery 1-7	Day of recovery 8-14
0	No. of animals	5	5
	No. of animals with abnormal findings	0	0
1000	No. of animals	5	5
	No. of animals with abnormal findings	0	0

Table 2-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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 2-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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 2-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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 2-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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 2-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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 2-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0
Parameter	No. of animals	1
Posture		
Normal		1
Convulsion		
None		1
Abnormal behavior		
None		1

Table 2-10 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-14 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	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 2-15 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 1 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, 3-Propanediol, 2-amino-2-ethyl

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 2-17 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 3 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 2-18 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 4 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 2-19 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Detailed clinical signs in male 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 2-20 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 6 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 2-21 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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 2-22 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Detailed clinical signs in male 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 2-23 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	1000
Parameter	No. of animals	5	5
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, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	1000
Parameter	No. of animals	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, 3-Propanediol, 2-amino-2-ethyl

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 3 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 2-26 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 4 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, 3-Propanediol, 2-amino-2-ethyl

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

Dose (mg/kg)	0	1000
Parameter / No. of animals	5	5
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, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	1000
Parameter	No. of animals	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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 5	1000 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, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-31 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Removal from cage					
	Easy	11	10	11	12
	Some resistance/avoidance	1	2	1	0
Vocalization					
	None	10	8	8	12
	Soft	2	4	3	0
	Moderate	0	0	1	0
Reactivity to handling					
	Easy	9	10	10	12
	Slightly awkward	3	2	2	0
Fur condition					
	Normal	12	12	12	12
Skin					
	Normal	12	12	12	12
Piloerection					
	Absent	12	12	12	12
Mucosal membranes					
	Normal	12	12	12	12
Secretions-Eye, Nose					
	Absent	12	12	12	12
Palpebral closure					
	Normal	12	12	12	12
Exophthalmos					
	Absent	12	12	12	12
Pupil size					
	Normal	12	12	12	12
Lacrimation					
	Normal	12	12	12	12
Salivation					
	None	12	12	12	12
Abnormal respiration					
	Absent	12	12	12	12

Table 2-32 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	12	12	12	12
Removal from cage					
Easy		12	12	12	11
Some resistance/avoidance		0	0	0	1
Vocalization					
None		10	11	11	9
Soft		2	1	0	3
Moderate		0	0	1	0
Reactivity to handling					
Easy		11	12	12	12
Slightly awkward		1	0	0	0
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-33 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Removal from cage					
	Easy	10	12	12	11
	Some resistance/avoidance	2	0	0	1
Vocalization					
	None	11	11	11	11
	Soft	0	1	1	0
	Moderate	1	0	0	1
Reactivity to handling					
	Easy	11	12	12	10
	Slightly awkward	1	0	0	2
Fur condition					
	Normal	12	12	12	12
Skin					
	Normal	12	12	12	12
Piloerection					
	Absent	12	12	12	12
Mucosal membranes					
	Normal	12	12	12	12
Secretions-Eye, Nose					
	Absent	12	12	12	12
Palpebral closure					
	Normal	12	12	12	12
Exophthalmos					
	Absent	12	12	12	12
Pupil size					
	Normal	12	12	12	12
Lacrimation					
	Normal	12	12	12	12
Salivation					
	None	12	12	12	12
Abnormal respiration					
	Absent	12	12	12	12

Table 2-34 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Removal from cage					
Easy		12	12	12	12
Vocalization					
None		10	11	11	11
Soft		1	1	1	1
Moderate		1	0	0	0
Reactivity to handling					
Easy		11	10	11	10
Slightly awkward		1	2	1	2
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-35 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 / 12	250 / 12	500 / 12	1000 / 12
Removal from cage					
	Easy	9	10	9	7
	Some resistance/avoidance	3	2	3	5
Vocalization					
	None	10	11	11	7
	Soft	2	0	1	5
	Moderate	0	1	0	0
Reactivity to handling					
	Easy	9	10	10	6
	Slightly awkward	3	2	2	6
Fur condition					
	Normal	12	12	12	12
Skin					
	Normal	12	12	12	12
Piloerection					
	Absent	12	12	12	12
Mucosal membranes					
	Normal	12	12	12	12
Secretions-Eye, Nose					
	Absent	12	12	12	12
Palpebral closure					
	Normal	12	12	12	12
Exophthalmos					
	Absent	12	12	12	12
Pupil size					
	Normal	12	12	12	12
Lacrimation					
	Normal	12	12	12	12
Salivation					
	None	12	12	12	12
Abnormal respiration					
	Absent	12	12	12	12

Table 2-36 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Removal from cage					
	Easy	11	11	9	9
	Some resistance/avoidance	0	1	3	2
	Difficult	1	0	0	1
Vocalization					
	None	9	9	10	9
	Soft	2	3	1	2
	Moderate	1	0	1	1
Reactivity to handling					
	Easy	11	11	11	10
	Slightly awkward	1	1	0	2
	Difficult	0	0	1	0
Fur condition					
	Normal	12	12	12	12
Skin					
	Normal	12	12	12	12
Piloerection					
	Absent	12	12	12	12
Mucosal membranes					
	Normal	12	12	12	12
Secretions-Eye, Nose					
	Absent	12	12	12	12
Palpebral closure					
	Normal	12	12	12	12
Exophthalmos					
	Absent	12	12	12	12
Pupil size					
	Normal	12	12	12	12
Lacrimation					
	Normal	12	12	12	12
Salivation					
	None	12	12	12	12
Abnormal respiration					
	Absent	12	12	12	12

Table 2-37 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Removal from cage					
Atypically docile		0	1	0	0
Easy		12	11	12	12
Vocalization					
None		12	12	10	12
Soft		0	0	2	0
Reactivity to handling					
Atypically docile		0	2	0	0
Easy		12	10	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-38 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Removal from cage					
Easy		12	12	12	12
Vocalization					
None		12	12	12	11
Soft		0	0	0	1
Reactivity to handling					
Easy		11	12	12	11
Slightly awkward		1	0	0	1
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-39 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-40 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	12	12	12	12
Removal from cage					
Easy		12	12	12	12
Vocalization					
None		12	12	12	10
Soft		0	0	0	2
Reactivity to handling					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-41 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	12	12	12	12
Removal from cage					
Easy		11	10	10	11
Some resistance/avoidance		1	2	2	1
Vocalization					
None		12	12	12	11
Soft		0	0	0	1
Reactivity to handling					
Easy		8	11	6	12
Slightly awkward		4	1	6	0
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-42 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	12	12	12	12
Removal from cage					
Easy		12	12	11	12
Some resistance/avoidance		0	0	1	0
Vocalization					
None		12	12	12	12
Reactivity to handling					
Easy		10	10	10	10
Slightly awkward		2	2	2	2
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-43 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Removal from cage					
Easy		12	12	12	12
Vocalization					
None		12	12	12	12
Reactivity to handling					
Easy		12	11	12	12
Slightly awkward		0	1	0	0
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-44 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	12	12	12	12
Removal from cage					
Easy		12	12	12	11
Some resistance/avoidance		0	0	0	1
Vocalization					
None		12	12	12	11
Soft		0	0	0	1
Reactivity to handling					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12

Table 2-45 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-46 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-47 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-48 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-49 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-50 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-51 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-52 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-53 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-54 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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
Removal from cage			
Easy		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5
Fur condition			
Normal		5	5
Skin			
Normal		5	5
Piloerection			
Absent		5	5
Mucosal membranes			
Normal		5	5
Secretions-Eye, Nose			
Absent		5	5
Palpebral closure			
Normal		5	5
Exophthalmos			
Absent		5	5
Pupil size			
Normal		5	5
Lacrimation			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5

Table 2-55 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-56 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-57 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-58 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-59 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-60 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

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

Table 2-61 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
	Normal	12	12	12	12
Gait					
	No/minimal location	0	0	1	0
	Normal	12	12	11	12
Arousal					
	Normal	12	12	12	12
Tremor					
	None	12	12	12	12
Convulsion					
	None	12	12	12	12
Abnormal behavior					
	None	12	12	12	12
Grooming					
	None	12	12	12	12
Rearing		2± 1	2± 1	3± 1	3± 1
Urination					
	None	11	10	10	12
	Small amount	1	2	2	0
Defecation count		0± 0	0± 0	0± 0	0± 1

