

R-958



## 最 終 報 告 書

試験名 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate 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

試験番号 : R-958

報告日 : 2009年5月29日

### 試験施設

株式会社ボゾリサーチセンター 御殿場研究所  
〒412-0039 静岡県御殿場市かまど 1284

### 試験委託者

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本資料は原本から複写したものに相違ありません。

株式会社 ボゾリサーチセンター

試験責任者 :

日付 : 2009年5月29日

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## 2. 試験実施概要

### 2.1 試験計画書

試験番号 : R-958  
試験表題 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
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

### 2.2 試験目的

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate を、雄には交配前 14 日間及び交配期間を通して剖検前日まで、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 日まで投与し、反復投与による一般毒性学的な影響を検索するとともに、雌雄動物の性腺機能、交尾行動、受胎及び分娩などの生殖発生に及ぼす影響を明らかにした。更に、一部の個体については 14 日間の回復期間を設け、毒性変化の可逆性を検討した。なお、本試験は株式会社ボゾリサーチセンター動物実験委員会の承認を受けて実施した。

### 2.3 試験委託者

厚生労働省医薬食品局審査管理課 化学物質安全対策室  
〒100-8916 東京都千代田区霞が関 1-2-2

### 2.4 試験受託者

株式会社ボゾリサーチセンター  
〒151-0065 東京都渋谷区大山町 36-7  
(旧住所: 〒156-0042 東京都世田谷区羽根木 1-3-11)

### 2.5 試験実施施設

株式会社ボゾリサーチセンター 御殿場研究所  
運営管理者: [REDACTED]

#### 2.5.1 動物試験

御殿場研究所  
〒412-0039 静岡県御殿場市かまど 1284

#### 2.5.2 病理標本観察

函南研究所  
〒419-0101 静岡県田方郡函南町桑原三本松 1308

## 2.6 被驗物質

供給者 : 厚生労働省医薬食品局審査管理課  
              化学物質安全対策室

名称 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate (CAS 番号 : 3012-65-5)

受領日 : 2006 年 9 月 29 日

保存場所 : 御殿場研究所 被験物質保存室及び第 1 研究棟  
              被験物質調製室

## 2.7 試験日程

試験開始日 : 2007年 1月 11日  
 動物入荷日 : 2007年 1月 15日  
 実験開始日 (投与開始日) : 2007年 1月 30日  
 交配開始日 : 2007年 2月 13日  
 分娩開始日 : 2007年 3月 7日  
 雄動物剖検日 : 2007年 3月 13日  
 回復開始日 : 2007年 3月 13日  
 雌動物剖検開始日 : 2007年 3月 12日  
 実験完了日 (動物試験終了日) : 2007年 3月 27日  
 試験終了日 : 2009年 5月 29日

## 2.8 試驗責任者

株式会社ボゾリサーチセンター 御殿場研究所 研究部  
池 谷 政 道 (2009年1月25日まで)  
石 田 茂 (2009年1月26日より)

## 2.9 試験担当者

動物試験担当者 : [REDACTED]  
臨床検査責任者 : [REDACTED]  
病理検査責任者 : [REDACTED]  
化学分析責任者 : [REDACTED]  
統計解析責任者 : [REDACTED] (2007年10月17日まで)  
[REDACTED] (2007年10月18日より)

## 2.10 試験成績の信頼性に影響を及ぼしたと思われる環境要因

本試験に関して、試験成績の信頼性に影響を及ぼしたと思われる環境要因はなかつた。なお、試験計画書に従わなかつたことは以下のとおりである。

- 1) 試験計画書における投与開始時の体重範囲は雄で 310~400 g、雌で 200~260 g と予想していたが、実際には予想体重範囲の上限を下記の雄 25 匹及び雌 5 匹が上回り、雄で 371~439 g、雌で 219~273 g となった。しかし、各群の平均体重がほぼ等しいことから、試験成績への影響はない判断した。

予想体重範囲の上限を上回った個体

雄： 1001 (405 g)、1007 (404 g)、1008 (439 g)、1009 (404 g)、1010 (418 g)、  
1013 (422 g)、1015 (405 g)、2004 (430 g)、2005 (405 g)、2006 (423 g)、  
2008 (410 g)、2011 (405 g)、3001 (407 g)、3004 (405 g)、3005 (405 g)、  
3008 (402 g)、3010 (430 g)、4002 (412 g)、4005 (415 g)、4006 (413 g)、  
4009 (427 g)、4010 (406 g)、4012 (404 g)、4016 (410 g)、4017 (435 g)  
雌： 1110 (272 g)、1114 (262 g)、4102 (273 g)、4110 (263 g)、4117 (266 g)

- 2) 試験計画書の「投与方法」の項

分娩後の投与液量は、試験計画書の記載「妊娠 7 日以降については妊娠 7 日の体重を基準に算出する。」に従わず、最新の体重を基準に算出し、投与した。試験計画書の明らかな記載モレに気づかなかつた事によるものであるが、結果としては通常の試験で用いられていることであり、試験成績に及ぼす影響はない判断する。

## 2.11 資料保存

株式会社ボゾリサーチセンターの保存方法に従い、試験計画書（試験計画書変更書を含む）原本、記録文書、生データ、報告書類（最終報告書は原本）及び標本（被験物質保存サンプルを含む）は株式会社ボゾリサーチセンター御殿場研究所の資料保存施設に最終報告書提出後 10 年間保存する。期間終了後の保存については、厚生労働省医薬食品局審査管理課 化学物質安全対策室と株式会社ボゾリサーチセンター間で協議し、その処置を決定する。ただし、長期保存に耐えられない生体試料（尿、血漿、血清）については、試験終了時に廃棄した。

## 2.12 試験責任者の記名・なつ印

2009 年 5 月 29 日

3. 試験従事者一覧

検疫・馴化 : [REDACTED]

群構成 : [REDACTED]

被験液の調製 : [REDACTED]

投与 : [REDACTED]

( 被験液の分析 : [REDACTED]

一般状態の観察 : [REDACTED]

詳細な一般状態の観察、機能検査、握力・自発運動量の測定

: [REDACTED]

体重・摂餌量測定 : [REDACTED]

( 膣垢検査・交配 : [REDACTED]

分娩及び授乳観察 : [REDACTED]

出生児の剖検（生後 4 日）

: [REDACTED]

尿検査（含、摂水量測定）

: [REDACTED]

採血、血液学・血液化学検査

: [REDACTED]

R-958

最終体重 :

剖検、器官重量測定 :

病理組織学検査 :

統計解析 :

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#### 4. 要約

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate の 0 (対照群: 注射用水)、100、300 及び 1000 mg/kg を、Sprague-Dawley 系 SPF ラットの雄には交配前 14 日間及び交配期間を通して剖検前日 (42 日間) まで、雌には交配前 14 日間及び交配期間並びに妊娠期間を通して授乳 4 日まで (41~47 日間) 投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0 及び 1000 mg/kg 投与群については 42 日間投与した後、14 日間の回復期間を設け、毒性変化の可逆性を検討した。

##### 1) 反復投与毒性

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

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

##### 2) 生殖発生毒性

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

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

これらの結果から、diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate の反復投与毒性に対する無影響量は雌雄とともに 300 mg/kg/day、生殖発生毒性に対しては雌雄親動物及び児動物に対する無影響量はいずれも 1000 mg/kg/day と判断した。1000 mg/kg 投与群で認められた胃の境界縁での扁平上皮の過形成には可逆性が認められた。

## 5. 緒言

厚生労働省医薬食品局審査管理課 化学物質安全対策室の委託により、diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate 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。

### 5.1 GLP

- ・ 「新規化学物質等に係る試験を実施する試験施設に関する基準について」  
(平成 15 年 11 月 21 日 : 薬食発第 1121003 号、平成 15・11・17 製局第 3 号、環保企発第 031121004 号、平成 17 年 4 月 1 日最終改正)

### 5.2 毒性試験ガイドライン

- ・ 「新規化学物質等に係る試験の方法について」  
(平成 15 年 11 月 21 日 : 薬食発第 1121002 号、平成 15・11・13 製局第 2 号、環保企発第 031121002 号、平成 17 年 4 月 1 日最終改正)
- ・ 「OECD Guideline for Testing of Chemicals 422」  
(OECD 理事会 : 1996 年 3 月 22 日)

### 5.3 動物の福祉

- ・ 「動物の愛護及び管理に関する法律」  
(昭和 48 年 10 月 1 日法律第 105 号、平成 17 年 6 月 22 日最終改正)
- ・ 「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」  
(平成 18 年 4 月 28 日環境省告示第 88 号)
- ・ 「動物実験の適正な実施に向けたガイドライン」  
(日本学術会議 平成 18 年 6 月 1 日)

## 6. 試験材料及び方法

### 6.1 被験物質

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylateは厚生労働省医薬食品局審査管理課 化学物質安全対策室から以下の情報とともに供給された（添付資料1）。

製造者	:	[REDACTED]
名称	:	diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate
CAS番号	:	3012-65-5
構造式又は示性式	:	C <sub>6</sub> H <sub>14</sub> O <sub>7</sub> N <sub>2</sub>
分子量	:	226.19
純度	:	100.0%
ロット番号	:	6803
性状	:	無色の結晶又は結晶性粉末
沸点	:	なし
水溶性	:	50%
水溶状	:	澄明
安定性	:	関連試験終了後に被験物質製造者にて純度を確認した結果、安定性に問題はなかった。（添付資料2）。
保存方法	:	室温（許容値：1~30°C、実測値：15~24°C）
保存場所	:	御殿場研究所 被験物質保存室及び第1研究棟2階被験物質調製室
残量の処置	:	被験物質 5 g を保存試料として御殿場研究所 被験物質保存室に保存し、動物試験終了後の残量はすべて [REDACTED] に返却した。

### 6.2 被験液の調製

#### 6.2.1 被験液の調製及び保存方法

濃度ごとに必要量の被験物質を秤量し、注射用水（株式会社大塚製薬工場、ロット番号：6F74）に徐々に加えて溶解して 20、60 及び 200 mg/mL 液を調製した。調製は 10 日間に 1 回以上の頻度で行い、使用時まで遮光容器（褐色ガラス瓶）に入れて冷暗所（冷蔵庫内、実測値：1~6°C）で保存し、使用前に室温に戻した。残液は吸水性のよいもの（新聞紙、ペーパータオル等）に吸収させて焼却処分した。

#### 6.2.2 被験液の安定性

本被験物質の 10 及び 200 mg/mL 液（媒体：注射用水）は、遮光容器で冷暗所（冷蔵庫内）10 日間保存後、室温 24 時間は安定であることが株式会社ボゾリサーチセンターで確認されている（添付資料3、試験番号：A-2001）。

### 6.2.3 被験液の濃度確認

雄の投与第1週と投与最終週に用いる各濃度液について株式会社ボヅリサーチセンター御殿場研究所でHPLC法により分析した。その結果、各濃度液とともに表示値に対する被験物質の割合は93.3~100.0%であり、いずれも許容範囲内（濃度：表示値に対する割合、100±10%）であった（添付資料4、5）。

#### [測定対象標準物質]

製造者	:	[REDACTED]
名称	:	diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate
ロット番号	:	6803
保存方法	:	室温（許容値：1~30°C、実測値：18~24°C）
保存場所	:	御殿場研究所 被験物質保存室及び生化学部標準物質保存場所

#### [測定実測試料の調製]

以下の表に従い、測定試料をn=1で採取し、HPLC移動相を用いて希釀して測定実測試料を調製した。

測定試料 (mg/mL)	1次希釀		2次希釀		希釀率
	採取量 (mL)	定容量 (mL)	採取量 (mL)	定容量 (mL)	
20	0.5	100	—	—	200
60	1	30	1	20	600
200	0.5	50	1	20	2000

#### [HPLC条件]

カラム	:	L-column ODS (5 μm、4.6 mm I.D.×150 mm、財団法人 化学物質評価研究機構)
カラム温度	:	40°C（カラムオーブン設定温度）
移動相	:	0.1 mol/L りん酸塩緩衝液（pH 2.1）
流速	:	1 mL/min
検出	:	UV（測定波長 215 nm）
試料注入量	:	10 μL
ニードル洗浄液	:	アセトニトリル/精製水、(1/4、v/v)

#### [測定値の算出]

標準試料溶液をHPLCへ3回連続注入し、diammonium hydrogen 2-hydroxypropane-

1,2,3-tricarboxylate のピーク面積値の平均値 (Qs) を求めた。また、測定実測試料を HPLC へ 1 回ずつ注入して diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate のピーク面積値 (Qt) を求め、以下の式により測定試料中の diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate 濃度を求めた。

$$\text{測定試料中 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate 濃度 (mg/mL)} = \frac{Qt}{Qs} \times A \times F \times \frac{1}{1000}$$

Qt : 測定実測試料の diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate のピーク面積値

Qs : 標準試料溶液の diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate の平均ピーク面積値

A : 標準試料溶液中の diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate 濃度 ( $\mu\text{g/mL}$ )

F : 希釈率

### 6.3 試験動物

Sprague-Dawley 系 SPF ラット [Crl:CD(SD)、日本チャールス・リバー株式会社、厚木飼育センター] 雌雄各 70 匹を 8 週齢で入手<sup>注)</sup>し、15 日間の検疫・馴化飼育を行った。その間、一般状態の観察（詳細な一般状態の観察を含む）、体重測定及び性周期検査（検疫期間終了後の 9 日間）を基に、雄は一般状態、雌は一般状態及び性周期にそれぞれ異常がなく、体重増加が良好な各 58 匹を選択し、10 週齢で投与に使用した。投与開始時の体重範囲は雄で 371 g~439 g、雌は 219 g~273 g であった。

なお、群分けは群分け当日（投与開始の前日）の体重により層別化し、各群の平均体重ができるだけ均等となるよう各群に割付けた。個体の割付けはコンピュータを用いたブロック配置法及び無作為抽出法の組み合わせ（ブロック配置法で必要な群を構成し、試験群及び群内の個体番号を無作為に割当てた）で行った。群分けから除外された動物のうち、雌は無処置動物として 15 匹を継続飼育した。残りの雄 15 匹はエーテル深麻酔下で安楽死させた。なお、継続飼育した無処置雌動物は死亡などにより交配すべき相手がいない動物が認められなかつたため、交配期間終了後エーテル深麻酔下で安楽死させた。

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

### 6.4 飼育条件

動物は、温度 21~26°C、相対湿度 42~64%、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：301 号室）でプラスチック製ケージ (W250×D350×H200 mm : 日本ケージ株式会社) で個別に、交配期間中は雌雄

各1匹の計2匹を収容した。なお、妊娠17日から授乳5日までは、床敷（ホワイトフレーク：日本チャールス・リバー株式会社）を入れたプラスチック製エコンケージ（W340×D400×H185 mm：日本クリア株式会社）に個別に収容した。飼料はNMF固体（滅菌：オリエンタル酵母工業株式会社、ロット番号：060919、061214、070115）をステンレス製給餌器を用いて自由に摂取させた。飲料水は水道水（御殿場市営水道水：給水瓶使用）を自由に摂取させた。

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

## 6.5 動物の識別

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

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

投与経路は、OECD Guideline for Testing of Chemicals 422に準じ、経口投与を選択した。投与期間は、主群の雄及び回復群の雌雄で交配前14日間、交配期間14日間及び交配期間終了後14日間の42日間、主群の雌で交配前14日間、交配期間及び妊娠期間を通して授乳4日までの41~47日間とした。

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

## 6.7 投与方法

投与方法は、げっ歯類の経口投与に際して一般的な強制経口投与とした。投与容量は5mL/kg体重とし、フレキシブル胃ゾンデを用いて強制経口投与した（08:11~12:03、ただし、投与時に分娩中であった動物は、分娩終了後の17:00~17:25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。なお、雌の妊娠期間中の妊娠7日以降については妊娠7日の体重を基準に算出した。

## 6.8 投与量及び群構成

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

5匹とした。群構成表を表1に示した。

表1.群構成表

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

## 6.9 投与量の設定根拠

先に実施した「diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate のラットを用いた14日間反復経口投与毒性試験(予備試験)」(投与量:100、300及び1000 mg/kg、株式会社ボゾリサーチセンター試験番号:C-R067)では、1000 mg/kgにおいて、雄で腎臓の相対重量に高値などがみられたが、軽度な変化であり、明らかな毒性所見とは考え難かった<sup>1)</sup>。したがって、本試験では予備試験同様に1000 mg/kgを高用量とし、以下公比約3で除して300及び100 mg/kgの3用量を設定した。

## 6.10 観察及び検査の方法

試験日の起算は下記の通りとした。

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

### 6.10.1 一般状態の観察

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

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

詳細な一般状態の観察は、投与開始前に1回、全個体について行った。また、主群の雄は投与期間中毎週1回、雌は交配前投与期間中及び交配期間中は毎週1回、妊娠期間中及び授乳期間中は指定された日(妊娠1、7、14及び20日、授乳4日)にそれぞれ行った。回復群は投与期間中及び回復期間中毎週1回行った。機能検査、握力及

び自発運動量の測定は、主群の雄は投与終了週（投与第 36 日）に、主群の雌は授乳 4 日（投与第 42~44 日）の F1 児剖検後に、回復群の雌雄は投与終了週（投与第 36 日）及び回復終了週（回復第 8 日）に 1 群当たり 5 匹について行った。上記の観察、検査及び測定は、動物をランダムに配置し、観察者に対して投与量などの情報を制限（ブラインド化）した状態で行った。なお、詳細な一般状態の観察及び機能検査の評価には実数データ項目以外はスコア化した評点法を用いた。

#### 1) 詳細な一般状態の観察

- ホームケージ内観察  
姿勢、痙攣、異常行動
- 手に持つての観察  
ホームケージからの取り出し易さ、ハンドリングに対する反応（取り扱いやすさ、発声など）、被毛・皮膚の状態（被毛の汚れ、粗毛、外傷、皮膚の色など）、眼球（眼球突出、眼瞼の開き具合）、眼・鼻の分泌物、可視粘膜、自律神経機能（流涙、流涎、立毛、瞳孔径、呼吸）
- オープンフィールド内観察  
覚醒状態、歩行、姿勢、振戦、痙攣、立ち上がり回数、排泄物（排糞数、排尿）、常同行動（身繕い、旋回など）、異常行動（自咬、後方突進など）

#### 2) 機能検査

聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射、空中正向反射、着地開脚幅

#### 3) 握力測定

機能検査に引き続き、CPU ゲージ MODEL-9502A（アイコーエンジニアリング株式会社）を用いて前肢及び後肢の握力を測定した。

#### 4) 自発運動量の測定

握力測定に引き続き、実験動物用自発運動センサー NS-AS01（株式会社ニューロサイエンス）を用いて自発運動量を測定した。測定は 1 時間とし、10 分間隔及び 0~60 分の集計を行った。

#### 6.10.3 体重測定

主群の雄は投与第 1、4、8、11、15、18、22、25、29、32、36、39、42 日及び剖検日に、回復群の雌雄は主群の雄の測定日に加え、回復第 1、4、8、11、14 日及び剖検日に、主群の雌は投与第 1、4、8、11、15 日（未交尾動物は投与第 18 日にも測定）、妊娠 0、4、7、11、14、17 及び 20 日並びに授乳 0 及び 4 日に体重を測定した。なお、午後の分娩観察時に分娩の終了が確認された個体の授乳 0 日の体重測定を除き 08:48~11:37 の間に行った。剖検日には相対器官重量算出のため、前日から約 16 時間絶食させた後の体重を測定した。

#### 6.10.4 摂餌量測定

全個体について、主群の雄は投与第 1、4、8、11、15、32、36、39 及び 42 日に、

回復群の雌雄は主群の雄の測定日に加え回復第1、4、8、11及び14日に、主群の雌は投与第1、4、8、11及び15日、妊娠1、4、7、11、14、17及び20日並びに授乳2及び4日に残餌量を測定し、前日の給餌量から1匹当たりの1日摂餌量を算出した。給餌量及び残餌量の測定は08:49~12:19の間に行つた。