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		4± 2	4± 2	3± 2	3± 2
Urination					
None		12	8	11	12
Small amount		0	4	1	0
Defecation count		0± 0	0± 1	1± 2	0± 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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
Normal		12	12	12	12
Gait					
No/minimal location		0	0	1	0
Normal		12	12	11	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		5± 2	3± 2	4± 3	3± 2*D
Urination					
None		11	10	10	10
Small amount		1	2	2	2
Defecation count		0± 0	0± 1	0± 1	0± 1

*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 2-64 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

	Dose (mg/kg)	0	250	500	1000
Parameter	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		5± 3	3± 3	5± 2	3± 1*D
Urination					
None		11	10	11	12
Small amount		1	2	1	0
Defecation count		0± 0	0± 1	0± 0	0± 0

*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 2-65 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		6± 3	5± 2	5± 2	4± 1**D
Urination					
None		8	9	12	9
Small amount		4	2	0	2
Moderate amount		0	1	0	1
Defecation count		0± 0	0± 0	0± 1	0± 0

**: $p<0.01$ (Significant difference from control group)
D: Dunnett's test

Table 2-66 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		6± 2	5± 2	5± 1	4± 2**D
Urination					
None		9	12	10	12
Small amount		2	0	2	0
Moderate amount		1	0	0	0
Defecation count		0± 0	0± 0	0± 1	0± 1

**: p<0.01 (Significant difference from control group)
D: Dunnett's test

Table 2-67 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		6± 2	5± 2	5± 2	7± 2
Urination					
None		12	12	12	12
Defecation count		0± 0	0± 0	0± 0	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		7± 2	7± 2	5± 2	5± 2
Urination					
None		12	12	10	12
Small amount		0	0	2	0
Defecation count		0± 0	0± 0	0± 0	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 1
Posture		
Normal		1
Gait		
Normal		1
Arousal		
Normal		1
Tremor		
None		1
Convulsion		
None		1
Abnormal behavior		
None		1
Grooming		
None		1
Rearing		5± 0
Urination		
None		1
Defecation count		0± 0

Table 2-70 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		7± 2	7± 2	6± 1	6± 2
Urination					
None		12	11	11	12
Small amount		0	1	1	0
Defecation count		0± 0	0± 0	0± 0	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
	Normal	12	12	12	12
Gait					
	Normal	12	12	12	12
Arousal					
	Normal	12	12	12	12
Tremor					
	None	12	12	12	12
Convulsion					
	None	12	12	12	12
Abnormal behavior					
	None	12	12	12	12
Grooming					
	None	12	12	12	12
Rearing		6± 1	7± 2	6± 1	6± 2
Urination					
	None	12	12	11	12
	Small amount	0	0	1	0
Defecation count		0± 0	0± 0	0± 0	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 / 12	250 / 12	500 / 12	1000 / 12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		6± 1	7± 2	6± 1	4± 2
Urination					
None		11	12	12	11
Small amount		1	0	0	1
Defecation count		0± 0	0± 0	0± 0	0± 0

No significant difference in any treated groups from control group.

Table 2-73 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		6± 2	6± 2	6± 1	6± 2
Urination					
None		12	11	12	12
Small amount		0	1	0	0
Defecation count		0± 0	0± 0	0± 0	0± 0

No significant difference in any treated groups from control group.

Table 2-74 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 12	250 12	500 12	1000 12
Posture					
Normal		12	12	12	12
Gait					
Normal		12	12	12	12
Arousal					
Normal		12	12	12	12
Tremor					
None		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Grooming					
None		12	12	12	12
Rearing		8± 1	8± 2	7± 2	7± 1
Urination					
None		12	12	12	12
Defecation count		0± 0	0± 0	0± 0	0± 0

No significant difference in any treated groups from control group.

Table 2-75 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Dose (mg/kg)	0	1000
Parameter / No. of animals	5	5
Posture		
Normal	5	5
Gait		
Normal	5	5
Arousal		
Reduced awareness	0	1
Normal	5	4
Tremor		
None	5	5
Convulsion		
None	5	5
Abnormal behavior		
None	5	5
Grooming		
None	5	5
Rearing	1± 1	2± 2
Urination		
None	2	5
Small amount	3	0
Defecation count	0± 1	0± 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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Gait			
Normal		5	5
Arousal			
Normal		5	5
Tremor			
None		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Grooming			
None		5	5
Rearing		2± 1	3± 1
Urination			
None		1	5
Small amount		3	0
Moderate amount		1	0
Defecation count		1± 2	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Gait			
Normal		5	5
Arousal			
Normal		5	5
Tremor			
None		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Grooming			
None		5	5
Rearing		2± 3	3± 2
Urination			
None		4	4
Small amount		0	1
Moderate amount		1	0
Defecation count		1± 2	0± 1

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, 3-Propanediol, 2-amino-2-ethyl

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
Posture			
Normal		5	5
Gait			
Normal		5	5
Arousal			
Normal		5	5
Tremor			
None		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Grooming			
None		5	5
Rearing		4± 2	5± 2
Urination			
None		4	5
Small amount		1	0
Defecation count		0± 1	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

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

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Gait			
No/minimal location		0	1
Normal		5	4
Arousal			
Normal		5	5
Tremor			
None		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Grooming			
None		5	5
Rearing		4± 1	4± 3
Urination			
None		5	5
Defecation count		0± 1	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Gait			
Normal		5	5
Arousal			
Normal		5	5
Tremor			
None		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Grooming			
None		5	5
Rearing		3± 1	3± 1
Urination			
None		5	4
Small amount		0	1
Defecation count		0± 0	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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
Posture			
Normal		5	5
Gait			
Normal		5	5
Arousal			
Normal		5	5
Tremor			
None		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Grooming			
None		5	5
Rearing		4± 1	4± 1
Urination			
None		4	5
Small amount		1	0
Defecation count		0± 0	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose (mg/kg)	0	1000
Parameter No. of animals	5	5
Posture		
Normal	5	5
Gait		
Normal	5	5
Arousal		
Normal	5	5
Tremor		
None	5	5
Convulsion		
None	5	5
Abnormal behavior		
None	5	5
Grooming		
None	5	5
Rearing	5± 1	6± 2
Urination		
None	3	4
Small amount	2	1
Defecation count	0± 0	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

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

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, 3-Propanediol, 2-amino-2-ethyl

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

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

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, 3-Propanediol, 2-amino-2-ethyl

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

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

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose (mg/kg)	0	1000
Parameter No. of animals	5	5
Posture		
Normal	5	5
Gait		
Normal	5	5
Arousal		
Normal	5	5
Tremor		
None	5	5
Convulsion		
None	5	5
Abnormal behavior		
None	5	5
Grooming		
None	5	5
Rearing	7± 1	9± 1*T
Urination		
None	5	4
Small amount	0	1
Defecation count	0± 0	0± 0

*: $p<0.05$ (Significant difference from control group)
T: Student's t-test

Table 2-88 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Gait			
Normal		5	5
Arousal			
Normal		5	5
Tremor			
None		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Grooming			
None		5	5
Rearing		7± 2	7± 2
Urination			
None		5	5
Defecation count		0± 0	0± 0

No significant difference between treated group and control group.

Table 2-89 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Dose (mg/kg)	0	1000
Parameter / No. of animals	5	5
Posture		
Normal	5	5
Gait		
Normal	5	5
Arousal		
Normal	5	5
Tremor		
None	5	5
Convulsion		
None	5	5
Abnormal behavior		
None	5	5
Grooming		
None	5	5
Rearing	6± 1	6± 1
Urination		
None	5	5
Defecation count	0± 0	0± 0

No significant difference between treated group and control group.

Table 2-90 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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
Posture			
Normal		5	5
Gait			
Normal		5	5
Arousal			
Normal		5	5
Tremor			
None		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Grooming			
None		5	5
Rearing		9± 2	9± 2
Urination			
None		5	5
Defecation count		0± 0	0± 0

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	250	500	1000
	No. of animals	5	5	5	5
Approach response					
No reaction/ignores		0	1	0	0
Normal		5	4	5	5
Touch response					
Normal		5	5	5	5
Auditory response					
Weak		1	2	2	2
Normal		4	3	3	3
Tail pinch response					
Normal		5	5	5	5
Pupillary reflex					
Pass, both		5	5	5	5
Aerial righting reflex					
Normal (landing on 4 limbs)		5	5	5	5
Landing foot splay (mm)		100±32	102±25	103±30	116±14

No significant difference in any treated groups from control group.

Table 2-92 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg) / No. of animals	0 5	250 5	500 5	1000 5
Approach response					
No reaction/ignores		1	0	0	0
Normal		4	5	5	5
Touch response					
Normal		5	5	5	5
Auditory response					
Normal		5	5	5	5
Tail pinch response					
Weak		1	1	1	0
Normal		4	4	4	5
Pupillary reflex					
Pass, both		5	5	5	5
Aerial righting reflex					
Normal (landing on 4 limbs)		5	5	5	5
Landing foot splay (mm)		77±14	74±24	74±18	91±11

No significant difference in any treated groups from control group.

Table 2-93 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Auditory response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
Normal (landing on 4 limbs)		5	5
Landing foot splay (mm)		86±35	114±22

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, 3-Propanediol, 2-amino-2-ethyl

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Auditory response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
Normal (landing on 4 limbs)		5	5
Landing foot splay (mm)		62±16	59±13

No significant difference between treated group and control group.

Table 2-95 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	1038	708
	S.D.	96	105
250	No.	5	5
	Mean	789	592
	S.D.	241	120
500	No.	5	5
	Mean	1075	619
	S.D.	307	127
1000	No.	5	5
	Mean	1154	734
	S.D.	65	97

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, 3-Propanediol, 2-amino-2-ethyl

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	913	418
	S.D.	153	98
250	No.	5	5
	Mean	882	611
	S.D.	176	197
500	No.	5	5
	Mean	879	673*
	S.D.	341	130D
1000	No.	5	5
	Mean	840	578
	S.D.	302	117

*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 2-97 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	963	745
	S.D.	150	215
1000	No.	5	5
	Mean	955	771
	S.D.	233	109

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, 3-Propanediol, 2-amino-2-ethyl

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	916	601
	S.D.	116	97
1000	No.	5	5
	Mean	920	614
	S.D.	41	152

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, 3-Propanediol, 2-amino-2-ethyl

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.	5	5	5	5	5	5	5
	Mean	431	324	260	235	215	129	1594
	S.D.	25	74	100	147	125	50	333
250	No.	5	5	5	5	5	5	5
	Mean	418	387	311	299	232	149	1796
	S.D.	26	44	72	57	120	153	264
500	No.	5	5	5	5	5	5	5
	Mean	385	344	296	247	212	182	1666
	S.D.	48	68	92	145	169	179	655
1000	No.	5	5	5	5	5	5	5
	Mean	411	378	299	271	168	79	1605
	S.D.	41	50	18	115	127	125	365

No significant difference in any treated groups from control group.

Table 2-100 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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.	5	5	5	5	5	5	5
	Mean	429	211	11	11	66	173	900
	S.D.	47	94	8	7	123	207	431
250	No.	5	5	5	5	5	5	5
	Mean	409	190	88	55	37	30	810
	S.D.	56	165	102	90	63	19	278
500	No.	5	5	5	5	5	5	5
	Mean	338	130	72	93	38	94	766
	S.D.	105	111	91	191	64	117	462
1000	No.	5	5	5	5	5	5	5
	Mean	361	221	189*	115	104	53	1043
	S.D.	64	143	106DT	159	133	54	314

*: $p<0.05$ (Significant difference from control group)
DT: Dunnett-type rank test

Table 2-101 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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.	5	5	5	5	5	5	5
	Mean	395	318	328	285	293	209	1829
	S.D.	25	38	38	42	88	96	191
1000	No.	5	5	5	5	5	5	5
	Mean	383	284	317	309	293	253	1840
	S.D.	35	74	89	49	100	90	314

No significant difference between treated group and control group.

Table 2-102 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	458	426	345	352	270	255	2106
	S.D.	55	39	39	63	112	156	340
1000	No.	5	5	5	5	5	5	5
	Mean	491	407	355	342	352	335	2284
	S.D.	17	46	67	37	37	53	127

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, 3-Propanediol, 2-amino-2-ethyl

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	12
	Mean	370.4	383.9	398.3	414.9	434.8	442.2	461.4	473.1	487.8	499.0	512.8	521.0	529.2	158.8
	S.D.	15.1	18.6	21.0	21.0	27.2	24.5	23.9	24.7	25.1	26.6	28.6	29.6	32.8	25.7
250	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	372.2	385.9	399.8	412.8	434.3	436.9	454.5	465.4	482.5	491.5	506.0	511.1	513.2	141.0
	S.D.	17.5	21.6	20.4	22.3	24.5	25.3	26.0	25.0	28.6	28.9	31.8	33.3	35.1	24.5
500	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	372.0	385.2	400.0	413.5	436.9	442.4	458.0	471.8	486.3	495.6	507.9	514.4	518.3	146.3
	S.D.	13.6	14.6	18.9	23.0	29.5	29.3	31.7	33.8	34.9	36.4	38.3	41.5	39.4	29.9
1000	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	373.0	384.5	400.7	416.8	440.1	445.1	463.9	476.8	493.3	501.7	518.8	527.6	530.7	157.7
	S.D.	15.4	13.7	18.8	22.0	25.1	24.1	26.7	29.8	28.0	28.2	31.2	31.3	29.1	15.8

Unit: g
No.: No. of animals
a): Day of administration
No significant difference in any treated groups from control group.

Table 3-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Administration 1	4	8	11	15a)	Gain 1-15
0	No.	12	12	12	12	12	12
	Mean	232.8	238.0	247.1	251.6	260.0	27.3
	S.D.	13.8	11.9	12.2	10.5	9.6	7.3
250	No.	12	12	12	12	12	12
	Mean	231.4	237.8	246.6	251.2	259.5	28.1
	S.D.	11.9	14.1	15.0	14.4	16.6	9.5
500	No.	12	12	12	12	12	12
	Mean	231.2	239.6	250.0	253.7	266.3	35.1
	S.D.	12.8	12.2	12.7	14.2	15.2	7.5
1000	No.	12	12	12	12	12	12
	Mean	233.9	240.1	249.4	253.6	265.5	31.6
	S.D.	7.8	9.9	11.6	11.5	13.8	14.3

Unit: g
No.: No. of animals
a): Day of administration
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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Administration 0	4	7	11	14	17	20a)	Gain 0-20
0	No.	12	12	12	12	12	12	12	12
	Mean	265.9	292.8	308.8	331.7	348.6	374.9	427.7	161.8
	S.D.	15.2	16.2	17.0	18.8	18.6	19.7	25.4	16.1
250	No.	12	12	12	12	12	12	12	12
	Mean	270.7	292.8	306.8	328.4	345.2	371.9	420.8	150.2
	S.D.	20.3	19.4	21.4	19.4	19.1	22.1	29.3	16.5
500	No.	12	12	12	12	12	12	12	12
	Mean	268.8	296.7	313.7	332.8	351.8	377.7	428.5	159.8
	S.D.	18.4	20.4	23.1	24.5	25.2	27.6	31.4	16.0
1000	No.	12	12	12	12	12	12	12	12
	Mean	273.4	301.2	313.8	336.2	353.6	381.8	432.4	159.0
	S.D.	8.4	10.1	9.2	10.0	9.9	12.1	16.8	14.5

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Administration 0	Administration 4a)	Gain 0-4
0	No.	12	12	12
	Mean	333.3	349.9	16.7
	S.D.	21.7	17.5	14.9
250	No.	12	12	12
	Mean	333.0	347.5	14.5
	S.D.	17.4	20.1	14.1
500	No.	12	12	12
	Mean	339.1	348.2	9.1
	S.D.	23.2	19.0	16.2
1000	No.	12	12	12
	Mean	336.3	350.6	14.3
	S.D.	10.8	16.6	13.0

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Day of administration 1	4	8	11	15	18	22	25	29	32	36	39	42	Gain 1-42
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	373.0	386.4	401.0	412.2	430.4	435.8	449.4	461.0	474.2	482.2	498.0	503.2	502.2	129.2
	S.D.	17.4	20.0	15.7	18.9	20.9	21.6	22.8	23.8	24.2	27.4	30.1	34.1	31.5	14.7
1000	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	371.4	381.8	392.6	407.0	423.6	430.0	451.2	460.0	476.8	486.2	501.2	510.6	512.8	141.4
	S.D.	20.2	18.5	23.2	26.0	26.8	29.5	28.7	32.1	33.2	39.4	40.6	42.3	41.5	26.6