#### 6.10.5 膀胱検査

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

#### 6.10.6 交配方法

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

#### 6.10.7 分娩及び授乳観察

##### 1) 母動物の観察

交尾確認雌動物は全例自然分娩させ、分娩状態の異常の有無を観察した。分娩終了の確認は妊娠21日から妊娠25日の午前中まで1日2回（午前、午後）行い、妊娠期間を0.5日単位で算出した。分娩が午後5時に終了していた場合、その日を授乳0日とした。妊娠25日の午前10時までに分娩しなかった300及び1000mg/kg投与群の各1例（動物番号：3106、4107）は、エーテル麻酔下で腹大動脈切断により放血致死させた後剖検を行い、妊娠の有無を確認した。その結果、着床が認められないことから、不妊と判断し、妊娠期間中のデータは統計処理から除外した。分娩が終了した母動物は胎盤及び羊膜の処理の有無を観察し、分娩終了日を授乳0日とし、授乳4日まで出生児を授乳させ、児集め、営巣及び授乳を指標として授乳状態を観察した。

分娩した母動物は授乳4日から一夜（約16~20時間）絶食させた授乳5日に、各群5匹は血液学検査及び血液化学検査のための採血後に、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た。

##### 2) 出生児の観察

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

生後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。

<sup>注1)</sup> : 頭部の陥没や裂、顔面の鼻吻や上下顎、口唇のゆがみや裂、眼瞼や耳介の大きさ、形状、左右のバランス、胸腔部のゆがみや大きさ、内部臓器の突出、尾部の長さ、形状、数、欠損、四肢部の長さ、形状、指の数、欠損及び左右のバランスに注意して観察し、正常と異なる場合を異常とした。

#### 6.10.8 尿検査（摂水量測定を含む）

投与最終週（投与第37~38日）及び回復終了週（回復第11~12日）に雄の全個体について、それぞれ採尿器をセットしたケージに収容し、絶食・自由摂水下で4時間尿を、次いで自由摂食・自由摂水下でその後の20時間尿を採取した。検査項目は以下の通りである。なお、採取した最初の4時間尿についてpH以下沈渣までの検査と尿量を、その後に得られた20時間尿を用いて浸透圧及び尿量の測定を行い、尿量は4時間の尿量及び20時間の尿量を合計して算出した。摂水量は、採尿器をセットしたケージに収容した状態で前日からの1日の摂取量を給水瓶を用いて測定した。

検査項目	測定方法
pH	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
たん白質	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
ケトン体	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
グルコース	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
潜血	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
ビリルビン	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
ウロビリノーゲン	オーションスティックス-7EA 試験紙 [アークレイ株式会社] <sup>a)</sup>
色調	肉眼観察
沈渣	鏡検法
尿量（4時間量）	目盛付スピッツ管を用いた容量測定（単位：mL）
浸透圧	冰点降下法 <sup>b)</sup> （単位：mOsm/kg）
尿量（20時間量）	メスシリンドーを用いた容量測定（単位：mL）
摂水量（24時間量）	重量測定

#### 使用測定機器

a) : AUTION MINI™ AM-4290 (アークレイ株式会社)

b) : 自動浸透圧測定装置 オートアンドスタート OM-6030 (アークレイ株式会社)

#### 6.10.9 血液学検査

最終投与翌日及び回復期間終了日に、前日から一夜（約16~20時間）絶食させた各群雌雄各5匹<sup>注1)</sup>について、エーテル麻酔下に開腹し、腹大動脈からEDTA-2K加採血瓶（SB-41：シスメックス株式会社）に血液を採取し、以下の項目について測定した。なお、全例について、May-Gruenwald-Giemsa染色法による血液塗抹標本を作製した。ただし、プロトロンビン時間、活性化部分トロンボプラスチン時間及びフィブリ

ノーゲン量については、3.8%クエン酸ナトリウム溶液加試験管（血液9容に対し1容の割合）に採取した血液を遠心分離（約3,000 rpm、約1,600×g、約10分間）して得られた血漿を用いて測定した。

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

#### 使用測定機器

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

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

注1)：主群の検査対象各群雌雄各5匹は以下の例とした。

雄	雌
1001~1005	1103、1104、1105、1107、1109
2001~2005	2106、2107、2108、2109、2110
3001~3005	3101、3104、3107、3109、3111
4001~4005	4101、4103、4106、4110、4111

注2)：好中球、好酸球、好塩基球、リンパ球、单球及び大型非染色球

#### 6.10.10 血液化学検査

血液学検査用試料と同時に採取した血液を凝固促進剤入り試験管（ベノジェクト II-オートセップ：テルモ株式会社）に取り、遠心分離（約3,000 rpm、約1,600×g、約10

分間)して得られた血清を用いて以下の項目について測定した。ただし、AST、ALT、LDH 及び  $\gamma$ -GTP については、ヘパリン加試験管(血液 1 mL 当たり約 20 単位のヘパリン)に採取した血液を遠心分離(約 3,000 rpm、約 1,600×g、約 10 分間)して得られた血漿を用いて測定した。

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

#### 使用測定機器

e) : 臨床化学自動分析装置 TBA-120FR 形 (株式会社東芝)

#### 6.10.11 病理学検査

##### 1) 剖検及び器官重量測定

すべての生存動物について、最終投与翌日及び回復期間終了日に、血液・血液化学検査に供した動物(各群雌雄各 5 匹)は採血後に、その他の動物はエーテル麻酔下で腹大動脈切断により放血致死させた。その後、それぞれ体外表・頭部・胸部・腹部を含む全身の器官・組織の肉眼による詳細な病理解剖を行い、結果を記録した。なお、雌動物(母動物)は授乳 5 日の剖検時に黄体数及び着床痕数を数えた。次いで、血液・血液化学検査に供した各群雌雄各 5 匹について、以下に示す器官(精巣及び精巣上体

は全例) の重量(絶対重量)を測定するとともに、絶対重量と剖検時の体重から体重100 g当たりの相対重量を算出した。なお、\*印をつけた両側性の器官については左右別々に測定し、その合計値で評価した。

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

## 2) 病理組織学検査

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

大脑、小脳、下垂体、脊髄(胸部)、坐骨神経、甲状腺、上皮小体、副腎、胸腺、脾臓、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、精囊、胸骨(骨髄を含む)、大腿骨(骨髄を含む)、肉眼的異常部位、個体識別部(耳介)

## 6.11 統計解析

- 1) 以下の式により各パラメータを算出した。

$$\text{交尾率}(\%) = (\text{交尾動物数}/\text{同居動物数}) \times 100$$

$$\text{受胎率}(\%) = (\text{妊娠した雌の数}/\text{交尾した雌の数}) \times 100$$

$$\text{授精率}(\%) = (\text{妊娠した雌の数}/\text{交尾した雄の数}) \times 100$$

$$\text{妊娠期間(日)} = \text{授乳0日} - \text{妊娠0日}$$

$$\text{出産率}(\%) = (\text{出生児出産雌数}/\text{妊娠雌数}) \times 100$$

$$\text{着床率}(\%) = (\text{着床痕数}/\text{黄体数}) \times 100$$

$$\text{死産児率}(\%) = (\text{死産児数}/\text{総出産児数}) \times 100$$

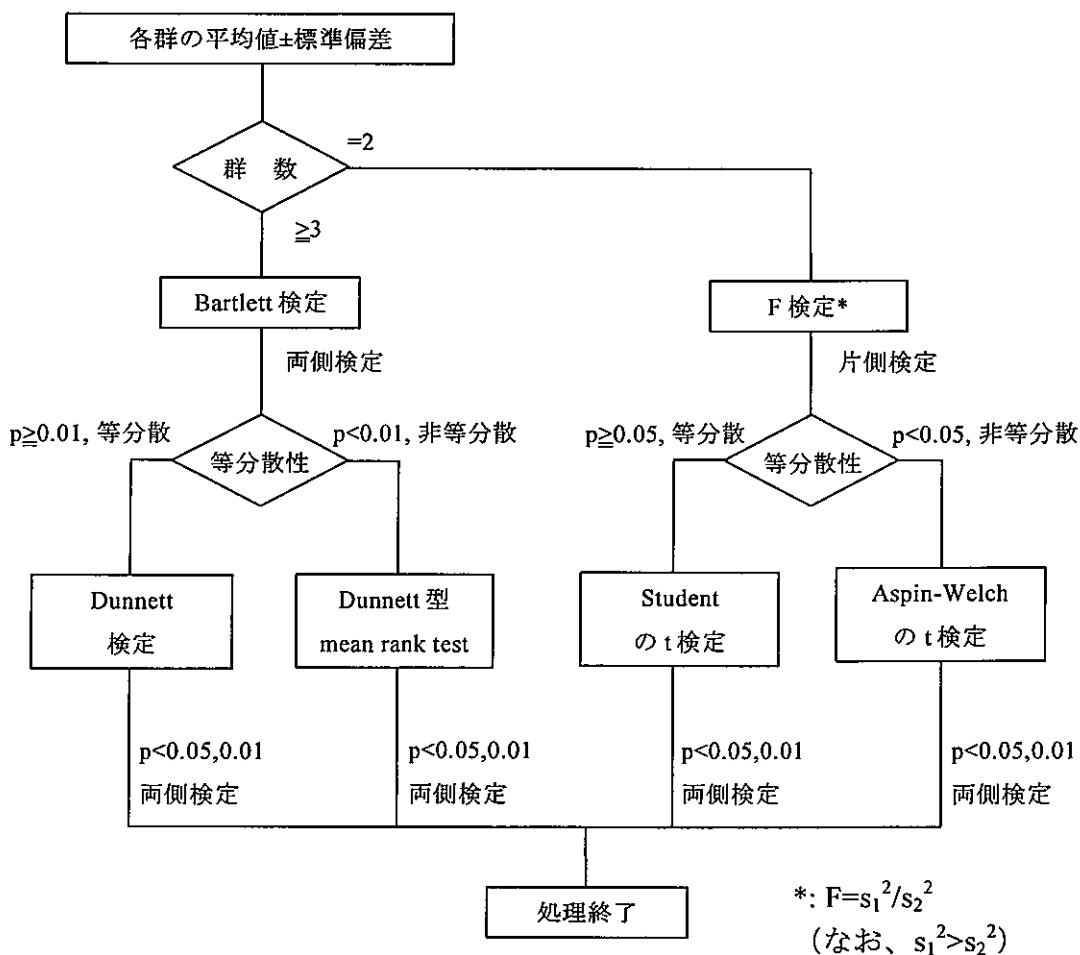
$$\text{出生率}(\%) = (\text{出生児数}/\text{総出産児数}) \times 100$$

$$\text{外表異常率}(\%) = (\text{外表異常児数}/\text{出生児数}) \times 100$$

$$\text{性比} = \text{雄数} / (\text{雄数} + \text{雌数})$$

$$\text{出生児生存率}(\%) = (\text{生後4日生存児数}/\text{生後0日出生児数}) \times 100$$

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



- 4) 交尾率、授精率、受胎率、出産率、出生児の性比、聴覚反応、接近反応、接触反応、疼痛反応、瞳孔反射、空中正向反射は、各群の交尾動物数、雌を妊娠させた雄動物数、妊娠雌動物数、生存児出産雌動物数、雄生存児数、雌生存児数、正常反射のみられた動物数の合計を求め、Yates の連続修正による  $\chi^2$  検定を行つた（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

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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）。

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## 7. 試験結果

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

主群及び回復群の動物とも異常はみられなかった。

### 7.2 詳細な一般状態の観察、機能検査、握力測定及び自発運動量の測定 (Fig. 1~6、Table 2-1~2-105、Appendix 25~324)

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

主群及び回復群のいずれの動物にも異常はみられなかった。

#### 2) 手に持つての観察 (Table 2-30~2-58、Appendix 109~192)

主群及び回復群のいずれの動物にも異常はみられなかった。

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

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

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

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

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

主群及び回復群のいずれの動物にも対照群と各投与群との間に差はなかった。

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

主群及び回復群とも対照群と各投与群との間に差はなかった。

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

主群及び回復群の雌雄ともに体重及び体重増加量には被験物質投与による影響は認められなかった。なお、主群の 1000 mg/kg 投与群の雌で交配前投与期間中（投与 1 日～15 日）の体重増加量が低く、その差は有意となったが、同時期の体重及びその後の体重増加量には差がないことから生理的変動範囲内の変化と判断した。

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

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

なお、主群では 300 mg/kg 投与群の雄で投与 36 日に有意な低値、回復群では 1000 mg/kg 投与群の雌で投与 42 日及び回復 8 日に有意な高値、同群の雄で回復 4 日

に有意な高値が認められたが、一時的に有意な変動であり、関連する体重推移への影響はみられないことから生理的変動範囲内の変化と判断した。

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

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

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投与群との間に差はなかった。

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

#### 1) 投与期間終了時検査

いずれの検査項目においても対照群と各投与群との間に差はなかった。

#### 2) 回復期間終了時検査

1000 mg/kg 投与群の雌で白血球数、リンパ球数及び好中球数の減少、白血球百分率における好酸球比率の増加がみられ、その差は有意となったが、同様の変動は投与期間終了時にはみられていないことから、生理的変動範囲内の変化と判断した。なお、雄動物では対照群と 1000 mg/kg 投与群との間に差は認められなかった。

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

#### 1) 投与期間終了時検査

1000 mg/kg 投与群の雄でグルコースの高値 (+16%) がみられ、その差は有意となった。他の検査項目では対照群と各投与群との間に差はなかった。

#### 2) 回復期間終了時検査

いずれの検査項目においても対照群と各投与群との間に差はなかった。

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

投与期間終了時検査では絶対及び相対重量の双方において、用量に関連した同一方向の変化（増加又は減少）はみられず、回復期間終了時検査においても対照群と各投与群との間に差はなかった。なお、以下の器官に対照群との間に有意差がみられたが、いずれも絶対もしくは相対重量のみの軽度な変化であり生理的変動範囲内の変化と考えられた。

#### 1) 投与期間終了時検査

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

甲状腺 : 相対重量の有意な低値が 300 mg/kg 投与群の雌にみら

れた。

## 2) 回復期間終了時検査

対照群及び 1000 mg/kg 投与群の雌雄とも変化はみられなかつた。

## 7.9 剖検所見 (Table 9、Appendix 437~552)

### 1) 投与期間終了時検査

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

精巣上体	:	黄色巣が対照群及び 100 mg/kg 投与群の各 1 例にみられた。
腎臓	:	結節が対照群の雄 1 例に、白色巣が 300 mg/kg 投与群の雌 1 例にみられた。
肺 (気管支を含む)	:	暗赤色巣が対照群の雌 1 例にみられた。
胃	:	腺胃の暗赤色巣が対照群の雄 1 例と雌 5 例、100 及び 300 mg/kg 投与群の雌各 2 例、1000 mg/kg 投与群の雄 2 例と雌 3 例にみられた。
膀胱	:	壁肥厚及び白色液貯留が 300 mg/kg 投与群の雌 1 例にみられた。

## 2) 回復期間終了時検査

対照群及び 1000 mg/kg 投与群の雌雄とも変化はみられなかつた。

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

### 1) 投与期間終了時検査

被験物質投与によると考えられる変化が胃にみられた。

胃	:	境界縁における扁平上皮の軽微又は軽度な過形成が 1000 mg/kg 投与群の雄 10 例と雌 7 例にみられた。
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その他、以下の所見がみられたが、出現状態及び病理組織学的性状から偶発病変と考えられた。

精巣上体	:	軽微な間質細胞浸潤が 1000 mg/kg 投与群の 1 例に、軽度又は中等度な精子肉芽腫が対照群及び 100 mg/kg 投与群の各 1 例にみられた。
心臓	:	軽微な限局性細胞浸潤が対照群の雌雄各 1 例にみられた。
盲腸	:	粘膜の軽微な細胞浸潤が 1000 mg/kg 投与群の雄 1 例にみられた。
腎臓	:	軽微な尿細管の再生が対照群の雄 3 例と雌 1 例、

300 mg/kg 投与群の雌 1 例、1000mg/kg 投与群の雄 5 例と雌 4 例に、軽微なヒアリン円柱形成が対照群の雄 1 例と 300 mg/kg 投与群の雌 1 例に、軽微な髓質の鉱質沈着が対照群の雄 2 例及び 1000 mg/kg 投与群の雄 3 例と雌 1 例に、軽微な間質細胞浸潤が対照群の雌雄各 1 例及び 1000 mg/kg 投与群の雄 2 例に、腎芽細胞腫が対照群の雄 1 例と 300 mg/kg 投与群の雌 1 例にみられた。

- ( 肝臓 : 門脈周囲肝細胞の軽微な空胞化が対照群の雌雄各 1 例及び 1000 mg/kg 投与群の雌 2 例に、軽微な微小肉芽腫が対照群の雌雄各 4 例及び 1000 mg/kg 投与群の雄 5 例と雌 2 例にみられた。
- ( 肺 (気管支を含む) : 動脈壁の軽微な鉱質沈着が対照群及び 1000 mg/kg 投与群の雄各 1 例に、軽微又は軽度な肺胞内泡沫細胞が対照群及び 1000 mg/kg 投与群の雌雄各 2 例に、軽微な肺胞内細胞浸潤が対照群の雌 2 例及び 1000 mg/kg 投与群の雄 1 例に、軽微な肺胞内出血が対照群の雌 1 例に、軽微な骨化生が 1000 mg/kg 投与群の雌 1 例にみられた。
- 下垂体 : 前葉の軽微な限局性細胞浸潤が対照群の雌 1 例にみられた。
- 精嚢 : 軽微な筋層細胞浸潤が 1000 mg/kg 投与群の 1 例にみられた。
- 脾臓 : 軽微又は軽度な髓外造血が対照群の雄 4 例と雌 5 例及び 1000 mg/kg 投与群の雄 4 例と雌 5 例にみられた。
- 胃 : 軽微又は軽度な腺胃の糜爛が対照群の雄 1 例と雌 5 例、100 及び 300 mg/kg 投与群の雌各 2 例及び 1000 mg/kg 投与群の雄 2 例と雌 3 例にみられた。
- 甲状腺 : 軽微な異所性胸腺組織が 1000 mg/kg 投与群の雄 1 例にみられた。
- 膀胱 : 粘膜下の軽度な細胞浸潤が 300 mg/kg 投与群の雌 1 例に、軽微な漿膜の鉱質沈着が対照群の雄 1 例に、軽度な粘膜の過形成が 300 mg/kg 投与群の雌 1 例にみられた。

## 2) 回復期間終了時検査

被験物質投与によると考えられる変化が胃にみられた。

- 胃 : 軽微な境界縁における扁平上皮の過形成が対照群の雌 1 例及び 1000 mg/kg 投与群の雄 1 例と雌 3 例にみられ、

投与期間終了時検査と比べ変化の程度は軽度であった。

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

胃 : 軽度な腺胃の拡張が対照群の雄 1 例にみられた。

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

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

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

交配開始後 6 日までに全組み合わせで交尾が認められた。なお、不妊であった組み合わせは 300 及び 1000 mg/kg 投与群の各 1 組のみであった。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投与群との間に差は認められなかった。

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

妊娠動物の分娩状態では、妊娠 21.5~22.5 日に全例が正常に分娩し、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数及び出生率には対照群と各投与群との間に差は認められなかった。

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つた。

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

性比及び出生時体重には対照群と各投与群との間に差はなく、外表異常はみられなかつた。

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

授乳期間中の死亡児は対照群で 2 例、100、300 及び 1000 mg/kg 投与群で 4、14 及び 1 例であった。なお、300 mg/kg 投与群の生後 4 日生存率が低く、その差は有意となつたが、発現状況に投与用量との関連はなく偶発的変化と判断された。他の項目については対照群と各投与群との間に差はなかつた。