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Day of administration 1	4	8	11	15	18	22	25	29	32	36	39	42	Gain 1-42
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	227.2	235.8	245.2	251.2	262.2	267.4	276.4	276.6	279.8	286.2	287.8	295.2	303.2	76.0
	S.D.	8.2	15.0	14.3	16.3	15.4	16.8	17.1	17.4	16.8	23.4	22.3	19.7	20.1	12.9
1000	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	233.8	239.4	249.6	253.8	266.2	268.4	273.6	284.8	289.2	292.8	295.4	302.4	306.2	72.4
	S.D.	6.5	12.8	12.3	6.6	6.3	5.4	4.8	9.6	8.1	9.0	9.1	7.4	6.7	9.0

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Day of recovery 1	4	8	11	14	Gain 1-14
0	No.	5	5	5	5	5	5
	Mean	509.2	514.6	519.8	530.4	532.6	23.4
	S.D.	33.4	33.7	29.4	36.6	33.8	7.6
1000	No.	5	5	5	5	5	5
	Mean	523.8	529.6	538.6	553.2	553.2	29.4
	S.D.	45.3	49.0	46.0	43.9	48.3	12.5

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Day of recovery 1	4	8	11	14	Gain 1-14
0	No.	5	5	5	5	5	5
	Mean	304.0	299.8	305.0	302.0	303.2	-0.8
	S.D.	20.8	19.7	23.2	24.7	22.3	3.1
1000	No.	5	5	5	5	5	5
	Mean	311.4	304.2	310.2	316.0	314.4	3.0
	S.D.	5.9	10.3	6.9	7.8	12.1	6.5

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, 3-Propanediol, 2-amino-2-ethyl

Food consumption of male rats (Main group)

Dose mg/kg		Pre-mating period					Post-mating period					
		1	4	8	11	15	25	29	32	36	39	42a)
0	No.	12	12	12	12	12	12	12	12	12	12	12
	Mean	29.9	29.1	28.6	34.2	32.8	32.3	33.0	32.7	31.6	32.8	36.1
	S.D.	4.2	4.4	5.1	5.5	2.5	2.6	2.2	3.6	2.1	3.5	3.7
250	No.	12	12	12	12	12	12	12	12	12	12	12
	Mean	28.7	29.6	29.3	32.3	32.3	30.2	32.0	31.3	31.4	30.8	32.3*
	S.D.	4.7	3.8	3.5	3.1	2.6	1.9	2.4	1.6	2.2	3.9	4.4D
500	No.	12	12	12	12	12	12	12	12	12	12	12
	Mean	30.8	28.3	30.5	31.6	33.0	31.7	32.5	32.5	30.9	31.3	33.3
	S.D.	3.7	5.3	4.0	4.3	4.0	3.4	3.5	4.0	3.3	3.8	3.7
1000	No.	12	12	12	12	12	12	12	12	12	12	12
	Mean	30.9	28.1	29.5	32.8	33.3	32.4	32.3	31.8	31.9	32.8	33.5
	S.D.	2.8	2.7	3.6	4.4	2.1	2.5	3.0	2.8	3.0	4.0	1.9

Unit: g/rat/day
No.: No. of animals
a): Day of administration
*: $p<0.05$ (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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Administration 1	4	8	11	15a)
0	No.	12	12	12	12	12
	Mean	20.8	19.0	21.4	22.3	22.1
	S.D.	4.0	2.7	2.4	2.1	1.5
250	No.	12	12	12	12	12
	Mean	21.7	19.7	20.3	22.3	21.6
	S.D.	2.5	2.6	4.2	1.4	3.4
500	No.	12	12	12	12	12
	Mean	18.8	21.0	22.0	20.9	23.1
	S.D.	2.4	2.8	1.9	4.1	3.3
1000	No.	12	12	12	12	12
	Mean	22.1	20.7	21.8	20.3	22.8
	S.D.	2.4	3.5	3.5	4.0	4.1

Unit: g/rat/day
No.: No. of animals
a): Day of administration
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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Administration 1	4	7	11	14	17	20a)
0	No.	12	12	12	12	12	12	12
	Mean	24.7	25.8	28.0	28.7	28.9	29.2	26.8
	S.D.	2.0	2.1	3.3	1.8	2.8	4.1	3.2
250	No.	12	12	12	12	12	12	12
	Mean	23.5	26.0	26.9	28.4	28.1	29.3	27.1
	S.D.	1.8	2.6	3.5	2.7	1.4	2.8	3.6
500	No.	12	12	12	12	12	12	12
	Mean	23.3	27.8	28.9	29.8	29.8	31.0	27.4
	S.D.	3.5	2.9	3.8	3.8	3.3	4.1	3.8
1000	No.	12	12	12	12	12	12	12
	Mean	23.0	28.4*	27.5	30.3	30.3	30.2	27.8
	S.D.	2.5	1.9D	1.7	2.6	2.2	1.6	2.5

Unit: g/rat/day
No.: No. of dams
a): Day of gestation
*: $p<0.05$ (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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Administration 2	4a)
0	No.	12	12
	Mean	32.2	48.6
	S.D.	4.8	4.8
250	No.	12	12
	Mean	32.2	47.3
	S.D.	4.8	5.5
500	No.	12	12
	Mean	31.5	46.5
	S.D.	4.2	5.7
1000	No.	12	12
	Mean	35.2	50.0
	S.D.	4.7	5.7

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Day of administration										
		1	4	8	11	15	25	29	32	36	39	42
0	No.	5	5	5	5	5	5	5	5	5	5	5
	Mean	26.6	29.6	29.0	31.4	31.2	31.0	29.8	30.2	31.4	30.2	31.6
	S.D.	4.0	4.2	3.5	1.3	3.3	2.7	2.3	2.8	3.4	3.3	1.1
1000	No.	5	5	5	5	5	5	5	5	5	5	5
	Mean	27.0	30.2	29.8	33.4	32.8	31.2	32.2	31.8	31.4	33.6	35.2
	S.D.	7.2	5.3	3.3	3.6	1.9	3.3	2.7	5.1	3.0	4.2	3.6

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Day of administration 1	4	8	11	15	25	29	32	36	39	42
0	No.	5	5	5	5	5	5	5	5	5	5	5
	Mean	17.6	19.4	21.8	22.4	21.4	19.0	22.4	23.2	22.0	23.2	26.2
	S.D.	2.5	3.0	5.0	4.8	3.5	1.6	1.9	5.1	3.4	2.5	3.3
1000	No.	5	5	5	5	5	5	5	5	5	5	5
	Mean	19.6	20.8	22.0	21.0	23.8	24.2**	25.0*	24.8	22.8	25.8	25.2
	S.D.	3.3	4.1	2.8	2.4	2.5	1.3T	1.6T	2.2	1.3	1.9	3.7

Unit: g/rat/day
No.: No. of animals
*: $p<0.05$; **: $p<0.01$ (Significant difference from control group)
T: Student's t-test

Table 4-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	5
	Mean	28.4	29.8	29.0	28.2	28.8
	S.D.	2.6	3.7	2.1	3.1	3.3
1000	No.	5	5	5	5	5
	Mean	32.4	32.8	31.2	32.0	30.4
	S.D.	4.3	6.1	3.1	3.9	4.3

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, 3-Propanediol, 2-amino-2-ethyl

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

Dose mg/kg		Day of recovery 1	4	8	11	14
0	No.	5	5	5	5	5
	Mean	22.4	23.6	25.2	20.2	23.2
	S.D.	2.3	5.0	3.6	1.3	4.4
1000	No.	5	5	5	5	5
	Mean	24.4	22.6	23.2	25.4**	24.0
	S.D.	2.7	3.8	4.5	1.1T	3.5

Unit: g/rat/day
No.: No. of animals
**: $p<0.01$ (Significant difference from control group)
T: Student's t-test

Table 5-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	1	0	5	10	1	0	3	13	1	0	0	0	15	2	0	0	0	0	17	0	0	0	0	0
250	12	0	0	0	0	0	0	0	12	0	1	8	3	0	0	0	10	1	1	0	0	0	12	0	0	0	0	0
500	12	0	0	0	0	0	0	0	7	5	0	4	7	1	0	0	5	6	1	0	0	0	12	0	0	0	0	0
1000	17	0	0	0	0	0	0	0	9	8	0	0	13	4	0	0	6	9	2	0	0	0	17	0	0	0	0	0

1) - : <10 mg/dL +- : 10 - 25 mg/dL + : 26 - 85 mg/dL ++ : 86 - 250 mg/dL +++ : 251 - 600 mg/dL ++++ : >600 mg/dL
2) - : <5 mg/dL +- : 5 - 7.5 mg/dL + : 7.6 - 30 mg/dL ++ : 31 - 70 mg/dL +++ : 71 - 125 mg/dL ++++ : >125 mg/dL
3) - : <30 mg/dL +- : 30 - 60 mg/dL + : 61 - 125 mg/dL ++ : 126 - 250 mg/dL +++ : 251 - 750 mg/dL ++++ : >750 mg/dL

Table 5-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	13	2	1	1	0	17	0	0	0	0	17	0	0	0	0	0	17	0
250	12	10	1	1	0	0	12	0	0	0	0	12	0	0	0	0	0	12	0
500	12	11	0	0	1	0	12	0	0	0	0	12	0	0	0	0	0	12	0
1000	17	16	0	1	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, 3-Propanediol, 2-amino-2-ethyl

Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	17	13	3	1	0	0	17	0	0	0	0	0	17	0	0	0	16	1	0	0	0	17	0	0	3	6	7	1	0	17	0	0	0	0
250	12	9	3	0	0	0	12	0	0	0	0	0	12	0	0	0	12	0	0	0	0	12	0	0	0	7	5	0	0	12	0	0	0	0
500	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	12	0	0	0	0	12	0	0	0	6	6	0	0	12	0	0	0	0
1000	17	17	0	0	0	0	17	0	0	0	0	0	17	0	0	0	15	2	0	0	0	17	0	0	0	12	3	2	0	17	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Water intake and urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
0	17	Mean	51	20.6	1923
		S.D.	14	6.3	368
250	12	Mean	44	18.3	2090
		S.D.	7	3.4	153
500	12	Mean	45	17.4	2106
		S.D.	8	5.1	241
1000	17	Mean	49	20.7	2035
		S.D.	8	3.7	230

No.: No. of animals
No significant difference in any treated groups from control group.

Table 5-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	0	1	1	3	0	0	2	3	0	0	0	2	0	3	0	0	0	5	0	0	0	0	0
1000	5	0	0	0	0	0	2	2	1	0	1	3	1	0	0	0	3	1	1	0	0	0	5	0	0	0	0	0

1) - : <10 mg/dL +- : 10 - 25 mg/dL + : 26 - 85 mg/dL ++ : 86 - 250 mg/dL +++ : 251 - 600 mg/dL ++++ : >600 mg/dL
2) - : <5 mg/dL +- : 5 - 7.5 mg/dL + : 7.6 - 30 mg/dL ++ : 31 - 70 mg/dL +++ : 71 - 125 mg/dL ++++ : >125 mg/dL
3) - : <30 mg/dL +- : 30 - 60 mg/dL + : 61 - 125 mg/dL ++ : 126 - 250 mg/dL +++ : 251 - 750 mg/dL ++++ : >750 mg/dL

Table 5-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	4	0	1	0	0	5	0	0	0	0	4	1	0	0	0	0	5	0
1000	5	4	1	0	0	0	5	0	0	0	0	5	0	0	0	0	0	5	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 5-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	3	2	0	0	5	0	0	0	0
1000	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	1	3	1	0	0	5	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Water intake and urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
0	5	Mean	48	13.4	1854
		S.D.	18	7.4	644
1000	5	Mean	52	10.8	1877
		S.D.	9	4.3	358

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

Hematology of male rats (Week 6 of administration)

Dose mg/kg	No.		RBC $\times10^4/\mu L$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC %	Reticulocyte %	Platelet $\times10^4/\mu L$	PT s	APTT s	Fibrinogen mg/dL
0	5	Mean	826	15.6	45	54.9	18.9	34.4	1.9	103.5	12.9	17.5	325
		S.D.	25	0.5	2	0.7	0.5	0.7	0.2	7.2	0.8	1.5	14
250	5	Mean	847	16.0	47	55.0	18.8	34.2	1.8	103.8	12.9	18.9	319
		S.D.	40	0.5	2	1.4	0.4	0.6	0.4	9.2	0.2	0.9	14
500	5	Mean	839	15.6	45	54.0	18.6	34.4	1.7	113.1	13.1	18.6	306
		S.D.	25	0.9	3	2.2	0.7	0.4	0.4	12.8	0.7	0.7	19
1000	5	Mean	807	14.9	43	53.8	18.5	34.4	2.4	115.8	12.3	17.9	336
		S.D.	24	0.7	2	1.2	0.5	0.5	0.3	10.3	0.3	0.6	51

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

Hematology of male rats (Week 6 of administration)

Dose mg/kg	No.		WBC	Differential leukocyte counts (%)							Erythroblast counts
			X10²/μL	Lymph.	Stab	Seg.	Eosino.	Baso.	Mono.	Others	(/200 leukocyte)
0	5	Mean	83	85.9	0.4	11.9	1.3	0.0	0.5	0.0	0
		S.D.	12	5.2	0.4	5.8	1.0	0.0	0.5	0.0	0
250	5	Mean	86	86.4	0.1	12.7	0.7	0.0	0.1	0.0	0
		S.D.	13	5.1	0.2	4.6	0.6	0.0	0.2	0.0	0
500	5	Mean	91	85.6	0.2	13.4	0.7	0.0	0.1	0.0	0
		S.D.	23	5.3	0.3	4.7	0.6	0.0	0.2	0.0	0
1000	5	Mean	106	83.4	0.2	15.8	0.2*	0.0	0.4	0.0	0
		S.D.	17	6.9	0.3	6.7	0.3D	0.0	0.2	0.0	0

No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 6-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Hematology of female rats (Day 4 of lactation)

Dose mg/kg	No.		RBC X10⁴/μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC %	Reticulocyte %	Platelet X10⁴/μL	PT s	APTT s	Fibrinogen mg/dL
0	5	Mean	694	14.1	41	58.7	20.4	34.8	4.7	126.4	12.6	17.6	362
		S.D.	10	0.4	2	1.4	0.4	0.7	1.4	8.9	0.3	3.0	43
250	5	Mean	689	13.8	40	58.6	20.1	34.3	4.9	140.9	12.6	16.1	334
		S.D.	65	0.8	2	2.4	0.9	0.4	2.3	19.8	0.3	0.5	83
500	5	Mean	717	14.4	42	58.0	20.0	34.6	3.9	128.3	13.0	16.1	359
		S.D.	31	0.4	1	2.1	0.6	0.5	0.7	9.3	0.3	1.3	78
1000	5	Mean	673	13.7	40	59.6	20.4	34.2	5.1	125.0	12.5	15.0	382
		S.D.	31	0.6	2	0.9	0.3	0.3	1.2	15.5	0.6	1.4	70

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

Hematology of female rats (Day 4 of lactation)

Dose mg/kg	No.		WBC	Differential leukocyte counts (%)							Erythroblast counts
			X10²/μL	Lymph.	Stab	Seg.	Eosino.	Baso.	Mono.	Others	(/200 leukocyte)
0	5	Mean	100	68.9	0.0	30.1	0.7	0.0	0.3	0.0	0
		S.D.	34	8.2	0.0	8.4	0.4	0.0	0.4	0.0	0
250	5	Mean	98	78.1	0.2	20.7	0.5	0.0	0.5	0.0	0
		S.D.	26	7.4	0.3	7.6	0.5	0.0	0.5	0.0	0
500	5	Mean	130	80.6*	0.5	18.3*	0.2	0.0	0.4	0.0	0
		S.D.	25	4.3D	0.6	4.9D	0.3	0.0	0.2	0.0	0
1000	5	Mean	132	71.8	0.2	26.7	0.5	0.0	0.8	0.0	0
		S.D.	41	3.4	0.3	3.4	0.5	0.0	0.4	0.0	0

No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 6-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Hematology of male rats (Day 14 of recovery)