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

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

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

胸腺の頸部残留が 100 mg/kg 投与群の雄 3 例と雌 1 例にみられたが、投与用量との

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関連のない偶発的変化であった。その他はいずれの出生児にも異常はみられなかった。

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## 8. 考察

*diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate* の 0 (対照群: 注射用水)、100、300 及び 1000 mg/kg を、Sprague-Dawley 系 SPF ラットの雄には交配前 14 日間及び交配期間を通して剖検前日 (42 日間) まで、雌には交配前 14 日間及び交配期間並びに妊娠期間を通して授乳 4 日まで (41~47 日間) 投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0 及び 1000 mg/kg 投与群については 42 日間投与した後、14 日間の回復期間を設け、毒性変化の可逆性を検討した。

### 1) 反復投与毒性

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

尿検査では、各投与群で投与 6 週検査時に pH の軽度な酸性化傾向及びリン酸塩結晶の発現程度及び頻度の減少が用量に関連してみられた。これらの変化は被験液が酸性 (pH : 4.9、50 g/L、25°C、添付資料 1 参照) であることから、被験物質の排泄に基づく変化と推察された。なお、血液・血液化学検査、尿路系の病理検査に異常はなく、毒性学的に意義のない変化と考えられた。

血液化学検査では、投与期間終了時検査において、1000 mg/kg 投与群の雄でグルコースの高値がみられたが、糖代謝の主要な場である肝臓、筋肉、脂肪組織、腎臓などに障害はみられず、尿中へのグルコースの排泄もなく、16%の増加と軽度であることから、毒性学的に意義のない変化と考えられた。

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

### 2) 生殖発生毒性

性周期、交尾までに要した日数、交尾率、授精率及び受胎率には被験物質投与の影響は認められなかった。更に、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数、出生率及び性比に被験物質投与の影響は認められず、授乳期間中の授乳状態にも異常が認められないことから、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、外表観察、出生時及び生後 4 日の体重及び生後 4 日剖検所見及び生存率に被験物質投与による変化は認められなかった。

これらの結果から、*diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate* の反

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復投与毒性に対する無影響量は雌雄とともに 300 mg/kg/day、生殖発生毒性に対しては雌雄親動物及び児動物に対する無影響量はいずれも 1000 mg/kg/day と判断した。1000 mg/kg 投与群で認められた胃の境界縁での扁平上皮の過形成には可逆性が認められた。

## 9. 文献

- 1) [REDACTED]: diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate のラットを用いた 14 日間反復経口投与毒性試験（予備試験）（株式会社ボヅリサーチセンター試験番号：C-R067、2007 年）
- 2) Shayne C. Gad and Carroll S. Weil (1994): Chapter 7. Statistics for Toxicologists, In Principles and Methods of Toxicology (A. Wallace Hayes, ed.), 3rd ed., pp.221-274, Raven Press, Ltd., New York.
- 3) 佐久間昭 (1981) : 薬効評価－計画と分析-II, pp.23-27, 387-389, 東京大学出版会, 東京.



小松

## 分析表

分析日：平成18年08月07日

製品名：試薬特級 くえん酸水素二アンモニウム

ロット番号：6803

性状	無色の結晶又は結晶性粉末
定性試験	適
品質	
純度	100.0 %
水溶状	澄明
強熱残分 (硫酸塩)	0.01 %
pH (50g/L, 25°C)	4.9
塩化物 (Cl)	5 ppm以下
りん酸塩 (PO <sub>4</sub> )	5 ppm以下
硫酸塩 (SO <sub>4</sub> )	0.005%以下
ナトリウム (Na)	0.02%以下
カリウム (K)	0.01%以下
銅 (Cu)	2 ppm以下
亜鉛 (Zn)	2 ppm以下
鉛 (Pb)	2 ppm以下
鉄 (Fe)	5 ppm以下
しゅう酸塩 (C <sub>2</sub> H <sub>2</sub> O <sub>4</sub> として)	0.01%以下
酒石酸塩 (C <sub>4</sub> H <sub>6</sub> O <sub>6</sub> として)	0.01%以下

製造年月日 2006年8月3日

総合判定	合 格	製造管理者	品質管理責任者	担当者



小松屋

## 分析表

分析日：平成19年07月11日

製品名：試薬特級 くえん酸水素二アンモニウム

ロット番号：6803（再）

性状	無色の結晶又は結晶性粉末
定性試験	適
品質	
純度	100.0 質量分率%
水溶状	澄明
強熱残分（硫酸塩）	0.01 質量分率%
pH (50g/L、25°C)	4.9
塩化物 (Cl)	5 質量分率 ppm以下
りん酸塩 (PO <sub>4</sub> )	5 質量分率 ppm以下
硫酸塩 (SO <sub>4</sub> )	0.005 質量分率%以下
ナトリウム (Na)	0.02 質量分率%以下
カリウム (K)	0.01 質量分率%以下
銅 (Cu)	2 質量分率 ppm以下
亜鉛 (Zn)	2 質量分率 ppm以下
鉛 (Pb)	2 質量分率 ppm以下
鉄 (Fe)	5 質量分率 ppm以下
しゅう酸塩 (C <sub>2</sub> H <sub>2</sub> O <sub>4</sub> として)	0.01 質量分率%以下
酒石酸塩 (C <sub>4</sub> H <sub>6</sub> O <sub>6</sub> として)	0.01 質量分率%以下

総合判定	合格	製造管理者	品質管理責任者	担当者

A-2001(1/2)

被験液中 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
安定性試験成績書

試験番号 : A-2001  
試験実施施設 : 株式会社ボゾリサーチセンター 御殿場研究所  
測定日 : 2007年1月12日 (調製直後)  
2007年1月16日 (冷所3日間保存+室温24時間保存)  
2007年1月23日 (冷所10日間保存+室温24時間保存)

測定方法 : HPLC

( 被験物質 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
媒 体 : 注射用水  
調製濃度 : 10 及び 200 mg/mL  
調製形態 : 溶液  
調製日 : 2007年1月12日  
保存条件 : 褐色ガラス瓶に入れ、冷所（冷蔵庫内、許容値：1～10°C）の後、室温にて保存

評価基準  
安定性 : 残存率 [調製直後の測定濃度の平均値を初期値 (100) として、それに対する保存後の測定濃度の平均値の割合] が 100±10%以内。

結果 : 次ページを参照。

判定 : 本被験液は 10 及び 200 mg/mLにおいては冷所 10 日間保存+室温 24 時間保存安定であることが確認された。

遵守した基準 : 「新規化学物質等に係る試験を実施する試験施設に関する基準について」(平成 15 年 11 月 21 日: 薬食発第 1121003 号、平成 15・11・17 製局第 3 号、環保企発第 031121004 号、平成 17 年 4 月 1 日最終改正)

試験責任者 : ██████████ 2007年 / 月 26日

A-2001(2/2)

## 結 果 :

調製濃度 (mg/mL)	測 定 濃 度 (mg/mL)	測 定 濃 度 (mg/mL)	
		調製直後	冷所 3 日間保存 +室温 24 時間保存
10	9.43	9.54	9.65
	9.67	9.76	9.45
	9.52	9.58	9.64
平均	9.54	9.63	9.58
残存率(%)	100	100.9	100.4
200	194	189	187
	187	188	188
	197	190	188
平均	193	189	187
残存率(%)	100	97.9	96.9

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
の被験液中濃度測定成績書

試験番号 : R-958  
 測定実施施設 : 株式会社ボゾリサーチセンター 御殿場研究所  
 ステージ : 雄の投与第1週  
 測定年月日 : 2007年1月29日  
 測定方法 : HPLC

## 被験液

被験物質 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
 (ロット番号 ; 6803)  
 媒体 : 注射用水  
 表示値 : 20、60 及び 200 mg/mL  
 調製形態 : 溶液  
 調製年月日 : 2007年1月26日

測定対象物質 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

判定基準 : 濃度許容範囲 ; 表示値±10%

## 結果 :

表示値 (mg/mL)	測定濃度 (mg/mL)	表示値に 対する割合 (%)
20	18.9	94.5
60	56.0	93.3
200	188	94.0

判定 : 適

化学分析責任者 :

2007 年 2 月 2 日

diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
の被験液中濃度測定成績書

試験番号 : R-958

測定実施施設 : 株式会社ボゾリサーチセンター 御殿場研究所

ステージ : 雄の投与最終週

測定年月日 : 2007年3月8日

測定方法 : HPLC

( 被験液

被験物質 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
(ロット番号 ; 6803)

媒 体 : 注射用水

表 示 値 : 20、60 及び 200 mg/mL

調製形態 : 溶液

調製年月日 : 2007年3月7日

測定対象物質 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

判定基準 : 濃度許容範囲 ; 表示値±10%

( 結 果 :

表示値 (mg/mL)	測定濃度 (mg/mL)	表示値に 対する割合 (%)
20	19.5	97.5
60	59.7	99.5
200	200	100.0

判 定 : 適

化学分析責任者 :

2007 年 3 月 12 日

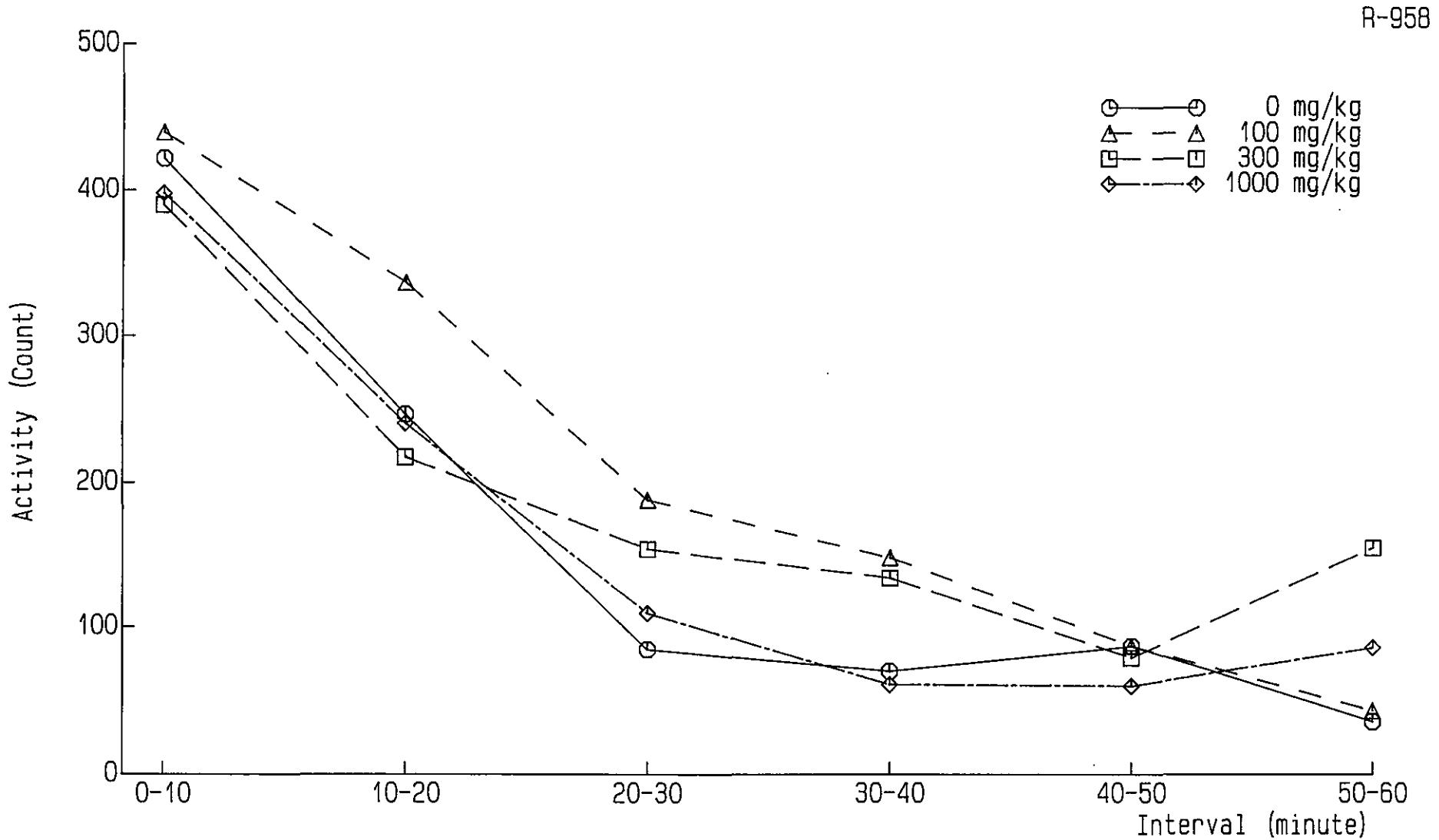


Fig.1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Motor activity of male rats (Main group, Week 6 of administration)

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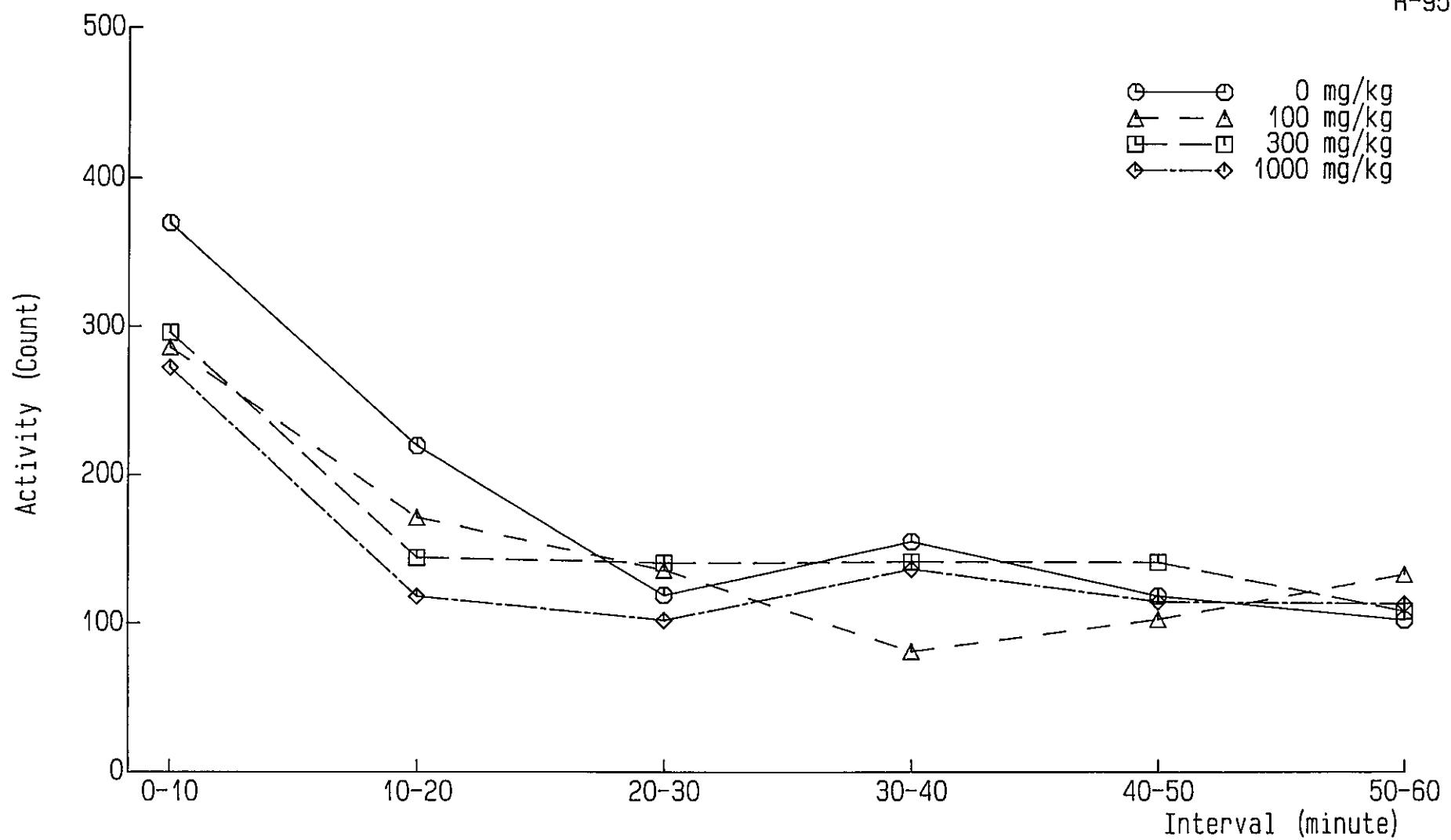


Fig.2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Motor activity of female rats (Main group, Day 4 of lactation)

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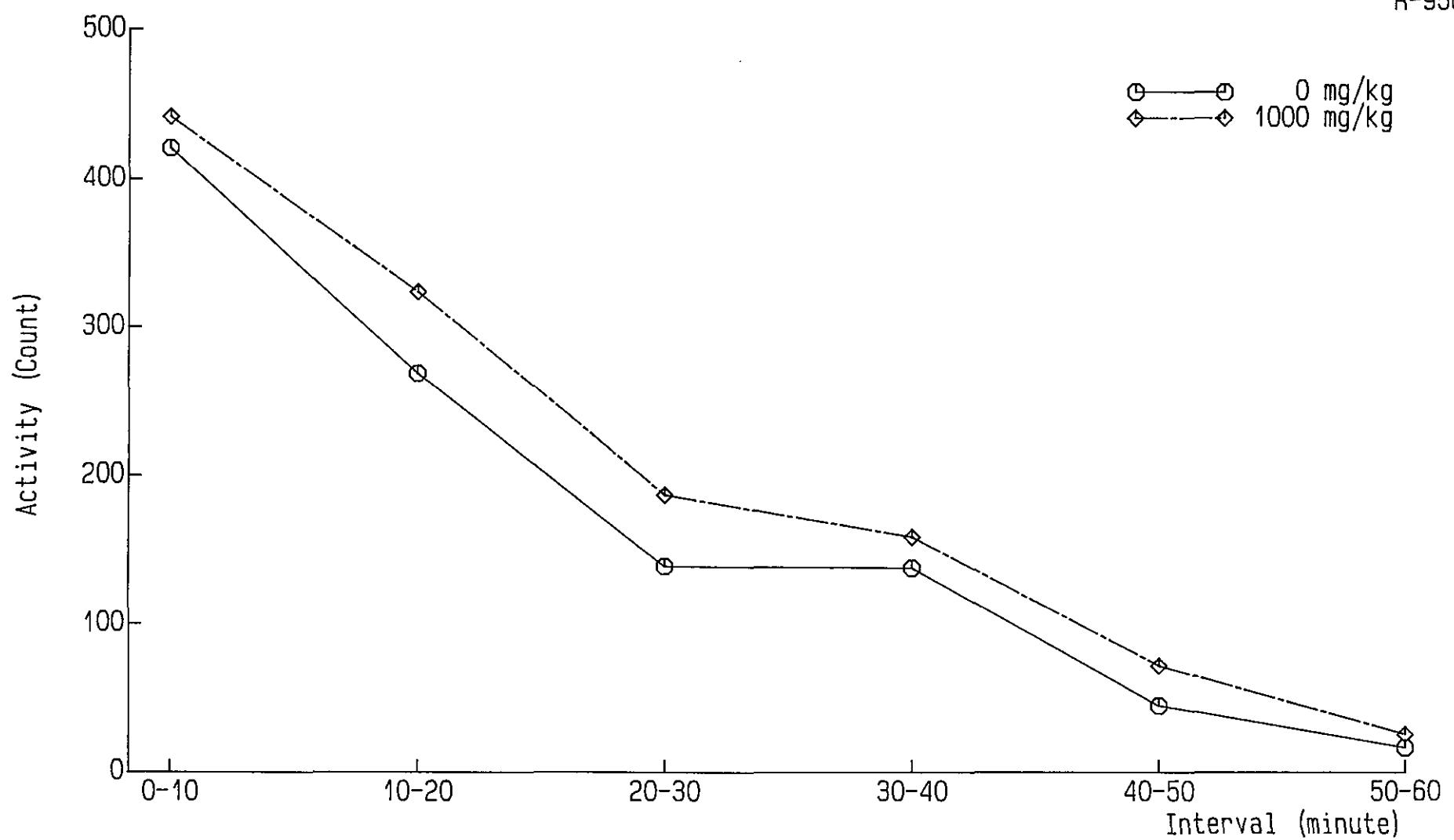