Dose mg/kg	No.		RBC $\times10^4/\mu L$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC %	Reticulocyte %	Platelet $\times10^4/\mu L$	PT s	APTT s	Fibrinogen mg/dL
0	5	Mean	875	16.2	47	53.6	18.5	34.5	1.7	101.9	13.7	19.5	293
		S.D.	31	0.4	2	1.3	0.4	0.4	0.4	13.0	0.2	1.4	30
1000	5	Mean	830*	15.3*	44*	53.3	18.5	34.6	1.8	114.2	13.2	17.5	305
		S.D.	24T	0.4T	1T	0.9	0.4	0.3	0.4	12.1	0.8	2.0	48

No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
T: Student's t-test

Table 6-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Hematology of male rats (Day 14 of recovery)

Dose mg/kg	No.		WBC $\times 10^2/\mu L$	Differential leukocyte counts (%)							Erythroblast counts (/200 leukocyte)
				Lymph.	Stab	Seg.	Eosino.	Baso.	Mono.	Others	
0	5	Mean	107	86.9	0.2	11.5	0.9	0.0	0.5	0.0	0
		S.D.	28	4.3	0.3	4.5	1.0	0.0	0.4	0.0	0
1000	5	Mean	105	85.6	0.1	12.5	1.2	0.0	0.6	0.0	0
		S.D.	22	3.8	0.2	4.3	1.0	0.0	0.4	0.0	0

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

Hematology of female rats (Day 14 of recovery)

Dose mg/kg	No.		RBC X10⁴/μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC %	Reticulocyte %	Platelet X10⁴/μL	PT s	APTT s	Fibrinogen mg/dL
0	5	Mean	800	15.6	45	56.2	19.5	34.7	1.9	104.7	12.2	15.3	231
		S.D.	27	0.8	3	2.7	0.8	0.5	0.2	11.7	0.3	1.9	26
1000	5	Mean	817	15.8	46	56.1	19.4	34.6	1.6*	112.2	12.3	15.2	224
		S.D.	25	0.6	2	0.9	0.4	0.4	0.1T	5.2	0.2	1.8	25

No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
T: Student's t-test

Table 6-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Hematology of female rats (Day 14 of recovery)

Dose mg/kg	No.		WBC $X10^2/\mu L$	Differential leukocyte counts (%)							Erythroblast counts (/200 leukocyte)
				Lymph.	Stab	Seg.	Eosino.	Baso.	Mono.	Others	
0	5	Mean	55	81.4	0.1	16.8	1.2	0.0	0.5	0.0	0
		S.D.	7	8.3	0.2	7.6	1.4	0.0	0.5	0.0	0
1000	5	Mean	52	83.3	0.4	14.3	1.7	0.0	0.3	0.0	0
		S.D.	11	5.2	0.4	4.5	0.8	0.0	0.4	0.0	0

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

Blood chemistry of male rats (Week 6 of administration)

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	γ-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	80	36	50	1	415	54	21	84	0.1	147
		S.D.	10	8	11	0	74	16	13	24	0.1	22
250	5	Mean	78	35	47	1	470	50	32	84	0.1	149
		S.D.	10	6	5	0	85	9	12	12	0.0	21
500	5	Mean	75	35	54	1	514	49	30	81	0.0	154
		S.D.	9	4	16	1	31	8	9	4	0.1	29
1000	5	Mean	73	31	50	1	428	55	49*	90	0.1	156
		S.D.	9	2	12	1	57	12	27D	14	0.1	12

No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 7-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Blood chemistry of male rats (Week 6 of administration)

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	0.29	146	4.8	108	9.7	6.9	6.4	2.7	0.73
		S.D.	2	0.03	1	0.2	1	0.1	0.3	0.1	0.1	0.03
250	5	Mean	15	0.30	145	4.7	108	9.8	6.9	6.3	2.8	0.80*
		S.D.	2	0.03	1	0.2	2	0.1	0.4	0.2	0.1	0.03D
500	5	Mean	17	0.32	144	5.0	108	9.7	7.3	6.1	2.7	0.80*
		S.D.	1	0.03	2	0.1	2	0.2	0.4	0.3	0.1	0.05D
1000	5	Mean	18*	0.29	144	4.6	105*	9.9	7.2	6.2	2.7	0.80**
		S.D.	1D	0.03	1	0.3	1D	0.4	0.5	0.4	0.2	0.03D

No.: No. of animals
*: $p<0.05$; **: $p<0.01$ (Significant difference from control group)
D: Dunnett's test

Table 7-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Blood chemistry of female rats (Day 4 of lactation)

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	γ-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	83	54	57	1	320	60	34	113	0.1	144
		S.D.	12	6	10	1	148	10	34	7	0.1	16
250	5	Mean	80	48	73	1	359	57	44	111	0.1	135
		S.D.	5	5	24	0	168	19	29	32	0.1	11
500	5	Mean	87	47	47	1	335	52	31	104	0.1	127
		S.D.	26	13	12	0	114	2	17	13	0.1	8
1000	5	Mean	85	51	59	1*	357	63	31	121	0.1	132
		S.D.	13	10	11	1DT	101	12	5	16	0.0	4

No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
DT: Dunnett-type rank test

Table 7-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Blood chemistry of female rats (Day 4 of lactation)

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	0.32	143	4.8	110	9.9	7.5	6.6	3.0	0.83
		S.D.	3	0.03	1	0.3	1	0.2	0.6	0.3	0.1	0.04
250	5	Mean	17	0.30	142	4.9	108	10.2	7.6	6.5	2.9	0.82
		S.D.	2	0.04	2	0.4	2	0.6	1.5	0.2	0.2	0.04
500	5	Mean	18	0.30	141	4.8	109	10.0	8.1	6.3	2.8	0.80
		S.D.	4	0.03	1	0.4	1	0.3	0.6	0.3	0.1	0.02
1000	5	Mean	20	0.31	141	4.8	108	10.3	8.2	6.4	2.8	0.81
		S.D.	2	0.05	1	0.2	2	0.3	1.0	0.2	0.1	0.03

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

Blood chemistry of male rats (Day 14 of recovery)

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	γ-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	69	32	43	1	354	44	26	74	0.0	149
		S.D.	6	5	10	1	88	8	7	11	0.0	17
1000	5	Mean	77	33	50	2	382	50	40	85	0.1	148
		S.D.	10	6	12	1	84	12	16	16	0.1	19

No.: No. of animals
No significant difference between treated group and control group.

Table 7-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Blood chemistry of male rats (Day 14 of recovery)

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	0.32	144	4.5	107	9.6	6.9	6.0	2.7	0.82
		S.D.	2	0.03	2	0.4	2	0.3	0.5	0.5	0.2	0.02
1000	5	Mean	15	0.32	144	4.6	105	9.8	7.1	6.0	2.7	0.81
		S.D.	2	0.05	1	0.1	1	0.2	0.4	0.3	0.2	0.03

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

Blood chemistry of female rats (Day 14 of recovery)

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	γ-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	160	71	105	2	218	77	12	134	0.1	142
		S.D.	169	55	121	1	70	19	4	23	0.1	12
1000	5	Mean	106	58	70	1	182	63	10	120	0.1	136
		S.D.	36	18	30	0	43	11	3	17	0.0	15

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

Blood chemistry of female rats (Day 14 of recovery)

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	0.32	142	4.3	111	9.7	5.4	6.7	3.0	0.83
		S.D.	5	0.04	1	0.2	1	0.2	0.9	0.4	0.1	0.03
1000	5	Mean	19	0.34	142	4.3	110	9.9	5.7	6.9	3.1	0.83
		S.D.	2	0.03	0	0.3	1	0.2	0.5	0.3	0.1	0.03

No.: No. of animals
No significant difference between treated group and control group.

Table 8-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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)
Absolute	0	No.	12	5	5	5	5	5
		Mean	494	2.14	24.9	370	1.42	12.62
		S.D.	28	0.13	4.2	58	0.15	1.50
	250	No.	12	5	5	5	5	5
		Mean	485	2.05	22.5	302	1.38	13.01
		S.D.	32	0.09	4.1	49	0.10	1.06
	500	No.	12	5	5	5	5	5
		Mean	488	2.09	24.9	341	1.37	12.14
		S.D.	39	0.04	1.4	49	0.09	1.05
	1000	No.	12	5	5	5	5	5
		Mean	502	2.10	29.5	391	1.41	14.38
		S.D.	29	0.04	5.2	79	0.09	1.40
Relative	0	No.		5	5	5	5	5
		Mean		0.43	4.9	74	0.28	2.51
		S.D.		0.03	0.7	12	0.01	0.23
	250	No.		5	5	5	5	5
		Mean		0.42	4.6	62	0.28	2.67
		S.D.		0.03	0.8	11	0.02	0.12
	500	No.		5	5	5	5	5
		Mean		0.45	5.3	73	0.29	2.60
		S.D.		0.03	0.4	6	0.02	0.15
	1000	No.		5	5	5	5	5
		Mean		0.41	5.7	75	0.27	2.78
		S.D.		0.03	0.9	11	0.02	0.19

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

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)	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)
Absolute	0	No.	5	5	5	12	12
		Mean	0.80	3.50	67	3.37	1246
		S.D.	0.13	0.48	13	0.26	112
	250	No.	5	5	5	12	12
		Mean	0.75	3.31	64	3.33	1231
		S.D.	0.12	0.21	6	0.38	105
	500	No.	5	5	5	12	12
		Mean	0.75	3.18	64	3.36	1246
		S.D.	0.10	0.16	13	0.30	134
	1000	No.	5	5	5	12	12
		Mean	0.82	3.60	74	3.25	1250
		S.D.	0.09	0.34	8	0.28	99
Relative	0	No.	5	5	5	12	12
		Mean	0.16	0.69	13	0.68	253
		S.D.	0.03	0.06	2	0.06	28
	250	No.	5	5	5	12	12
		Mean	0.15	0.68	13	0.69	254
		S.D.	0.02	0.03	1	0.07	20
	500	No.	5	5	5	12	12
		Mean	0.16	0.68	14	0.69	257
		S.D.	0.03	0.05	3	0.06	33
	1000	No.	5	5	5	12	12
		Mean	0.16	0.70	14	0.65	250
		S.D.	0.02	0.04	2	0.07	25

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

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)
Absolute	0	No.	5	5	5	5	5	5
		Mean	299	1.93	20.9	301	0.99	9.70
		S.D.	16	0.08	1.8	74	0.05	1.09
	250	No.	5	5	5	5	5	5
		Mean	305	1.94	19.6	262	0.97	10.25
		S.D.	11	0.04	1.5	72	0.09	1.06
	500	No.	5	5	5	5	5	5
		Mean	306	1.91	22.4	262	1.01	10.06
		S.D.	17	0.05	6.1	56	0.05	0.73
	1000	No.	5	5	5	5	5	5
		Mean	317	1.96	20.0	333	1.06	10.72
		S.D.	10	0.06	2.1	103	0.12	0.58
Relative	0	No.		5	5	5	5	5
		Mean		0.65	7.0	100	0.33	3.23
		S.D.		0.02	0.3	22	0.01	0.20
	250	No.		5	5	5	5	5
		Mean		0.64	6.4	86	0.32	3.36
		S.D.		0.03	0.6	25	0.04	0.29
	500	No.		5	5	5	5	5
		Mean		0.62	7.3	86	0.33	3.30
		S.D.		0.03	1.7	17	0.01	0.28
	1000	No.		5	5	5	5	5
		Mean		0.62	6.3	105	0.33	3.38
		S.D.		0.02	0.8	33	0.03	0.16

No.: No. of animals
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, 3-Propanediol, 2-amino-2-ethyl

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	0.60	2.00	87
		S.D.	0.05	0.12	7
	250	No.	5	5	5
		Mean	0.62	2.18	89
		S.D.	0.13	0.04	10
	500	No.	5	5	5
		Mean	0.73	2.33*	99
		S.D.	0.07	0.21D	10
	1000	No.	5	5	5
		Mean	0.65	2.36*	101
		S.D.	0.03	0.32D	15
Relative	0	No.	5	5	5
		Mean	0.20	0.67	29
		S.D.	0.01	0.04	2
	250	No.	5	5	5
		Mean	0.20	0.72	29
		S.D.	0.05	0.02	4
	500	No.	5	5	5
		Mean	0.23*	0.76	33
		S.D.	0.01DT	0.08	3
	1000	No.	5	5	5
		Mean	0.21	0.74	32
		S.D.	0.01	0.08	4

No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test
DT: Dunnett-type rank test

Table 8-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Organ weight of male 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	499	2.16	24.5	319	1.47	12.28
			S.D.	33	0.10	5.3	128	0.16	1.19
	1000	5	Mean	516	2.09	26.7	406	1.43	13.11
			S.D.	45	0.11	3.5	114	0.15	1.61
Relative	0	5	Mean		0.44	4.9	63	0.29	2.46
			S.D.		0.03	0.8	21	0.03	0.18
	1000	5	Mean		0.41	5.2	78	0.28	2.53
			S.D.		0.03	0.5	19	0.02	0.16

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, 3-Propanediol, 2-amino-2-ethyl

Organ weight of male rats (Recovery group)

	Dose mg/kg	No. of animals		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)
Absolute	0	5	Mean	0.85	3.25	63	3.44	1351
			S.D.	0.14	0.26	5	0.28	118
	1000	5	Mean	0.85	3.29	68	3.30	1395
			S.D.	0.15	0.18	9	0.45	103
Relative	0	5	Mean	0.17	0.65	13	0.69	271
			S.D.	0.03	0.06	1	0.05	15
	1000	5	Mean	0.16	0.64	13	0.65	272
			S.D.	0.02	0.04	2	0.13	37

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, 3-Propanediol, 2-amino-2-ethyl

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	281	1.95	15.9	329	0.95	7.95
			S.D.	22	0.05	1.8	51	0.07	0.49
	1000	5	Mean	294	2.01	20.4*	360	0.95	7.75
			S.D.	8	0.05	3.1T	50	0.07	0.42
Relative	0	5	Mean		0.70	5.7	117	0.34	2.83
			S.D.		0.06	0.4	15	0.02	0.17
	1000	5	Mean		0.69	6.9	122	0.32	2.64
			S.D.		0.04	1.2	15	0.02	0.15

*: $p<0.05$ (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, 3-Propanediol, 2-amino-2-ethyl

Organ weight of female rats (Recovery group)

	Dose mg/kg	No. of animals		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)
Absolute	0	5	Mean	0.53	2.09	76
			S.D.	0.09	0.20	11
	1000	5	Mean	0.48	2.09	76
			S.D.	0.09	0.10	7
Relative	0	5	Mean	0.19	0.74	27
			S.D.	0.03	0.06	3
	1000	5	Mean	0.16	0.71	26
			S.D.	0.03	0.05	2

No significant difference between treated group and control group.

Table 9 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Gross pathological findings (Main group)

Organs	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	250	500	1000	0	250	500	1000
Findings	Number:	12	12	12	12	12	12	12	12
Stomach									
Focus,dark red		0	0	0	0	0	0	2	0
Testis									
Small		0	1	0	0	-	-	-	-

No lesions were noted in recovery group.