Fig.3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1, 2, 3-tricarboxylate  
Motor activity of male rats (Recovery group, Week 6 of administration)

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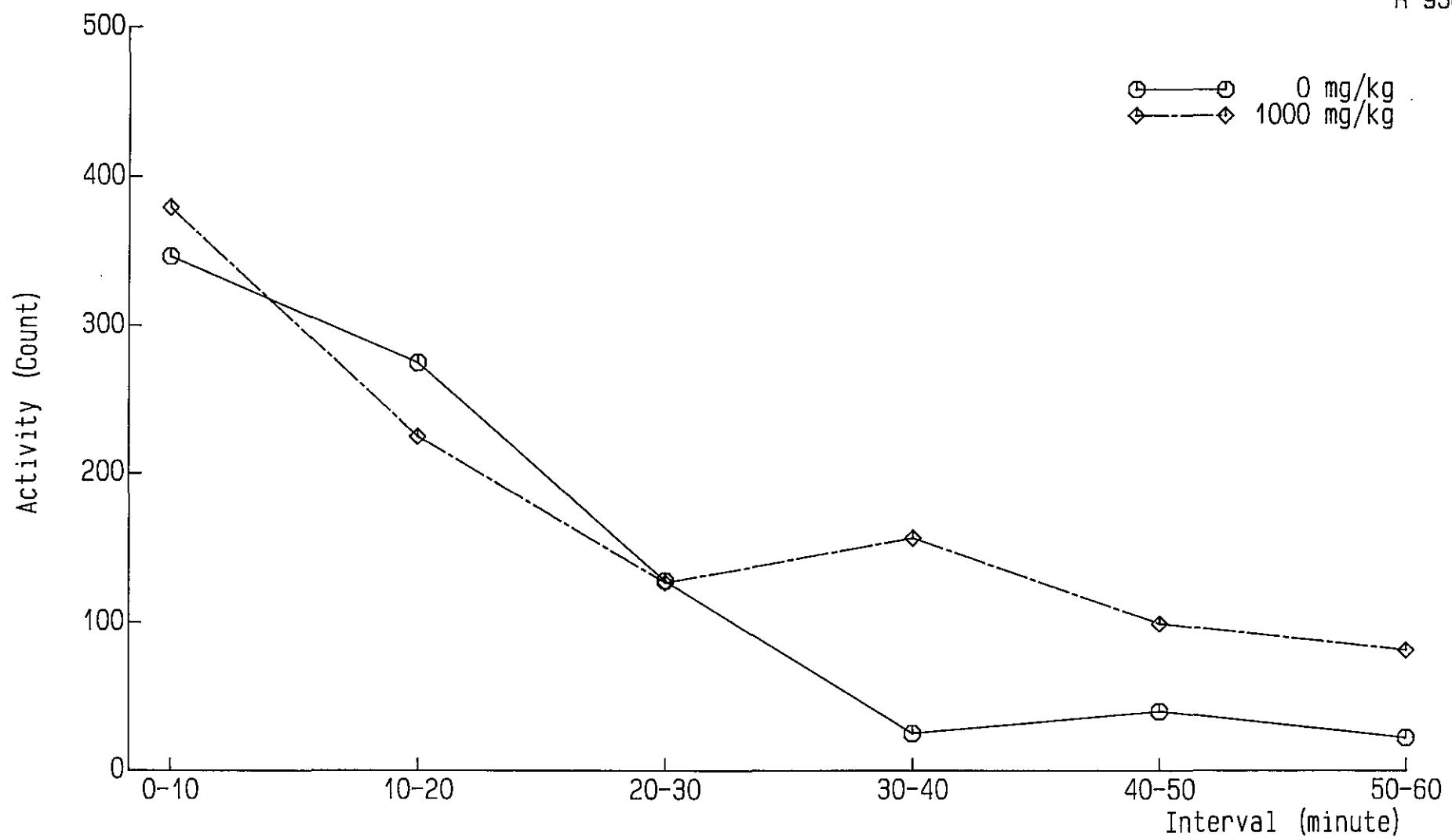


Fig.4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Motor activity of female rats (Recovery group, Week 6 of administration)

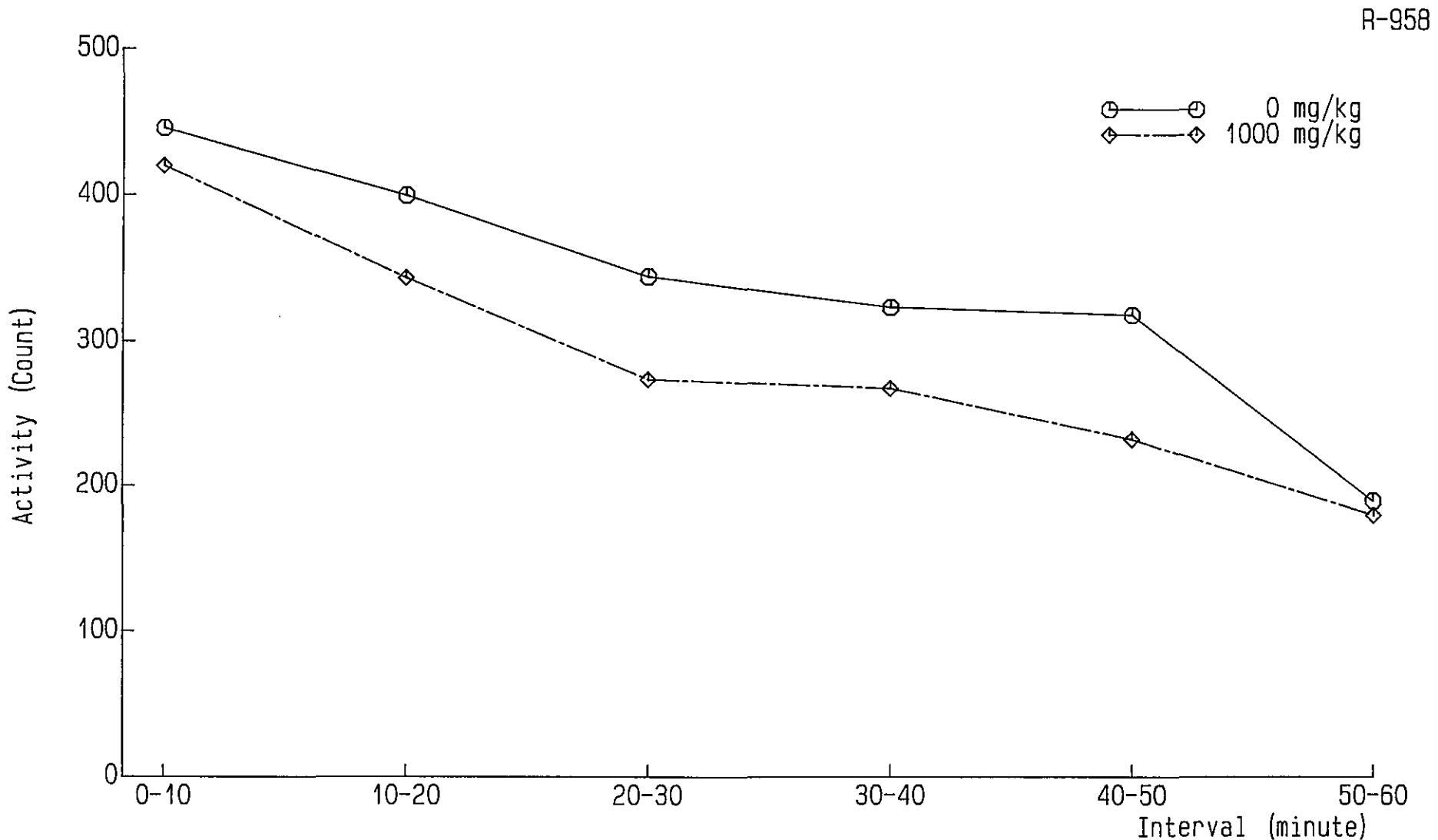


Fig.5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Motor activity of male rats (Recovery group, Week 2 of recovery)

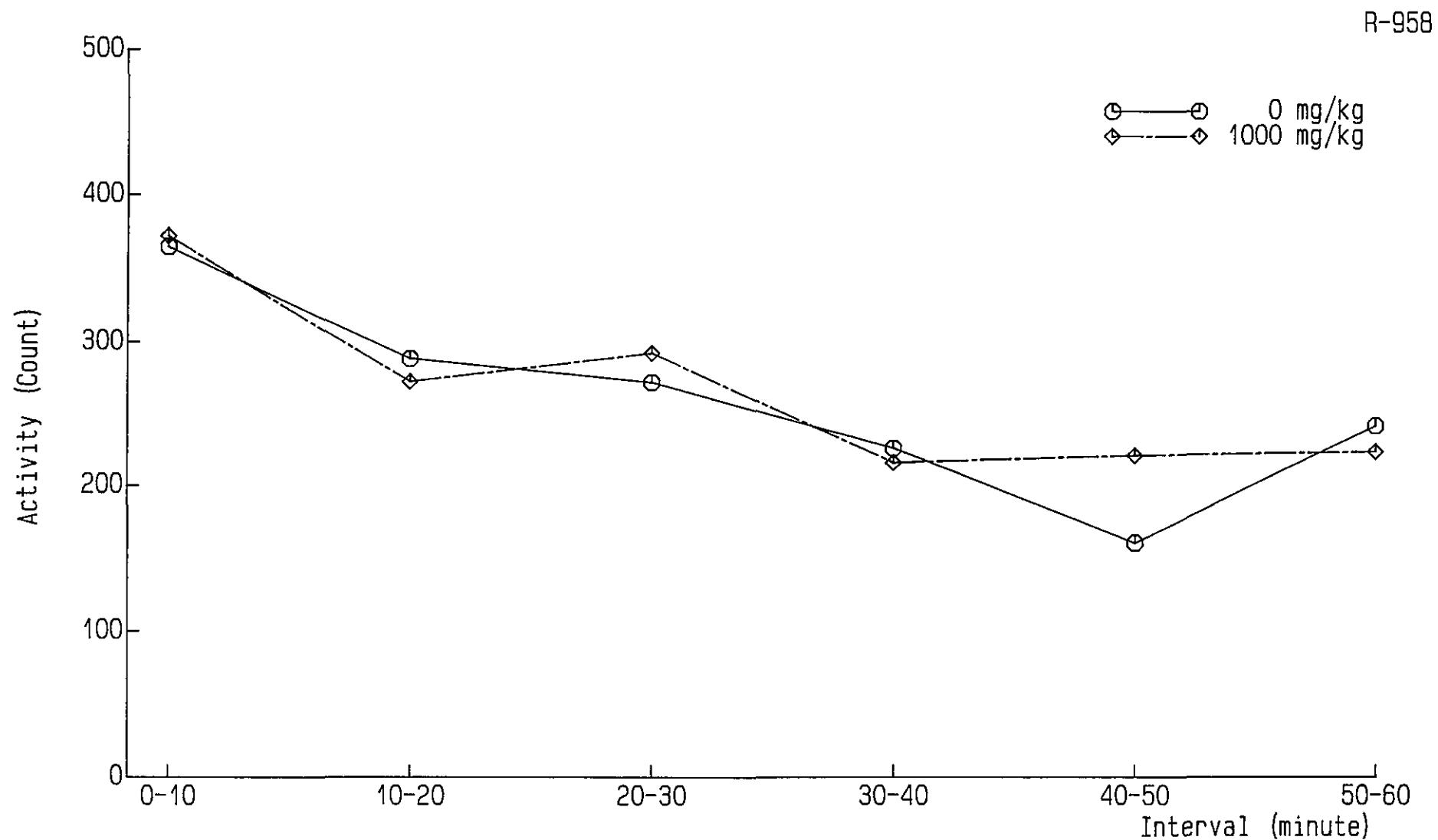


Fig.6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Motor activity of female rats (Recovery group, Week 2 of recovery)

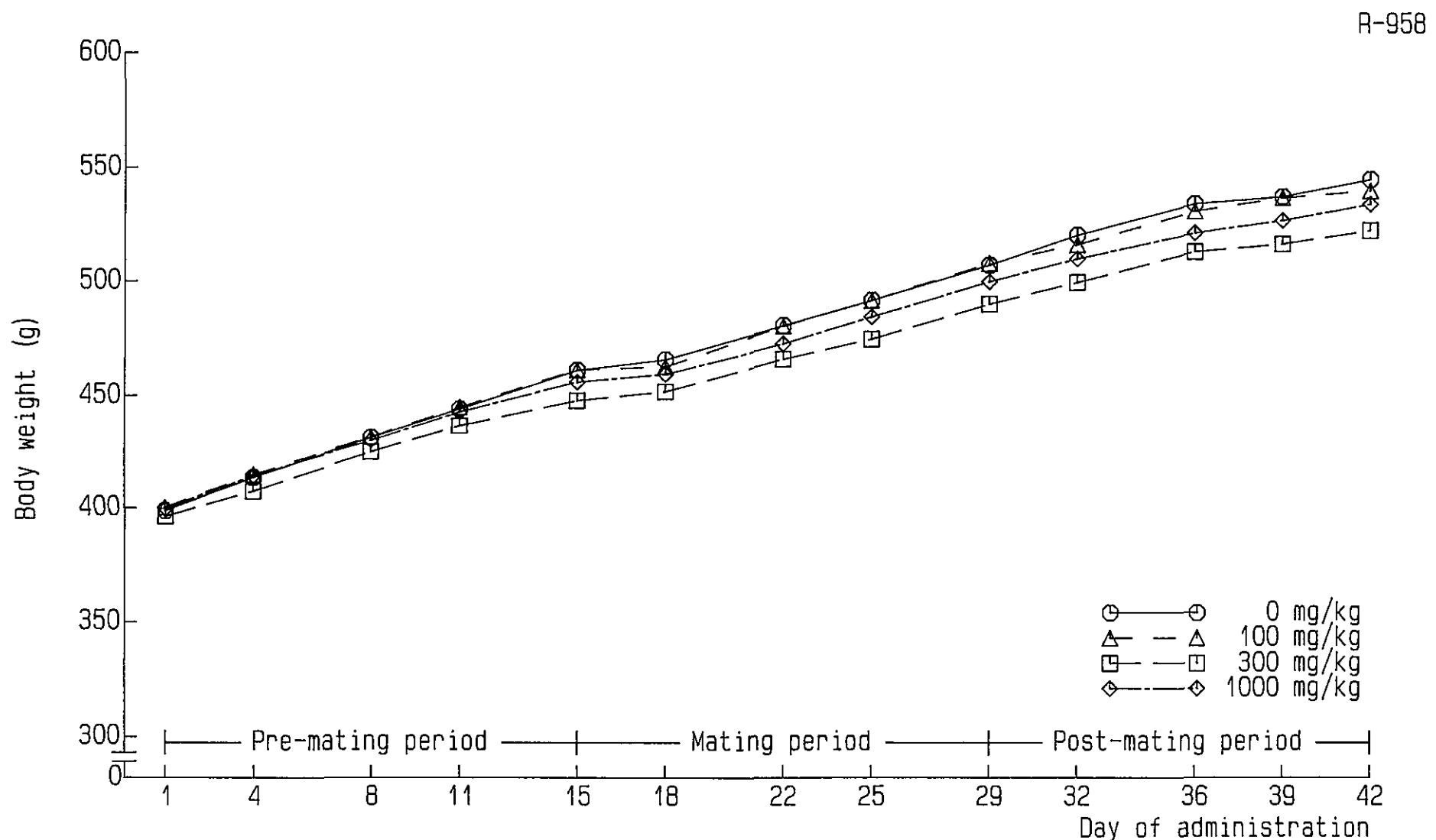


Fig. 7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Body weight changes of male rats (Main group)

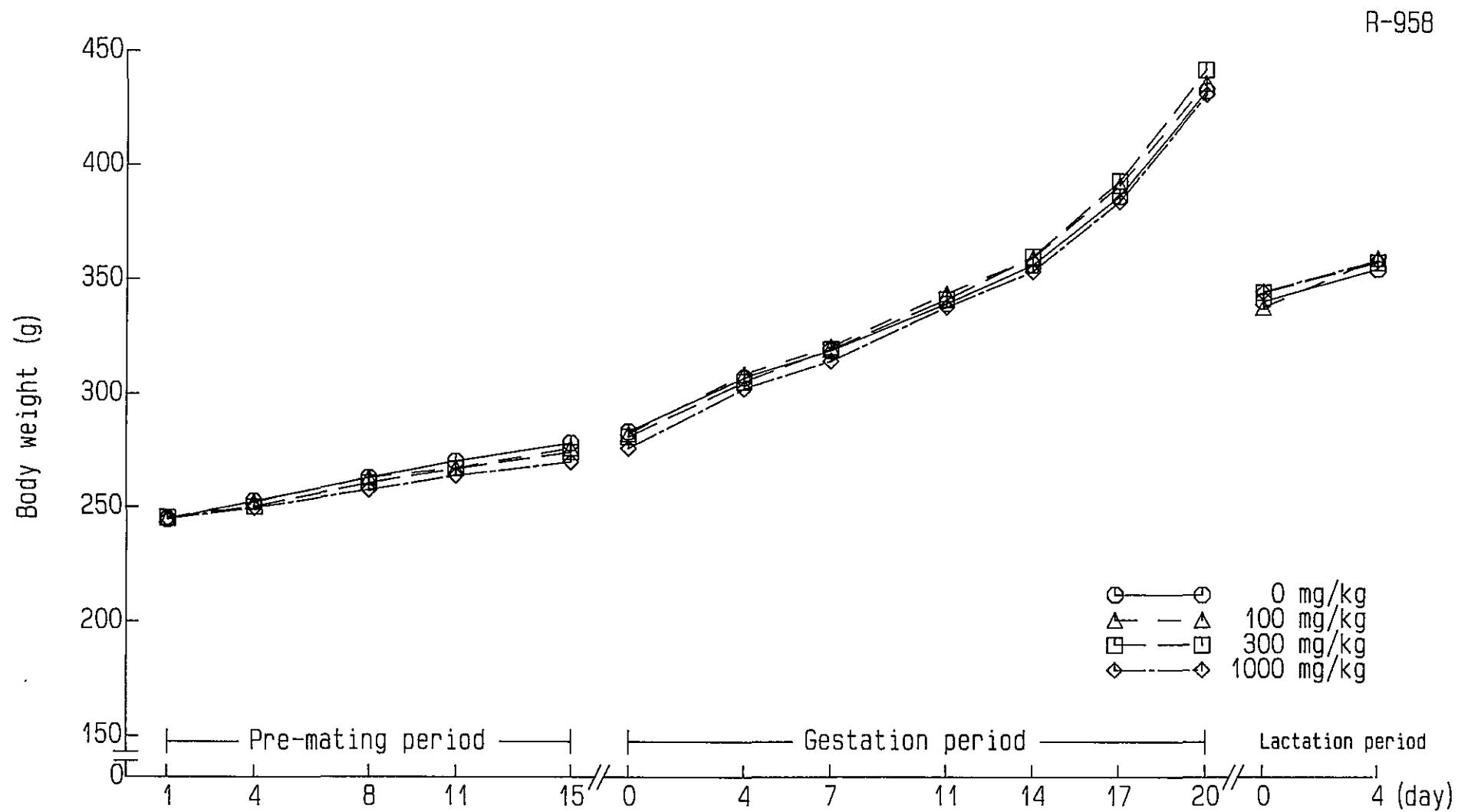


Fig.8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1, 2, 3-tricarboxylate  
Body weight changes of female rats (Main group)