Table 10-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Histopathological findings (Main group)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	M 0 5	M 250 5	M 500 5	M 1000 5	F 0 5	F 250 5	F 500 5	F 1000 5
Epididymis									
Number examined		5	0	0	5	-	-	-	-
Cell debris,duct		0	0	0	1	-	-	-	-
slight		0	0	0	1	-	-	-	-
Femur + marrow									
Number examined		5	0	0	5	5	0	0	5
Fibrosis,marrow		0	0	0	0	1	0	0	1
slight		0	0	0	0	1	0	0	1
Heart									
Number examined		5	0	0	5	5	0	0	5
Myocarditis,focal		2	0	0	0	0	0	0	0
slight		2	0	0	0	0	0	0	0
Kidney									
Number examined		5	0	0	5	5	0	0	5
Basophilia,tubular		3	0	0	1	0	0	0	0
slight		3	0	0	1	0	0	0	0
Eosinophilic body,tubular cell		1	0	0	2	0	0	0	0
slight		0	0	0	2	0	0	0	0
mild		1	0	0	0	0	0	0	0
Liver									
Number examined		5	0	0	5	5	0	0	5
Vacuolation,hepatocyte,periportal		3	0	0	5	2	0	0	3
slight		3	0	0	4	2	0	0	3
mild		0	0	0	1	0	0	0	0
Hematopoiesis,extramedullary		0	0	0	0	1	0	0	3
slight		0	0	0	0	1	0	0	3
Microgranuloma		4	0	0	3	4	0	0	3
slight		4	0	0	3	4	0	0	3
Lung(bronchus)									
Number examined		5	0	0	5	5	0	0	5
Accumulation,foam cell		1	0	0	0	1	0	0	1
slight		1	0	0	0	1	0	0	1
Pituitary									
Number examined		5	0	0	5	5	0	0	5
Pseudocyst,intermediate		1	0	0	0	0	0	0	0
present		1	0	0	0	0	0	0	0
Spleen									
Number examined		5	0	0	5	5	0	0	5
Hematopoiesis,extramedullary		5	0	0	5	5	0	0	5
slight		5	0	0	4	1	0	0	0
mild		0	0	0	1	4	0	0	5
Stomach									
Number examined		5	5	5	5	5	5	5	5
Cell infiltration		0	0	0	3	0	0	0	0
slight		0	0	0	2	0	0	0	0
mild		0	0	0	1	0	0	0	0
Erosion,glandular stomach		0	0	0	3	0	2	2	1
slight		0	0	0	2	0	2	2	1
mild		0	0	0	1	0	0	0	0
Increased number,globule leukocyte		1	0	2	4	0	0	0	1
slight		0	0	2	2	0	0	0	1
mild		1	0	0	2	0	0	0	0
Thickening,mucosa,glandular stomach		0	0	0	3	0	0	0	0
slight		0	0	0	2	0	0	0	0
mild		0	0	0	1	0	0	0	0
Thickening,limiting ridge		1	0	2	5	0	0	0	0
slight		1	0	2	0	0	0	0	0
mild		0	0	0	5	0	0	0	0

Table 10-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Histopathological findings (Main group)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	250	500	1000	0	250	500	1000
	Number:	5	5	5	5	5	5	5	5
Sternum + marrow									
Number examined		5	0	0	5	5	0	0	5
Fibrosis,marrow		0	0	0	0	1	0	0	0
slight		0	0	0	0	1	0	0	0
Testis									
Number examined		5	0	0	5	-	-	-	-
Atrophy,seminiferous tubular		0	0	0	1	-	-	-	-
mild		0	0	0	1	-	-	-	-
Urinary bladder									
Number examined		5	0	0	5	5	0	0	5
Hyperplasia,mucosal		0	0	0	0	0	0	0	1
slight		0	0	0	0	0	0	0	1

Table 10-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Histopathological findings (Recovery group)

Organs	Sex:	M	M	F	F
	Dose(mg/kg):	0	1000	0	1000
Findings	Number:	5	5	5	5
Stomach					
Number examined		5	5	5	5
Erosion,glandular stomach		0	0	1	0
slight		0	0	1	0
Increased number,globule leukocyte		0	3	0	1
slight		0	3	0	1
Thickening,limiting ridge		0	5	0	0
slight		0	5	0	0

Table 11 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	5	7	3.6±0.5	4.1±0.3
250	12	0	0	0	5	7	3.6±0.5	4.3±0.4
500	12	0	0	0	1	11	3.9±0.3	4.1±0.1
1000	12	0	0	0	4	8	3.7±0.5	4.1±0.3

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, 3-Propanediol, 2-amino-2-ethyl

Mating and fertility of animals (Main group)

	Male				Female			
Dose mg/kg	No. of males	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±1.7	12/12(100.0)	12/12(100.0)	12	2.7±1.7	12/12(100.0)	12/12(100.0)
250	12	2.6±1.2	12/12(100.0)	12/12(100.0)	12	2.6±1.2	12/12(100.0)	12/12(100.0)
500	12	2.4±0.9	12/12(100.0)	12/12(100.0)	12	2.4±0.9	12/12(100.0)	12/12(100.0)
1000	12	2.8±1.1	12/12(100.0)	12/12(100.0)	12	2.8±1.1	12/12(100.0)	12/12(100.0)

a): (No. of copulated animals / No. of mated animals) X 100
b): (No. of males which inseminated females / No. of copulated males) X 100
c): (No. of pregnant animals / No. of copulated females) X 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, 3-Propanediol, 2-amino-2-ethyl

Delivery data on dams

Dose mg/kg		No. of pregnant females	No. of females with liveborn	Delivery index % a)	Gestation period	No. of corpora lutea	No. of implantations	Implantation index % b)	No. of stillborn (%)c)	No. of liveborn	Live birth index % d)
0	Total	12	12	100.0		207	192		3	183	
	Mean				22.0	17.3	16.0	92.9	(1.5)	15.3	98.5
	S.D.				0.4	1.5	1.5	5.4	(3.8)	1.3	3.8
250	Total	12	12	100.0		200	188		1	171	
	Mean				22.3	16.7	15.7	94.0	(0.6)	14.3	99.4
	S.D.				0.3	2.1	2.2	5.1	(1.9)	3.0	1.9
500	Total	12	12	100.0		209	199		2	178	
	Mean				22.1	17.4	16.6	95.1	(1.0)	14.8	99.0
	S.D.				0.3	1.5	1.9	5.1	(2.4)	2.9	2.4
1000	Total	12	12	100.0		201	193		2	182	
	Mean				22.2	16.8	16.1	96.4	(1.1)	15.2	98.9
	S.D.				0.4	2.2	1.8	5.9	(2.7)	1.7	2.7

a): (No. of females which delivered live pups / No. of pregnant females) X 100
b): (No. of implantations / No. of corpora lutea) X 100
c): (No. of stillborn pups / No. of stillborn and liveborn pups) X 100
d): (No. of liveborn pups / No. of stillborn and liveborn pups) X 100
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, 3-Propanediol, 2-amino-2-ethyl

External examination of liveborn pups

Dose mg/kg	No. of dams		No. of males	No. of females	Sex ratio a)	Body weight(g) Male	Body weight(g) Female	External b) abnormalities(%)c)
		Total	106	77	0.58			0
0	12	Mean	8.8	6.4		6.4	6.2	(0.0)
		S.D.	1.9	2.0		0.5	0.4	(0.0)
		Total	92	79	0.54			0
250	12	Mean	7.7	6.6		6.9*	6.5	(0.0)
		S.D.	3.0	2.8		0.5D	0.5	(0.0)
		Total	78	100	0.44*C			0
500	12	Mean	6.5	8.3		6.7	6.3	(0.0)
		S.D.	2.0	2.8		0.5	0.4	(0.0)
		Total	101	81	0.55			1d)
1000	12	Mean	8.4	6.8		6.7	6.3	(0.5)
		S.D.	2.0	1.9		0.4	0.4	(1.7)

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) X 100
d): Vestigial tail
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test
C: Chi-square test

Table 15 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

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	183	179	
	Mean		15.3	14.9	97.9
	S.D.		1.3	1.2	3.1
250	Total	12	171	165	
	Mean		14.3	13.8	97.0
	S.D.		3.0	2.6	4.8
500	Total	12	178	174	
	Mean		14.8	14.5	98.1
	S.D.		2.9	2.6	2.9
1000	Total	12	182	178	
	Mean		15.2	14.8	98.0
	S.D.		1.7	1.6	5.3

a): (No. of live pups on day 4 / No. of liveborn pups on day 0) X 100
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, 3-Propanediol, 2-amino-2-ethyl

Body weight of pups

Dose mg/kg		Male		Female	
		0	4	0	4a)
0	No.	12	12	12	12
	Mean	6.4	9.8	6.2	9.5
	S.D.	0.5	0.8	0.4	1.0
250	No.	12	12	12	12
	Mean	6.9*	10.9	6.5	10.2
	S.D.	0.5D	1.5	0.5	1.4
500	No.	12	12	12	12
	Mean	6.7	10.1	6.3	9.7
	S.D.	0.5	1.2	0.4	1.2
1000	No.	12	12	12	12
	Mean	6.7	10.1	6.3	9.5
	S.D.	0.4	1.0	0.4	1.2

Unit: g
No.: No. of dams
a): Day after birth
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 17 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 1, 3-Propanediol, 2-amino-2-ethyl

Gross pathological findings in pups on day 4 after birth

Dose (mg/kg)	0	250	500	1000
Male				
No. of pups examined	104	89	78	99
No. of pups with abnormal findings	0	0	0	0
Female				
No. of pups examined	75	76	96	79
No. of pups with abnormal findings	0	0	0	0