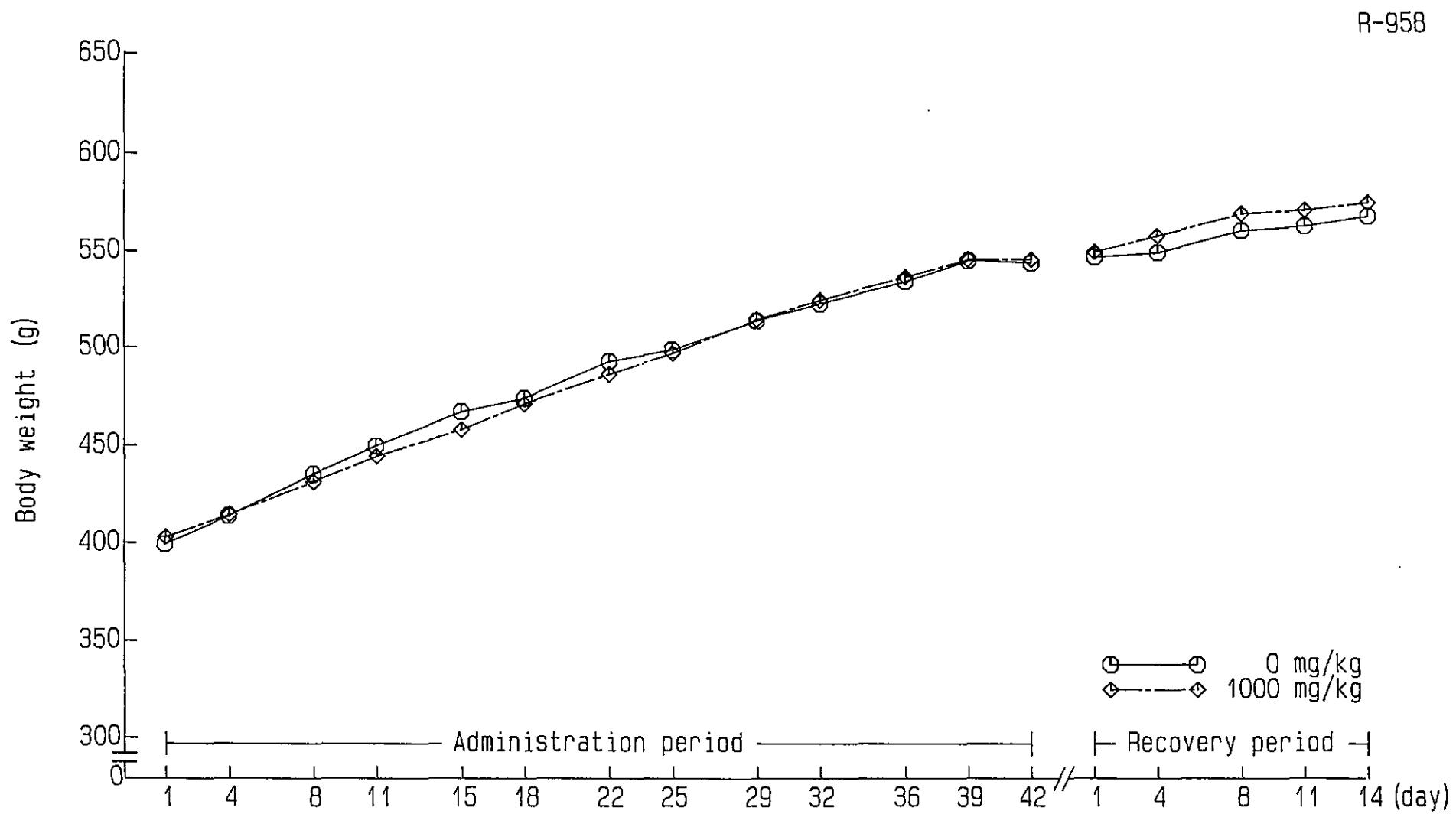


Fig.9 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Body weight changes of male rats (Recovery group)

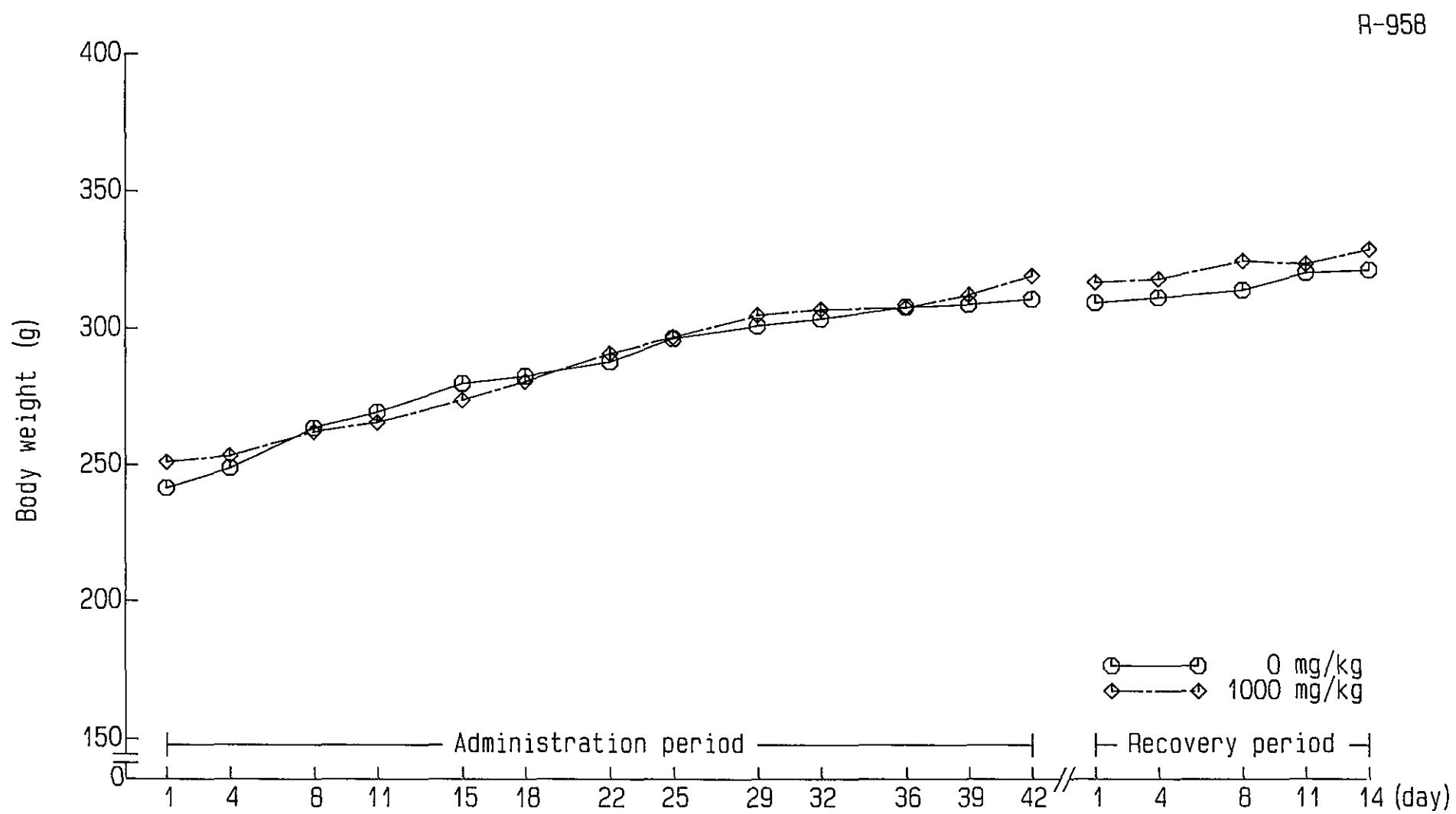


Fig.10 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Body weight changes of female rats (Recovery group)

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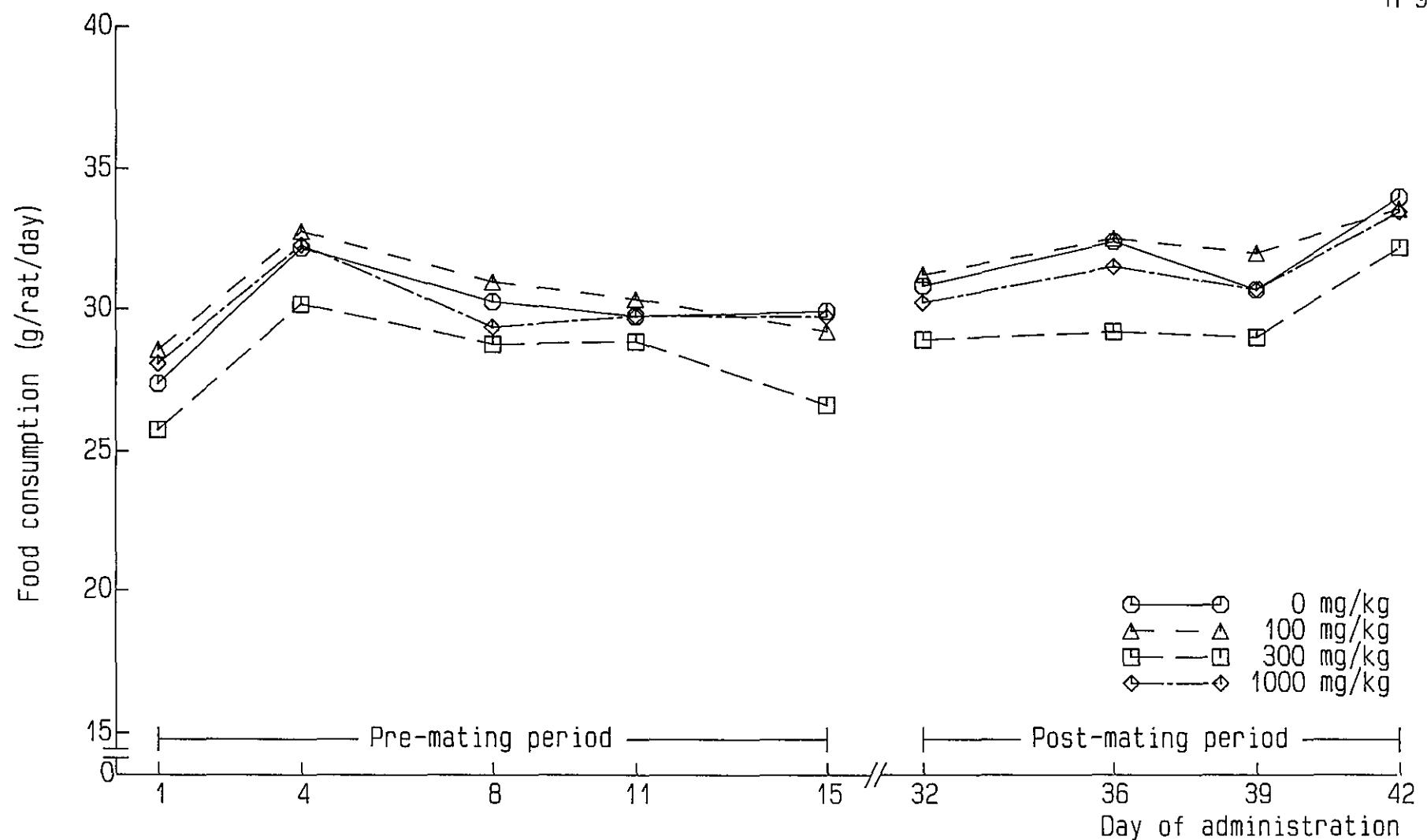


Fig.11 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Food consumption of male rats (Main group)

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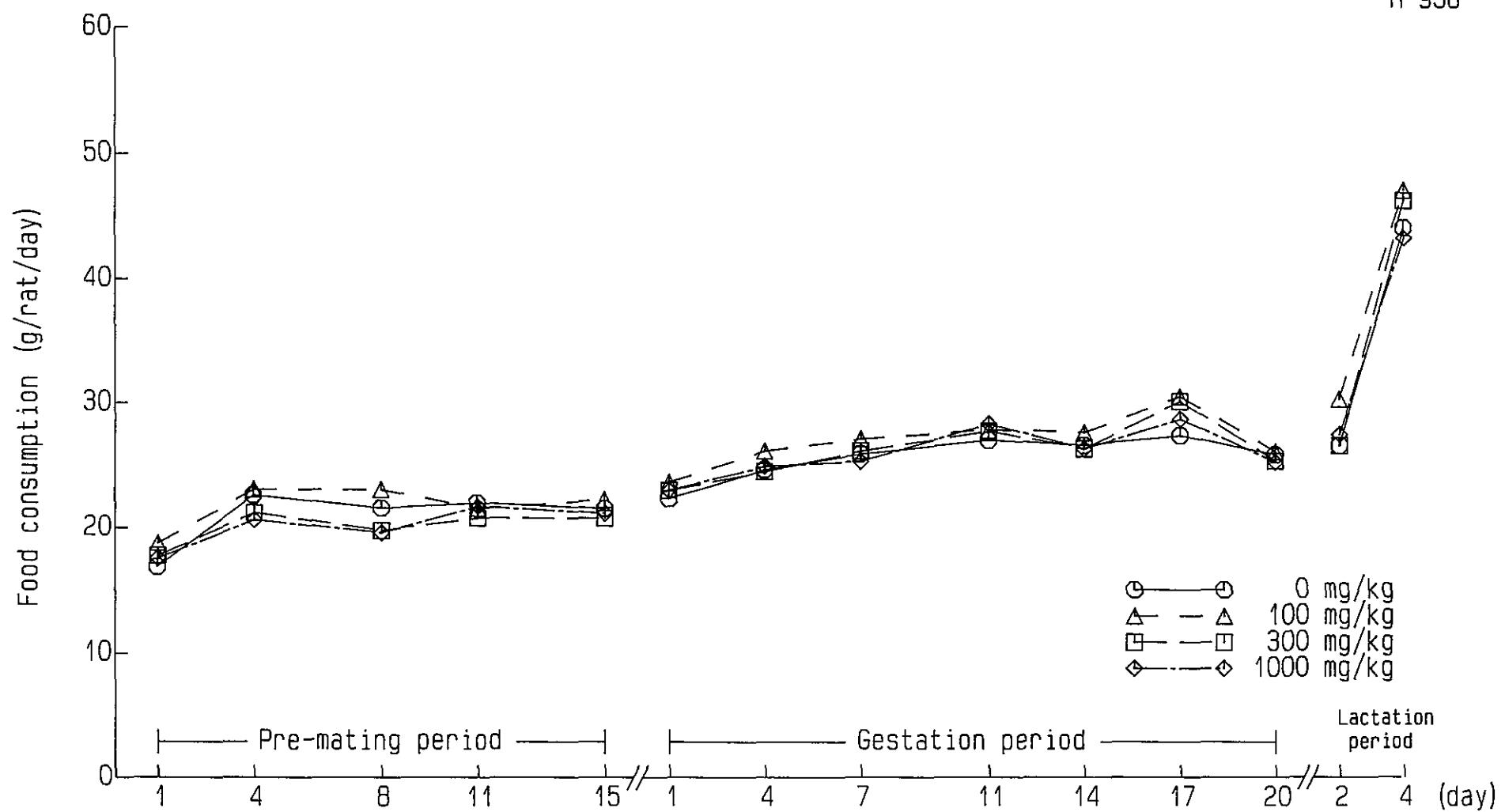


Fig.12 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1, 2, 3-tricarboxylate  
Food consumption of female rats (Main group)

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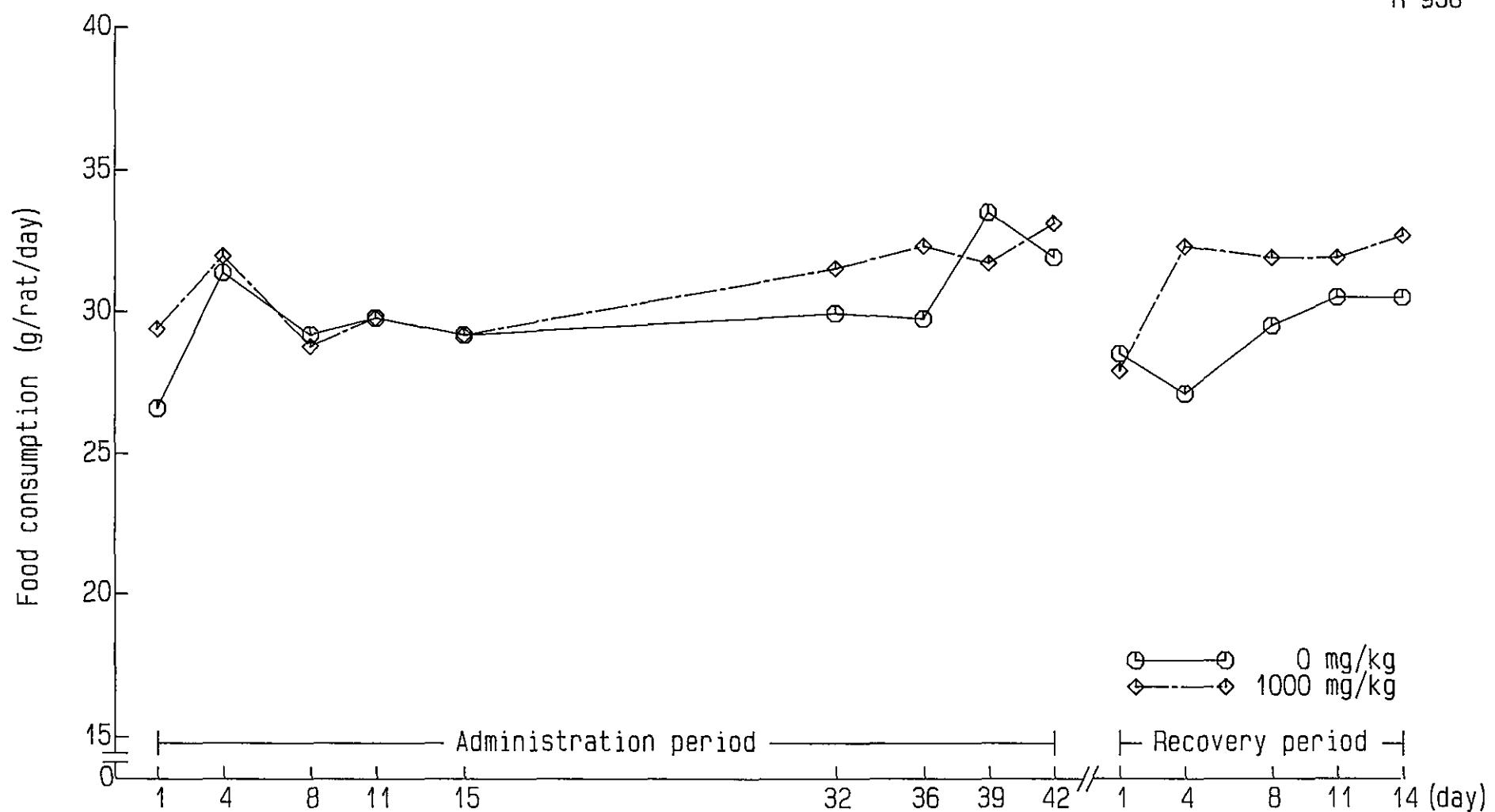


Fig.13 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1, 2, 3-tricarboxylate  
Food consumption of male rats (Recovery group)

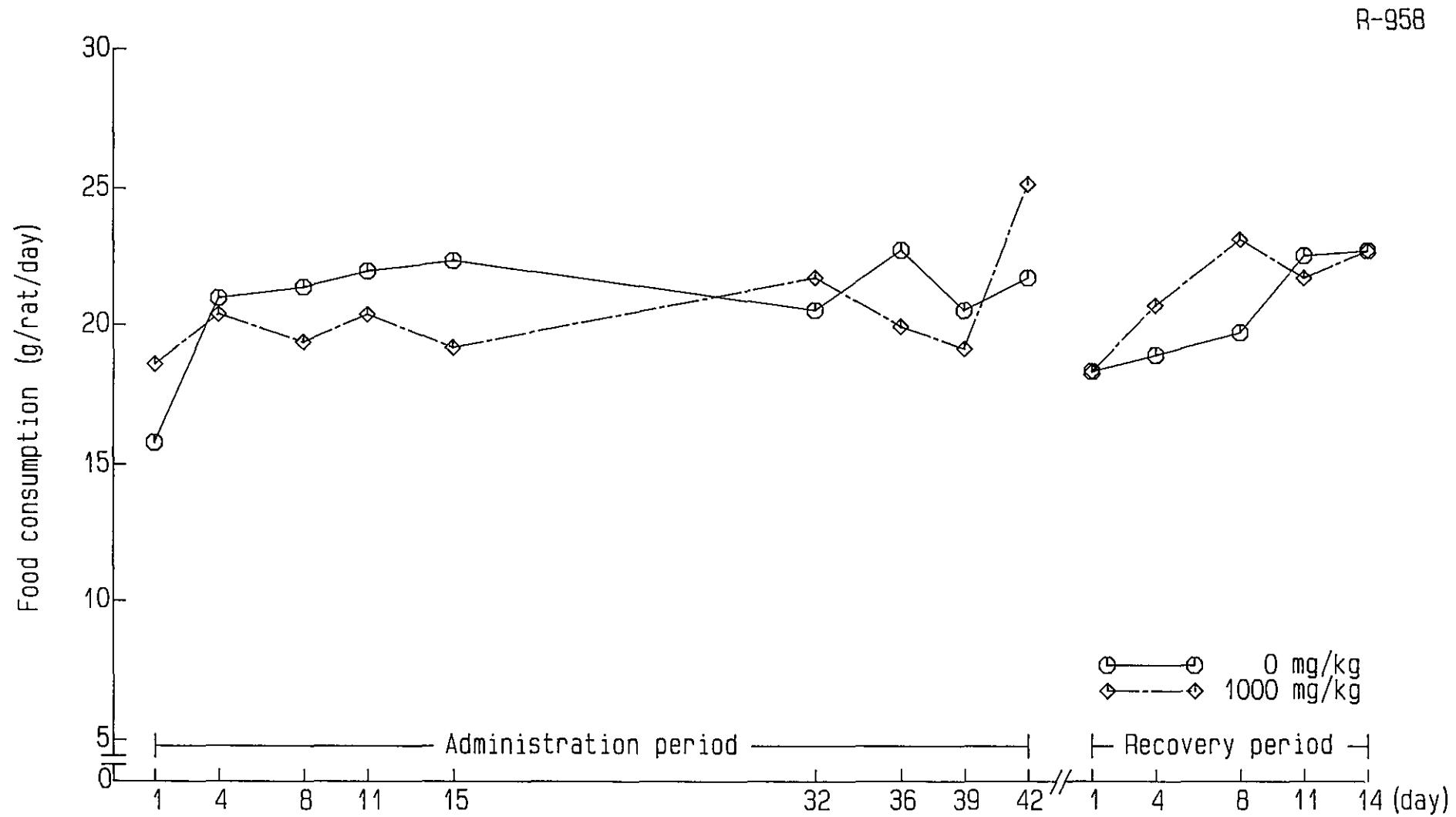


Fig.14 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Food consumption of female rats (Recovery group)

Table 1-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Clinical signs in male rats (Main group)

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

Table 1-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Table 1-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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	9	0
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	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	0
300	No. of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	8	0
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000	No. of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	9	0
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a): Day of gestation

Table 1-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

a): Day of lactation

Table 1-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Table 1-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Table 2-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-9

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	11	11
Posture					
Normal		12	12	11	11
Convulsion					
None		12	12	11	11
Abnormal behavior					
None		12	12	11	11

Table 2-10

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	11	11
Posture					
Normal		12	12	11	11
Convulsion					
None		12	12	11	11
Abnormal behavior					
None		12	12	11	11

Table 2-11

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-12

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-13

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	11	11
Posture					
Normal		12	12	11	11
Convulsion					
None		12	12	11	11
Abnormal behavior					
None		12	12	11	11

Table 2-14

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-15

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-16

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 2-17

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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
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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-19

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 2-20

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-21

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-22

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-23

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Detailed clinical signs in female 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 2-24

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-25

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-26

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-27

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Detailed clinical signs in female 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 2-28

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Detailed clinical signs in female 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 2-29

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-30

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-31

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		No. of animals	12	12	12
Ease of removal from cage					
Easy		11	11	11	11
Some resistance/avoidance		1	1	1	1
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		10	10	8	9
Soft		1	2	2	2
Moderate		1	0	2	1
Reactivity to handling					
Easy		11	11	10	10
Slightly awkward		0	1	2	1
Difficult		1	0	0	1

Table 2-32

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-33

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-34

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-35

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)				
		0	100	300	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy					
Some resistance/avoidance	12 0	10 2	11 1	11 1	
Fur condition					
Normal	12	12	12	12	
Skin					
Normal	12	12	12	12	
Secretions-Eye, Nose					
Absent	12	12	12	12	
Exophthalmos					
Absent	12	12	12	12	
Palpebral closure					
Normal	12	12	12	12	
Mucosal membranes					
Normal	12	12	12	12	
Lacration					
Normal	12	12	12	12	
Piloerection					
Absent	12	12	12	12	
Pupil size					
Normal	12	12	12	12	
Salivation					
None	12	12	12	12	
Abnormal respiration					
Absent	12	12	12	12	
Vocalization					
None	11	11	11	9	
Soft	1	0	1	3	
Moderate	0	1	0	0	
Reactivity to handling					
Easy	12 0	11 1	11 1	11 1	
Slightly awkward					

Table 2-36

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-37

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-38

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-39

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-40

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-41

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-42

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-43

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-44

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-45

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-46

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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
Ease of removal from cage			
Easy	4	4	
Some resistance/avoidance	1	1	
Fur condition			
Normal	5	5	
Skin			
Normal	5	5	
Secretions-Eye, Nose			
Absent	5	5	
Exophthalmos			
Absent	5	5	
Palpebral closure			
Normal	5	5	
Mucosal membranes			
Normal	5	5	
Lacration			
Normal	5	5	
Piloerection			
Absent	5	5	
Pupil size			
Normal	5	5	
Salivation			
None	5	5	
Abnormal respiration			
Absent	5	5	
Vocalization			
None	4	5	
Soft	1	0	
Reactivity to handling			
Easy	5	5	

Table 2-47

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-48

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Table 2-49

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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
Ease of removal from cage			
Easy	5	5	
Fur condition			
Normal	5	5	
Skin			
Normal	5	5	
Secretions-Eye, Nose			
Absent	5	5	
Exophthalmos			
Absent	5	5	
Palpebral closure			
Normal	5	5	
Mucosal membranes			
Normal	5	5	
Lacration			
Normal	5	5	
Piloerection			
Absent	5	5	
Pupil size			
Normal	5	5	
Salivation			
None	5	5	
Abnormal respiration			
Absent	5	5	
Vocalization			
None	5	4	
Soft	0	1	
Reactivity to handling			
Easy	5	5	

Table 2-50

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-51

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-52

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-53

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-54

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-55

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-56

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-57

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-58

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 2-59

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

No significant difference in any treated groups from control group.

Table 2-60

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

	Dose (mg/kg)	0	100	300	1000
Parameter	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		1	1	1	2
Normal		11	11	11	10
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)		3 $\pm$ 2	4 $\pm$ 2	3 $\pm$ 3	3 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		10	12	11	10
Small amount		2	0	1	2

No significant difference in any treated groups from control group.

Table 2-61

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		1	0	0	0
Normal		11	12	12	12
Posture					
Normal		12	12	12	12
C grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)		3 $\pm$ 2	4 $\pm$ 2	4 $\pm$ 2	3 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		9	10	10	11
Small amount		3	2	2	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

No significant difference in any treated groups from control group.

Table 2-64

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		0	1	0	0
Normal		12	11	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean+S.D.)		4± 1	4± 3	4± 2	4± 2
Defecation count (Mean+S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	9	10	10
Small amount		1	2	1	2
Moderate amount		0	1	1	0

No significant difference in any treated groups from control group.

Table 2-65

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	No. of animals	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)		5 $\pm$ 2	5 $\pm$ 3	6 $\pm$ 3	6 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		12	12	12	12

No significant difference in any treated groups from control group.

Table 2-66

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		0	0	1	0
Normal		12	12	11	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean $\pm$ S.D.)		6 $\pm$ 2	6 $\pm$ 3	5 $\pm$ 3	7 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		12	12	12	12

No significant difference in any treated groups from control group.

Table 2-67

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	11	11
Arousal					
Normal		12	12	11	11
Convulsion					
None		12	12	11	11
Abnormal behavior					
None		12	12	11	11
Stereotypy					
None		12	12	11	11
Gait					
Normal		12	12	11	11
Posture					
Normal		12	12	11	11
Grooming					
None		12	12	11	11
Rearing (Mean $\pm$ S.D.)		7 $\pm$ 2	7 $\pm$ 3	6 $\pm$ 2	7 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		12	11	11	11
Small amount		0	1	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	11	11
Arousal					
Normal		12	12	11	11
Convulsion					
None		12	12	11	11
Abnormal behavior					
None		12	12	11	11
Stereotypy					
None		12	12	11	11
Gait					
Normal		12	12	11	11
Posture					
Normal		12	12	11	11
Grooming					
None		12	12	11	11
Rearing (Mean $\pm$ S.D.)		6 $\pm$ 1	7 $\pm$ 2	6 $\pm$ 3	6 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		11	12	11	11
Small amount		1	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	11	11
Arousal					
Normal		12	12	11	11
Convulsion					
None		12	12	11	11
Abnormal behavior					
None		12	12	11	11
Stereotypy					
None		12	12	11	11
Gait					
Normal		12	12	11	11
Posture					
Normal		12	12	11	11
Grooming					
None		12	12	11	11
Rearing (Mean $\pm$ S.D.)		5 $\pm$ 1	6 $\pm$ 2	6 $\pm$ 2	5 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		12	12	11	11

No significant difference in any treated groups from control group.

Table 2-70

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	12	12	11	11
Arousal					
Normal		12	12	11	11
Convulsion					
None		12	12	11	11
Abnormal behavior					
None		12	12	11	11
Stereotypy					
None		12	12	11	11
Gait					
Normal		12	12	11	11
Posture					
Normal		12	12	11	11
Grooming					
None		12	12	11	11
Rearing (Mean $\pm$ S.D.)		6 $\pm$ 2	6 $\pm$ 1	4 $\pm$ 2	5 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		12	11	10	11
Small amount		0	1	1	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
		12	12	11	11
Arousal					
Normal		12	12	11	11
Convulsion					
None		12	12	11	11
Abnormal behavior					
None		12	12	11	11
Stereotypy					
None		12	12	11	11
Gait					
Normal		12	12	11	11
Posture					
Normal		12	12	11	11
Grooming					
None		12	12	11	11
Rearing (Mean $\pm$ S.D.)		8 $\pm$ 3	8 $\pm$ 2	7 $\pm$ 1	8 $\pm$ 2
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Urination					
None		12	12	11	11

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	1000
		5	5
Arousal			
Normal	5	5	
Convulsion			
None	5	5	
Abnormal behavior			
None	5	5	
Stereotypy			
None	5	5	
Gait			
Normal	5	5	
Posture			
Normal	5	5	
Grooming			
None	5	5	
Rearing (Mean $\pm$ S.D.)	3 $\pm$ 2	3 $\pm$ 2	
Defecation count (Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 1	
Urination			
None	4	5	
Small amount	1	0	

No significant difference between treated group and control group.

Table 2-73

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

No significant difference between treated group and control group.

Table 2-74

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
No/minimal location		1	0
Normal		4	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean $\pm$ S.D.)		2 $\pm$ 2	4 $\pm$ 1
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Urination			
None		4	4
Small amount		0	1
Moderate amount		1	0

No significant difference between treated group and control group.

Table 2-75

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
No/minimal location		1	0
Normal		4	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean $\pm$ S.D.)		3 $\pm$ 3	3 $\pm$ 0
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Urination			
None		4	4
Small amount		1	0
Moderate amount		0	1

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	1000
		5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean $\pm$ S.D.)	4 $\pm$ 4	4 $\pm$ 1	
Defecation count (Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	
Urination			
None	4	4	
Moderate amount	1	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Croombing			
None		5	5
Rearing (Mean $\pm$ S.D.)		4 $\pm$ 3	5 $\pm$ 1
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Urination			
None		2	3
Small amount		2	1
Moderate amount		1	1

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

No significant difference between treated group and control group.

Table 2-80

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

No significant difference between treated group and control group.

Table 2-81

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean $\pm$ S.D.)		6 $\pm$ 4	8 $\pm$ 4
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Urination			
None		5	5

No significant difference between treated group and control group.

Table 2-82

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

	Dose (mg/kg)	0	1000
Parameter	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean $\pm$ S.D.)		7 $\pm$ 3	9 $\pm$ 4
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Urination			
None		5	5

No significant difference between treated group and control group.

Table 2-83

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

No significant difference between treated group and control group.

Table 2-84

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

No significant difference between treated group and control group.

Table 2-85

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

No significant difference between treated group and control group.

Table 2-86

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

No significant difference between treated group and control group.

Table 2-87

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	No. of animals	Dose (mg/kg)	0	1000
			5	5
Arousal				
Normal		5	5	
Convulsion				
None		5	5	
Abnormal behavior				
None		5	5	
Stereotypy				
None		5	5	
Gait				
Normal		5	5	
Posture				
Normal		5	5	
Grooming				
None		5	5	
Rearing (Mean $\pm$ S.D.)		8 $\pm$ 1	7 $\pm$ 1	
Defecation count (Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	
Urination				
None		4	5	
Small amount		1	0	

No significant difference between treated group and control group.

Table 2-88

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	5	5	5	5
Auditory response					
Normal		5	5	5	5
Approach response					
Normal		5	5	5	5
Touch response					
Normal		5	5	5	5
Tail pinch response					
Normal		5	5	5	5
Pupillary reflex					
Pass, both		5	5	5	5
Aerial righting reflex					
(Total score: Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Landing foot splay (mm: Mean $\pm$ S.D.)		74 $\pm$ 19	85 $\pm$ 12	84 $\pm$ 12	77 $\pm$ 17

No significant difference in any treated groups from control group.

Table 2-89

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	100	300	1000
	No. of animals	5	5	5	5
Auditory response					
Normal		5	5	5	5
Approach response					
Normal		5	5	5	5
Touch response					
Normal		5	5	5	5
Tail pinch response					
Normal		5	5	5	5
Pupillary reflex					
Pass, both		5	5	5	5
Aerial righting reflex (Total score: Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	
Landing foot splay (mm: Mean $\pm$ S.D.)	58 $\pm$ 28	63 $\pm$ 3	79 $\pm$ 31	60 $\pm$ 17	

No significant difference in any treated groups from control group.

Table 2-90

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Landing foot splay (mm: Mean $\pm$ S.D.)		69 $\pm$ 27	86 $\pm$ 15

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal	5	5	
Approach response			
Normal	5	5	
Touch response			
Normal	5	5	
Tail pinch response			
Normal	5	5	
Pupillary reflex			
Pass, both	5	5	
Aerial righting reflex (Total score: Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	
Landing foot splay (mm: Mean $\pm$ S.D.).	61 $\pm$ 27	57 $\pm$ 16	

No significant difference between treated group and control group.

Table 2-92

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean $\pm$ S.D.)		0 $\pm$ 0	0 $\pm$ 0
Landing foot splay (mm: Mean $\pm$ S.D.)		85 $\pm$ 16	92 $\pm$ 14

No significant difference between treated group and control group.

Table 2-93

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal	5	5	
Approach response			
Normal	5	5	
Touch response			
Normal	5	5	
Tail pinch response			
Normal	5	5	
Pupillary reflex			
Pass, both	5	5	
Aerial righting reflex (Total score: Mean $\pm$ S.D.)	0 $\pm$ 0	0 $\pm$ 0	
Landing foot splay (mm: Mean $\pm$ S.D.)	75 $\pm$ 14	64 $\pm$ 6	

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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	935	785
	S.D.	163	143
100	No.	5	5
	Mean	1035	765
	S.D.	191	258
300	No.	5	5
	Mean	1046	972
	S.D.	151	156
1000	No.	5	5
	Mean	1083	993
	S.D.	238	186

No significant difference in any treated groups from control group.

Table 2-95

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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	1370	844
	S.D.	129	147
100	No.	5	5
	Mean	1278	742
	S.D.	150	88
300	No.	5	5
	Mean	1504	861
	S.D.	153	67
1000	No.	5	5
	Mean	1251	710
	S.D.	200	102

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1496	925
	S.D.	81	108
1000	No.	5	5
	Mean	1541	925
	S.D.	311	58

No significant difference between treated group and control group.

Table 2-97

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1150	811
	S.D.	117	101
1000	No.	5	5
	Mean	1181	809
	S.D.	163	79

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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	1637	954
	S.D.	195	119
1000	No.	5	5
	Mean	1735	991
	S.D.	91	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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	1234	836
	S.D.	63	65
1000	No.	5	5
	Mean	1237	845
	S.D.	231	174

No significant difference between treated group and control group.

Table 2-100

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No. Mean S.D.	5 422 50	5 247 145	5 85 89	5 70 56	5 88 154	5 36 30
100	No. Mean S.D.	5 440 33	5 337 56	5 189 82	5 149 117	5 88 119	5 43 88
300	No. Mean S.D.	5 390 49	5 218 111	5 155 133	5 135 127	5 80 77	5 157 143
1000	No. Mean S.D.	5 398 56	5 241 75	5 110 65	5 61 67	5 60 68	5 87 125
Total							
							948 263 1245 344 1134 461 957 252

No significant difference in any treated groups from control group.

Table 2-101

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No. Mean S.D.	5 370 74	5 220 146	5 120 105	5 157 132	5 120 104	5 104 135
100	No. Mean S.D.	5 286 129	5 172 108	5 137 115	5 82 88	5 104 93	5 135 139
300	No. Mean S.D.	5 296 114	5 145 175	5 142 177	5 143 133	5 143 152	5 110 137
1000	No. Mean S.D.	5 272 70	5 119 100	5 103 119	5 138 100	5 116 91	5 115 102

No significant difference in any treated groups from control group.

Table 2-102

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Interval (minutes)							
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)	
0	No. Mean S.D.	5 421 29	5 269 49	5 140 151	5 139 151	5 45 85	5 17 13	5 1032 395
1000	No. Mean S.D.	5 442 39	5 324 72	5 188 138	5 160 63	5 72 80	5 26 23	5 1213 354

No significant difference between treated group and control group.

Table 2-103

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	No.	Interval (minutes)						Total(0-60)
		0-10	10-20	20-30	30-40	40-50	50-60	
0	No.	5	5	5	5	5	5	5
0	Mean	347	275	129	25	40	22	837
0	S.D.	65	100	116	48	70	20	249
1000	No.	5	5	5	5	5	5	5
1000	Mean	380	225	128	158	100	82	1074
1000	S.D.	48	104	162	171	129	99	596

No significant difference between treated group and control group.

Table 2-104

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 446	400	345	324	319	191	2024
	S.D. 39	22	43	26	40	117	127
1000	No. 5	5	5	5	5	5	5
	Mean 420	344	274	268	233	181	1719
	S.D. 43	72	107	146	84	134	504

No significant difference between treated group and control group.

Table 2-105

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	No.	Interval (minutes)						Total(0-60)
		0-10	10-20	20-30	30-40	40-50	50-60	
0	No.	5	5	5	5	5	5	5
0	Mean	365	289	273	227	162	243	1558
0	S.D.	77	97	115	104	113	150	380
1000	No.	5	5	5	5	5	5	5
1000	Mean	372	273	293	217	222	225	1603
1000	S.D.	72	128	136	101	135	128	464

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Body weight of male rats (Main group)

Dose mg/kg	Pre-mating period					Mating period				Post-mating period				Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42a)	
0	No.	12	12	12	12	12	12	12	12	12	12	12	12	12
0	Mean	398.8	413.5	431.5	444.4	461.6	466.3	481.4	492.2	507.8	520.7	534.5	537.8	545.3
0	S.D.	18.2	20.0	20.2	20.6	22.2	20.7	24.1	26.6	29.5	30.6	31.9	34.2	36.6
100	No.	12	12	12	12	12	12	12	12	12	12	12	12	12
100	Mean	400.3	414.8	431.9	445.2	461.8	463.3	481.0	492.2	508.4	516.7	531.2	537.3	540.2
100	S.D.	15.5	17.8	20.9	24.1	26.2	25.5	26.7	28.3	30.1	31.1	32.4	34.9	36.8
300	No.	12	12	12	12	12	12	12	12	12	12	12	12	12
300	Mean	396.5	407.4	425.2	436.8	448.1	452.2	466.7	475.4	490.7	500.3	513.7	516.8	522.8
300	S.D.	14.8	13.9	16.1	16.5	19.4	21.4	22.2	24.3	26.5	26.1	28.2	30.3	32.8
1000	No.	12	12	12	12	12	12	12	12	12	12	12	12	12
1000	Mean	399.8	414.3	430.3	443.2	456.4	459.9	473.3	485.1	500.6	510.4	521.9	527.3	534.3
1000	S.D.	15.2	16.6	20.3	21.0	25.0	24.6	24.0	25.5	25.9	27.7	26.9	28.6	30.6

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of administration					Gain 1-15
	1	4	8	11	15	
0	No.	12	12	12	12	12
	Mean	244.5	252.6	263.1	270.6	278.8
	S.D.	11.7	13.7	15.6	16.9	9.7
100	No.	12	12	12	12	12
	Mean	245.2	252.3	263.1	267.5	276.4
	S.D.	12.2	10.3	11.8	12.8	12.5
300	No.	12	12	12	12	12
	Mean	245.3	250.3	260.8	267.2	274.5
	S.D.	10.5	14.9	14.7	17.4	19.3
1000	No.	12	12	12	12	12
	Mean	244.8	249.8	257.7	264.1	270.3
	S.D.	13.8	13.6	14.7	13.5	13.1

Unit: g

No.: No. of animals

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

D: Dunnett's test

Table 3-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Administration							Gain 0-20
	0	4	7	11	14	17	20a)	
0	No.	12	12	12	12	12	12	12
	Mean	283.9	307.7	319.4	340.1	357.0	386.8	433.4
	S.D.	16.9	18.6	20.6	20.1	21.0	22.6	25.9
100	No.	12	12	12	12	12	12	12
	Mean	282.7	308.3	321.1	344.3	359.9	391.9	436.7
	S.D.	12.1	13.7	14.6	16.5	19.5	24.2	27.8
300	No.	11	11	11	11	11	11	11
	Mean	281.5	305.8	319.9	341.9	360.5	393.7	442.5
	S.D.	13.3	13.7	16.4	17.7	20.4	20.7	20.3
1000	No.	11	11	11	11	11	11	11
	Mean	276.5	302.8	314.9	338.4	354.2	384.5	431.9
	S.D.	15.6	17.6	16.6	23.3	20.9	23.1	26.6

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Administration		Gain 0-4
	0	4a)	
0	No.	12	12
	Mean	341.3	355.3
	S.D.	23.7	18.5
100	No.	12	12
	Mean	338.8	360.1
	S.D.	27.4	24.1
300	No.	11	11
	Mean	345.1	358.3
	S.D.	26.4	14.9
1000	No.	11	11
	Mean	345.5	359.1
	S.D.	19.9	30.5
			14.0

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of administration													Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42	
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5
0	Mean	399.2	414.0	435.4	449.8	467.2	474.2	492.8	499.0	514.0	522.8	534.2	545.4	544.0
0	S.D.	15.1	19.1	17.0	17.9	22.6	18.2	21.9	19.8	20.6	24.3	24.9	28.2	30.1
1000	No.	5	5	5	5	5	5	5	5	5	5	5	5	5
1000	Mean	403.2	414.8	431.6	444.8	458.2	471.4	486.4	497.0	514.6	524.8	536.6	545.8	546.0
1000	S.D.	21.1	23.1	25.8	28.4	30.5	34.1	32.2	33.0	33.9	34.1	36.3	39.5	39.1

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of administration													Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42	
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5
0	Mean	241.4	249.0	263.8	269.6	280.2	282.8	288.2	296.8	301.6	304.0	308.4	309.4	311.4
0	S.D.	13.7	14.9	13.9	16.5	18.0	17.1	16.1	19.4	18.8	21.4	20.9	22.0	21.4
1000	No.	5	5	5	5	5	5	5	5	5	5	5	5	5
1000	Mean	251.2	253.6	262.6	266.0	274.2	281.0	291.2	297.2	305.4	307.4	308.2	312.8	319.8
1000	S.D.	11.6	15.1	9.2	9.7	10.6	10.2	9.6	14.7	13.5	15.9	16.0	17.0	15.6

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of recovery					Gain 1-14
	1	4	8	11	14	
0	No.	5	5	5	5	5
	Mean	547.0	549.6	561.0	563.2	568.2
	S.D.	29.8	29.1	33.1	29.9	32.5
1000	No.	5	5	5	5	5
	Mean	549.8	558.2	569.4	571.2	575.2
	S.D.	39.8	37.7	41.0	40.0	40.7

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of recovery					Gain 1-14
	1	4	8	11	14	
0	No. 5	5	5	5	5	5
0	Mean 310.0	312.0	314.8	321.2	322.2	12.2
0	S.D. 25.3	23.6	22.1	26.5	28.0	8.1
1000	No. 5	5	5	5	5	5
1000	Mean 317.6	318.8	325.4	324.4	329.8	12.2
1000	S.D. 21.0	16.4	18.5	25.3	29.3	14.2

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Food consumption of male rats (Main group)

Dose mg/kg	Pre-mating period					Post-mating period			
	1	4	8	11	15	32	36	39	42a)
0	No.	12	12	12	12	12	12	12	12
0	Mean	27.4	32.2	30.3	29.8	30.0	30.9	32.5	30.8
0	S.D.	3.9	2.5	3.0	2.5	3.0	2.2	3.0	3.4
100	No.	12	12	12	12	12	12	12	12
100	Mean	28.6	32.8	31.0	30.4	29.3	31.3	32.6	32.1
100	S.D.	3.2	3.1	3.0	5.1	4.1	3.0	2.2	3.1
300	No.	12	12	12	12	12	12	12	12
300	Mean	25.8	30.2	28.8	28.9	26.7	29.0	29.3**	29.1
300	S.D.	2.6	3.0	2.3	2.0	1.9	2.1	1.9D	3.3
1000	No.	12	12	12	12	12	12	12	12
1000	Mean	28.1	32.3	29.4	29.8	29.8	30.3	31.6	30.8
1000	S.D.	3.8	3.3	3.9	2.5	4.0	2.8	3.0	2.4

Unit: g/rat/day

No.: No. of animals

a): Day of administration

\*\*: p<0.01 (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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of administration					
	1	4	8	11	15	
0	No. Mean S.D.	12 16.9 2.5	12 22.7 2.4	12 21.7 2.4	12 22.1 3.0	12 21.7 2.4
100	No. Mean S.D.	12 18.8 3.6	12 23.2 2.6	12 23.2 2.6	12 21.7 2.2	12 22.4 3.1
300	No. Mean S.D.	12 17.8 3.2	12 21.3 3.3	12 19.9 2.5	12 20.9 3.3	12 20.9 4.0
1000	No. Mean S.D.	12 17.6 3.4	12 20.7 3.4	12 19.7 3.2	12 21.8 2.1	12 21.3 2.4

Unit: g/rat/day

No.: No. of animals

No significant difference in any treated groups from control group.

Table 4-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Administration						
	1	4	7	11	14	17	20a)
0	No. Mean S.D.	12 22.5 3.4	12 24.8 2.8	12 26.1 2.7	12 27.2 2.9	12 26.8 3.5	12 27.6 2.5
100	No. Mean S.D.	12 23.8 4.0	12 26.3 3.2	12 27.3 3.9	12 28.0 3.5	12 27.8 3.6	12 30.7 5.0
300	No. Mean S.D.	11 23.2 2.3	11 24.7 2.7	11 26.3 3.3	11 27.9 4.1	11 26.5 3.4	11 30.3 3.2
1000	No. Mean S.D.	11 23.2 2.8	11 25.1 2.3	11 25.5 3.0	11 28.5 4.0	11 26.5 3.7	11 28.9 3.3
							25.5 2.5

Unit: g/rat/day

No.: No. of dams

a): Day of gestation

No significant difference in any treated groups from control group.

Table 4-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg		Administration	
		2	4a)
0	No.	12	12
0	Mean	26.8	44.3
0	S.D.	6.2	5.4
100	No.	12	12
100	Mean	30.5	47.3
100	S.D.	7.5	6.0
300	No.	11	11
300	Mean	26.8	46.5
300	S.D.	6.1	4.3
1000	No.	11	11
1000	Mean	27.7	43.5
1000	S.D.	3.1	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of administration								
	1	4	8	11	15	32	36	39	42
0	No.	5	5	5	5	5	5	5	5
	Mean	26.6	31.4	29.2	29.8	29.2	30.0	29.8	33.6
	S.D.	2.6	2.6	0.8	0.8	1.1	1.4	1.8	2.8
1000	No.	5	5	5	5	5	5	5	5
	Mean	29.4	32.0	28.8	29.8	29.2	31.6	32.4	31.8
	S.D.	3.0	4.7	3.0	3.7	3.6	2.4	3.6	2.2

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of administration								
	1	4	8	11	15	32	36	39	42
0	No.	5	5	5	5	5	5	5	5
0	Mean	15.8	21.0	21.4	22.0	22.4	20.6	22.8	20.6
0	S.D.	4.3	3.8	3.1	3.3	3.8	3.0	3.4	1.9
1000	No.	5	5	5	5	5	5	5	5
1000	Mean	18.6	20.4	19.4	20.4	19.2	21.8	20.0	19.2
1000	S.D.	1.1	2.4	3.3	2.7	4.3	2.5	5.1	6.5
									25.2*
									1.8T

Unit: g/rat/day

No.: No. of animals

\*: p<0.05 (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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	Day of recovery				
	1	4	8	11	14
0	No.	5	5	5	5
	Mean	28.6	27.2	29.6	30.6
	S.D.	5.1	2.9	4.8	2.4
1000	No.	5	5	5	5
	Mean	28.0	32.4*	32.0	32.0
	S.D.	1.6	2.9T	3.9	2.9

Unit: g/rat/day

No.: No. of animals

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

T: Student's t-test

Table 4-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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
	Mean	18.4	19.0	19.8	22.6
	S.D.	2.7	2.3	2.2	4.0
1000	No.	5	5	5	5
	Mean	18.4	20.8	23.2*	21.8
	S.D.	4.8	1.5	2.3T	2.2

Unit: g/rat/day

No.: No. of animals

\*: p<0.05 (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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

1) - : &lt;10 mg/dL

+- : 10 - 25 mg/dL

+ : 26 - 85 mg/dL

++ : 86 - 250 mg/dL

+++ : 251 - 600 mg/dL

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

2) - : &lt;5 mg/dL

+- : 5 - 7.5 mg/dL

+ : 7.6 - 30 mg/dL

++ : 31 - 70 mg/dL

+++ : 71 - 125 mg/dL

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

3) - : &lt;30 mg/dL

+- : 30 - 60 mg/dL

+ : 61 - 125 mg/dL

++ : 126 - 250 mg/dL

+++ : 251 - 750 mg/dL

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

Table 5-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	4) Occult blood					5) Bilirubin					6) Urobilinogen					7) Color		
		-	+-	+	++	+++	-	+	++	+++	++++	-	+	++	+++	++++	LY	Y	DY
0	17	14	2	1	0	0	17	0	0	0	0	17	0	0	0	0	0	17	0
100	12	9	3	0	0	0	12	0	0	0	0	12	0	0	0	0	0	12	0
300	12	8	3	0	1	0	12	0	0	0	0	12	0	0	0	0	0	12	0
1000	17	15	2	0	0	0	17	0	0	0	0	16	1	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose mg/kg	No.	URINE SEDIMENT												CRYSTALLIZATION																
		RBC				WBC				SEC				SREC				Cast			PS			CO						
		-	+-	+	++	-	+-	+	++	-	+-	+	++	-	+-	+	++	-	+-	+	-	+-	+	++	-	+-	+	++		
0	17	17	0	0	0	0	17	0	0	0	0	0	17	0	0	0	0	17	0	0	1	9	7	0	0	17	0	0	0	0
100	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	0	12	0	0	2	5	5	0	0	12	0	0	0	0
300	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	0	12	0	0	5	5	2	0	0	12	0	0	0	0
1000	17	16	1	0	0	0	17	0	0	0	0	0	17	0	0	0	0	17	0	0	14	3	0	0	0	17	0	0	0	0

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

Table 5-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Water intake and urinalysis (Week 6 of administration)

Male

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
0	17	Mean	49	22.7	1769
		S.D.	10	7.5	451
100	12	Mean	47	21.2	1868
		S.D.	12	7.7	431
300	12	Mean	44	19.2	1876
		S.D.	6	7.5	357
1000	17	Mean	46	20.6	1863
		S.D.	9	6.1	333

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

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

Table 5-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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	3	2	0	0	0	5	0	0	0	0	4	1	0	0	0	0	5	0
1000	5	4	0	0	1	0	5	0	0	0	0	4	1	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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

URINE SEDIMENT															CRYSTALLIZATION														
Dose mg/kg	No.	RBC				WBC				SEC				SREC				Cast			PS			CO					
		-	+-	++	+++	-	+-	++	+++	-	+-	++	+++	-	+-	++	+++	-	+-	+	-	+-	++	+++	-	+-	++	+++	
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	0	5	0	0	0	2	3	0	0	5	0	0	0
1000	5	4	0	1	0	0	5	0	0	0	0	0	5	0	0	0	0	5	0	0	0	4	1	0	0	5	0	0	0

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

Table 5-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Water intake and urinalysis (Week 2 of recovery)

Male

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
0	5	Mean	53	20.2	1952
		S.D.	16	8.9	600
1000	5	Mean	49	21.5	1724
		S.D.	9	3.1	161

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Hematology (Week 6 of administration)

Male

Dose mg/kg	No.	RBC X10 <sup>4</sup> /μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let X10 <sup>4</sup> /μL	PT s	APTT s	Fibri- nogen mg/dL
0	5	Mean 903	16.7	44.2	49.0	18.5	37.8	1.8	112.9	14.7	25.6	298
		S.D. 17	0.5	1.4	1.2	0.5	0.5	0.2	13.7	1.3	3.6	41
100	5	Mean 918	16.7	43.7	47.6	18.2	38.2	1.8	111.6	15.2	21.9	301
		S.D. 29	0.4	1.2	0.7	0.2	0.5	0.5	12.3	1.0	3.0	34
300	5	Mean 907	16.5	43.6	48.1	18.3	37.9	1.7	109.6	15.2	23.0	298
		S.D. 49	0.4	1.1	2.5	1.0	0.2	0.2	7.0	1.8	2.9	15
1000	5	Mean 916	16.8	44.8	49.0	18.4	37.6	1.5	114.4	15.1	23.3	293
		S.D. 32	0.4	1.3	2.1	0.7	0.4	0.3	14.1	1.8	3.1	18

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 diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Hematology (Week 6 of administration)

Male

Dose mg/kg	No.	WBC X10 <sup>3</sup> /μL	Differential leukocyte counts (%)					Differential leukocyte counts (X10 <sup>2</sup> /μL)							
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	
0	5	Mean	99.9	75.5	20.3	1.4	0.5	1.9	0.5	75.7	20.0	1.3	0.5	1.9	0.5
		S.D.	25.7	6.3	5.9	0.7	0.0	0.4	0.2	20.9	6.8	0.5	0.1	0.4	0.4
100	5	Mean	116.0	77.7	17.7	1.5	0.5	2.0	0.6	91.8	19.1	1.6	0.5	2.2	0.7
		S.D.	30.3	8.3	7.3	0.7	0.1	0.7	0.5	33.5	5.9	0.5	0.2	0.3	0.6
300	5	Mean	94.2	75.0	19.9	1.2	0.4	2.9	0.6	70.7	18.7	1.1	0.4	2.7	0.6
		S.D.	11.4	5.6	5.5	0.5	0.1	0.8	0.4	11.0	5.2	0.4	0.1	0.8	0.3
1000	5	Mean	102.2	77.9	17.8	1.0	0.5	2.3	0.5	80.1	17.8	1.0	0.5	2.3	0.5
		S.D.	29.7	7.0	6.1	0.4	0.1	0.6	0.2	26.5	5.6	0.3	0.2	0.6	0.2

LUC : Large unstained cells

No significant difference in any treated groups from control group.

Table 6-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Hematology (Day 4 of lactation)

Female

Dose mg/kg	No.	RBC X10 <sup>6</sup> /μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let X10 <sup>4</sup> /μL	PT s	APTT s	Fibri- nogen mg/dL
0	5	Mean 755	14.4	38.8	51.4	19.1	37.2	5.1	144.0	12.4	17.6	297
		S.D. 16	0.3	0.5	1.3	0.4	0.6	1.4	18.7	0.9	3.3	35
100	5	Mean 741	14.6	39.3	53.0	19.7	37.2	5.9	134.6	12.2	17.3	286
		S.D. 37	0.6	2.0	2.3	0.5	0.7	0.4	9.5	1.4	3.4	28
300	5	Mean 768	14.8	40.3	52.6	19.3	36.7	5.7	136.5	12.7	16.7	347
		S.D. 76	1.1	2.7	2.0	0.6	0.4	1.9	17.6	1.2	2.3	86
1000	5	Mean 772	14.7	39.9	51.8	19.1	36.9	5.0	140.4	12.5	18.4	287
		S.D. 48	0.8	2.2	2.1	0.6	0.4	1.3	12.6	0.7	1.8	24

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Hematology (Day 4 of lactation)

Female

Dose mg/kg	No.	WBC X10 <sup>3</sup> /μL	Differential leukocyte counts (%)					Differential leukocyte counts (X10 <sup>3</sup> /μL)							
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	
0	5	Mean	121.3	63.5	32.0	0.9	0.3	2.7	0.6	77.1	38.7	1.0	0.4	3.3	0.8
		S.D.	36.1	6.8	6.9	0.4	0.1	0.4	0.3	24.2	13.4	0.3	0.2	1.3	0.6
100	5	Mean	127.4	60.0	35.9	0.7	0.3	2.6	0.6	75.8	46.5	0.9	0.3	3.1	0.7
		S.D.	24.1	8.9	9.4	0.3	0.1	1.1	0.3	14.7	19.7	0.4	0.1	1.2	0.3
300	5	Mean	107.0	64.9	30.1	0.9	0.3	3.2	0.6	69.0	32.5	1.0	0.3	3.5	0.6
		S.D.	14.8	8.4	8.2	0.6	0.1	0.5	0.2	10.4	12.2	0.4	0.1	0.9	0.2
1000	5	Mean	150.2	60.7	35.4	0.7	0.3	2.4	0.6	94.2	50.1	0.9	0.5	3.6	1.0
		S.D.	42.9	12.1	12.2	0.4	0.1	0.2	0.4	36.9	12.4	0.4	0.2	1.1	0.7

LUC : Large unstained cells

No significant difference in any treated groups from control group.

Table 6-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Hematology (Day 14 of recovery)

Male

Dose mg/kg	No.	RBC X10 <sup>6</sup> /μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let X10 <sup>3</sup> /μL	PT s	APTT s	Fibri- nogen mg/dL
0	5	Mean	916	16.4	43.6	47.6	17.9	37.7	2.0	116.2	14.7	22.2
		S.D.	22	0.3	0.7	1.2	0.4	0.5	0.3	5.2	1.4	3.9
1000	5	Mean	926	16.7	44.2	47.8	18.0	37.7	1.8	118.1	14.7	22.8
		S.D.	12	0.3	1.3	1.6	0.4	0.4	0.6	14.1	0.6	4.0
												299
												45
												293
												43

No significant difference between treated group and control group.

Table 6-6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Hematology (Day 14 of recovery)

Male

Dose mg/kg	No.	WBC X10 <sup>3</sup> /μL	Differential leukocyte counts (%)					Differential leukocyte counts (X10 <sup>2</sup> /μL)							
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	
0	5	Mean	96.7	79.7	16.4	1.4	0.3	1.7	0.4	77.2	15.7	1.3	0.4	1.7	0.4
		S.D.	28.7	4.8	4.9	0.7	0.2	0.5	0.1	24.4	6.0	0.6	0.2	0.8	0.2
1000	5	Mean	113.1	81.3	15.1	1.1	0.4	1.7	0.4	91.5	17.5	1.1	0.5	2.0	0.5
		S.D.	33.7	6.1	6.0	0.4	0.1	0.4	0.2	26.8	10.8	0.3	0.2	0.8	0.3

LUC : Large unstained cells

No significant difference between treated group and control group.

Table 6-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Hematology (Day 14 of recovery)

Female

Dose mg/kg	No.	RBC X10 <sup>6</sup> /μL	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let X10 <sup>3</sup> /μL	PT s	APTT s	Fibri- nogen mg/dL
0	5	Mean	816	15.8	40.9	50.2	19.4	38.6	1.6	116.8	12.4	18.4
		S.D.	41	0.2	1.1	1.7	0.7	0.5	0.5	13.3	0.6	1.4
1000	5	Mean	840	16.0	42.0	49.9	19.1	38.2	1.5	115.7	12.9	19.3
		S.D.	28	0.6	1.9	0.7	0.2	0.4	0.4	9.9	0.1	3.7

No significant difference between treated group and control group.

Table 6-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Hematology (Day 14 of recovery)

Female

Dose mg/kg	No.	WBC X10 <sup>3</sup> /μL	Differential leukocyte counts (%)					Differential leukocyte counts (X10 <sup>3</sup> /μL)							
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	
0	5	Mean	63.5	74.5	22.0	1.2	0.3	1.6	0.4	47.1	14.2	0.7	0.2	1.0	0.3
		S.D.	9.2	4.0	3.8	0.3	0.1	0.6	0.2	5.2	3.8	0.2	0.1	0.5	0.1
1000	5	Mean	46.1**	75.0	20.6	2.0*	0.2	1.7	0.5	34.7**	9.4*	0.9	0.1	0.8	0.2
		S.D.	5.8T	4.4	4.5	0.5T	0.1	0.7	0.1	6.0T	1.7T	0.3	0.1	0.2	0.1

LUC : Large unstained cells

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

T : Student's t-test

Table 7-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Blood chemistry (Week 6 of administration)

Male

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	5	Mean	75	29	59	1	383	50	34	81	0.1	134
		S.D.	11	7	13	0	55	8	17	13	0.1	2
100	5	Mean	72	34	58	1	461	42	33	74	0.1	142
		S.D.	8	5	11	1	102	9	6	12	0.0	14
300	5	Mean	75	37	55	1	367	44	26	73	0.1	142
		S.D.	7	5	14	1	60	8	10	9	0.0	15
1000	5	Mean	66	32	51	1	380	47	38	80	0.1	156*
		S.D.	7	3	6	0	41	9	18	15	0.0	13D

\* : p&lt;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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Blood chemistry (Week 6 of administration)

Male

Dose mg/kg	No.		BUN mg/dL	Crea- tinine mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	16	0.26	144	4.9	108	9.5	6.5	6.2	2.8	0.81
		S.D.	2	0.04	1	0.1	1	0.3	0.3	0.3	0.1	0.04
100	5	Mean	14	0.25	144	4.7	107	9.5	6.6	6.1	2.8	0.85
		S.D.	2	0.05	1	0.3	1	0.2	0.6	0.3	0.1	0.04
300	5	Mean	15	0.23	143	4.8	109	9.4	6.3	6.0	2.8	0.85
		S.D.	2	0.03	1	0.2	2	0.1	0.5	0.2	0.1	0.05
1000	5	Mean	13	0.24	144	4.7	107	9.6	6.3	6.0	2.8	0.85
		S.D.	2	0.05	1	0.2	1	0.2	0.3	0.2	0.1	0.05

No significant difference in any treated groups from control group.

Table 7-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Blood chemistry (Day 4 of lactation)

Female

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	5	Mean	81	50	56	1	234	48	25	91	0.1	143
		S.D.	16	16	7	0	56	12	9	14	0.1	8
100	5	Mean	73	46	52	1	223	56	34	104	0.1	138
		S.D.	5	7	10	0	73	12	7	17	0.0	8
300	5	Mean	118	82	61	1	257	58	36	105	0.1	138
		S.D.	79	63	8	1	83	20	26	33	0.0	15
1000	5	Mean	87	57	58	1	227	55	43	110	0.1	145
		S.D.	24	21	10	0	118	16	9	24	0.0	7

No significant difference in any treated groups from control group.

Table 7-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Blood chemistry (Day 4 of lactation)

Female

Dose mg/kg	No.		BUN mg/dL	Crea- tinine mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	15	0.32	142	4.3	108	10.0	7.2	6.4	3.0	0.87
		S.D.	1	0.04	1	0.4	1	0.4	1.6	0.5	0.2	0.02
100	5	Mean	15	0.27	141	4.3	109	10.0	6.7	6.2	2.9	0.87
		S.D.	2	0.03	1	0.3	2	0.4	0.8	0.5	0.1	0.06
300	5	Mean	17	0.28	142	4.8	108	10.2	7.9	6.4	2.9	0.85
		S.D.	2	0.03	2	0.2	3	0.4	0.7	0.2	0.1	0.07
1000	5	Mean	16	0.30	141	4.3	108	10.1	7.0	6.5	3.0	0.88
		S.D.	3	0.03	1	0.4	2	0.3	1.3	0.3	0.1	0.02

No significant difference in any treated groups from control group.

Table 7-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Blood chemistry (Day 14 of recovery)

Male

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	5	Mean	61	29	54	1	366	52	36	84	0.1	141
		S.D.	5	3	6	0	74	11	20	12	0.0	17
1000	5	Mean	66	33	54	1	336	53	42	86	0.1	140
		S.D.	9	4	7	0	45	8	23	11	0.0	7

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Blood chemistry (Day 14 of recovery)

Male

Dose mg/kg	No.		BUN mg/dL	Crea- tinine mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	15	0.25	145	4.4	107	9.7	6.2	6.4	2.8	0.79
		S.D.	2	0.04	1	0.3	2	0.3	0.5	0.3	0.1	0.04
1000	5	Mean	15	0.24	145	4.3	108	9.9	5.9	6.2	2.8	0.81
		S.D.	1	0.03	1	0.3	0	0.2	0.2	0.1	0.1	0.02

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Blood chemistry (Day 14 of recovery)

Female

Dose mg/kg	No.	AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	5	Mean	77	33	62	2	189	66	15	120	0.1
		S.D.	30	13	18	1	25	13	5	18	0.0
1000	5	Mean	65	50	55	2	178	54	14	104	0.1
		S.D.	3	40	9	1	80	7	6	18	0.0
											146
											5
											136
											15

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Blood chemistry (Day 14 of recovery)

Female

Dose mg/kg	No.		BUN mg/dL	Crea- tinine mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	17	0.30	145	4.0	111	10.0	4.9	6.8	3.2	0.91
		S.D.	2	0.03	1	0.4	1	0.3	0.4	0.2	0.1	0.05
1000	5	Mean	17	0.27	144	4.3	112	9.9	4.9	6.6	3.2	0.93
		S.D.	2	0.02	2	0.4	2	0.2	0.2	0.4	0.2	0.06

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Organ weight of male rats (Main group)

	Dose mg/kg	Body weight g	Brain	Thyroid (R+L)	Thymus	Heart	Liver
			g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	0	No. Mean S.D.	5 487 22	5 2.11 0.08	5 23.1 2.9	5 281 59	5 1.45 0.10
	100	No. Mean S.D.	5 495 15	5 2.19 0.06	5 22.9 3.5	5 309 38	5 1.48 0.08
	300	No. Mean S.D.	5 483 30	5 2.11 0.10	5 23.1 5.2	5 288 72	5 1.38 0.10
Relative	1000	No. Mean S.D.	5 498 32	5 2.06 0.04	5 24.0 4.8	5 295 52	5 1.46 0.06
	0	No. Mean S.D.	5 0.44 0.03	5 4.7 0.6	5 57 12	5 0.30 0.01	5 2.48 0.13
	100	No. Mean S.D.	5 0.44 0.02	5 4.6 0.8	5 62 8	5 0.30 0.01	5 2.55 0.16
	300	No. Mean S.D.	5 0.44 0.03	5 4.7 0.8	5 59 13	5 0.29 0.02	5 2.56 0.15
	1000	No. Mean S.D.	5 0.42 0.03	5 4.8 0.9	5 60 12	5 0.29 0.02	5 2.65 0.17

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Organ weight of male rats (Main group)

	Dose mg/kg	Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Body weight g	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)
	0	No. 5 Mean 0.76 S.D. 0.08	5 4.08 66 1.73	5 66 12	12 510 33	12 3.52 0.24	12 1310 111
Absolute	100	No. 5 Mean 0.78 S.D. 0.11	5 3.41 60 0.28	5 60 3	12 511 32	12 3.33 0.40	12 1303 89
	300	No. 5 Mean 0.85 S.D. 0.21	5 3.28 64 0.26	5 64 6	12 489 31	12 3.33 0.32	12 1324 82
	1000	No. 5 Mean 0.79 S.D. 0.08	5 3.37 70 0.19	5 70 12	12 500 28	12 3.30 0.28	12 1295 131
	0	No. 5 Mean 0.16 S.D. 0.02	5 0.84 14 0.37	5 14 2		12 0.70 0.07	12 258 27
Relative	100	No. 5 Mean 0.16 S.D. 0.03	5 0.69 12 0.06	5 12 1		12 0.65 0.07	12 256 21
	300	No. 5 Mean 0.18 S.D. 0.03	5 0.68 13 0.05	5 13 1		12 0.68 0.07	12 271 17
	1000	No. 5 Mean 0.16 S.D. 0.01	5 0.68 14 0.05	5 14 2		12 0.66 0.06	12 259 23

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Organ weight of female rats (Main group)

Dose mg/kg	No.	Body weight g	Brain	Thyroid (R+L)	Thymus	Heart	Liver
			g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	0	5	5	5	5	5	5
	Mean	306	2.03	19.0	225	0.99	10.16
	S.D.	13	0.04	2.6	42	0.08	0.57
100	No.	5	5	5	5	5	5
	Mean	315	1.95	16.4	209	0.98	10.39
	S.D.	22	0.04	2.4	33	0.05	1.46
300	No.	5	5	5	5	5	5
	Mean	318	1.98	14.9	202	1.04	10.62
	S.D.	16	0.04	1.8	76	0.07	0.64
1000	No.	5	5	5	5	5	5
	Mean	310	1.94*	16.2	232	0.98	10.52
	S.D.	15	0.08D	4.3	53	0.10	1.07
Relative	0	No.	5	5	5	5	5
	Mean		0.66	6.2	74	0.33	3.32
	S.D.		0.03	0.9	16	0.02	0.10
100	No.	5	5	5	5	5	5
	Mean		0.62	5.2	66	0.31	3.29
	S.D.		0.04	0.6	10	0.02	0.30
300	No.	5	5	5	5	5	5
	Mean		0.62	4.7*	64	0.33	3.34
	S.D.		0.04	0.5D	24	0.04	0.19
1000	No.	5	5	5	5	5	5
	Mean		0.63	5.2	75	0.32	3.39
	S.D.		0.05	1.4	20	0.03	0.27

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

D: Dunnett's test

Table 8-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 0.62	2.03	93
		S.D. 0.05	0.06	8
	100	No. 5	5	5
		Mean 0.63	2.16	83
		S.D. 0.13	0.20	14
	300	No. 5	5	5
		Mean 0.68	2.26	88
		S.D. 0.07	0.31	10
	1000	No. 5	5	5
		Mean 0.65	2.07	89
		S.D. 0.13	0.10	13
Relative	0	No. 5	5	5
		Mean 0.20	0.67	31
		S.D. 0.01	0.03	4
	100	No. 5	5	5
		Mean 0.20	0.69	27
		S.D. 0.03	0.04	3
	300	No. 5	5	5
		Mean 0.21	0.71	28
		S.D. 0.03	0.08	3
	1000	No. 5	5	5
		Mean 0.21	0.67	29
		S.D. 0.03	0.05	4

No significant difference in any treated groups from control group.

Table 8-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 S.D.	530 30	2.15 0.06	26.7 4.8	293 72	1.47 0.19
	1000	5	Mean S.D.	534 40	2.20 0.09	24.4 4.3	271 50	1.49 0.09
Relative	0	5	Mean S.D.		0.41 0.03	5.1 1.1	55 15	0.28 0.02
	1000	5	Mean S.D.		0.41 0.03	4.6 0.9	51 7	2.49 0.15

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 S.D.	0.79 0.10	3.52 0.31	62 8	3.54 0.16
	1000	5	Mean S.D.	0.83 0.13	3.38 0.44	67 6	3.40 0.26
Relative	0	5	Mean S.D.	0.15 0.02	0.67 0.06	12 2	0.67 0.04
	1000	5	Mean S.D.	0.15 0.03	0.63 0.08	13 2	0.64 0.07

No significant difference between treated group and control group.

Table 8-7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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	299	2.05	16.7	282	0.95
			S.D.	26	0.04	1.8	35	0.09
	1000	5	Mean	307	1.99	19.7	292	0.93
			S.D.	23	0.07	2.7	86	0.03
Relative	0	5	Mean		0.69	5.6	94	2.54
			S.D.		0.05	0.6	8	0.12
	1000	5	Mean		0.65	6.4	95	2.41
			S.D.		0.03	0.8	28	0.20

No significant difference between treated group and control group.

Table 8-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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 S.D.	0.58 0.11	1.93 0.32
	1000	5	Mean S.D.	0.55 0.07	2.21 0.14
Relative	0	5	Mean S.D.	0.19 0.02	0.64 0.05
	1000	5	Mean S.D.	0.18 0.02	0.73 0.10

No significant difference between treated group and control group.

Table 9

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Gross pathological findings (Main group)

Organs Findings	Sex: Dose(mg/kg): Number:	M 0 12	M 100 12	M 300 12	M 1000 12	F 0 12	F 100 12	F 300 12	F 1000 12
Epididymis									
Focus,yellow		1	1	0	0	-	-	-	-
Kidney									
Nodule		1	0	0	0	0	0	0	0
Focus,white		0	0	0	0	0	0	1	0
Lung(bronchus)									
Focus,dark red		0	0	0	0	1	0	0	0
Stomach									
Focus,dark red,glandular stomach		1	0	0	2	5	2	2	3
Urinary bladder									
Thickening,wall		0	0	0	0	0	0	1	0
Content,white fluid		0	0	0	0	0	0	1	0

-: Not applicable

No lesions were noted in recovery groups.

Table 10-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Histopathological findings (Main group)

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

-: Not applicable

Table 10-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Histopathological findings (Main group)

Organs	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	100	300	1000	0	100	300	1000
Findings	Number:	12	12	12	12	12	12	12	12
<b>Kidney (continued)</b>									
Urinary cast,hyaline (continued)									
minimal		1	0	0	0	0	0	1	0
Mineralization,medullary		2	0	0	3	0	0	0	1
minimal		2	0	0	3	0	0	0	1
Cell infiltration,interstitial		1	0	0	2	1	0	0	0
minimal		1	0	0	2	1	0	0	0
NEPHROBLASTOMA		1	0	0	0	0	0	1	0
present		1	0	0	0	0	0	1	0
<b>Liver</b>									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		1	0	0	0	0	0	0	2
Vacuolation,hepatocyte,periportal		1	0	0	0	1	0	0	2
minimal		1	0	0	0	1	0	0	2
Microgranuloma		4	0	0	5	4	0	0	2
minimal		4	0	0	5	4	0	0	2
<b>Lung(bronchus)</b>									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		2	0	0	2	2	0	0	2
Mineralization,arterial wall		1	0	0	1	0	0	0	0
minimal		1	0	0	1	0	0	0	0
Alveolar macrophage		2	0	0	2	2	0	0	2
minimal		2	0	0	1	2	0	0	2
mild		0	0	0	1	0	0	0	0
Cell infiltration,alveolar		0	0	0	1	2	0	0	0
minimal		0	0	0	1	2	0	0	0
Hemorrhage,alveolar		0	0	0	0	1	0	0	0
minimal		0	0	0	0	1	0	0	0
Metaplasia,osseous		0	0	0	0	0	0	0	1
minimal		0	0	0	0	0	0	0	1
<b>Lymph node,mesenteric</b>									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
<b>Lymph node,submandibular</b>									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
<b>Parathyroid</b>									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
<b>Pituitary</b>									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	4	0	0	5
Cell infiltration,anterior,focal		0	0	0	0	1	0	0	0
minimal		0	0	0	0	1	0	0	0
<b>Sciatic nerve</b>									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
<b>Seminal vesicle</b>									
Number examined		5	0	0	5	-	-	-	-
Not remarkable		5	0	0	4	-	-	-	-
Cell infiltration,muscle layer		0	0	0	1	-	-	-	-
minimal		0	0	0	1	-	-	-	-

- : Not applicable

Table 10-3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Histopathological findings (Main group)

Organs	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	100	300	1000	0	100	300	1000
Findings	Number:	12	12	12	12	12	12	12	12
Spinal cord(thoracic)									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
Spleen									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	1	0	0	1	5	0	0	0	5
Hematopoiesis,extramedullary	4	0	0	4	5	0	0	0	5
minimal	3	0	0	4	1	0	0	0	1
mild	1	0	0	0	4	0	0	0	4
Sternum+Marrow									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
Stomach									
Number examined	12	12	12	12	12	12	12	12	12
Not remarkable	11	12	12	2	7	10	10	4	3
Erosion,glandular stomach	1	0	0	1	3	0	0	0	0
minimal	1	0	0	1	3	0	0	0	0
mild	0	0	0	1	2	2	2	3	3
Hyperplasia,squamous,limiting ridge	0	0	0	10	0	0	0	0	7
minimal	0	0	0	8	0	0	0	0	6
mild	0	0	0	2	0	0	0	0	1
Testis									
Number examined	5	0	0	5	-	-	-	-	-
Not remarkable	5	0	0	5	-	-	-	-	-
Thymus									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	5	5	0	0	0	5
Thyroid									
Number examined	5	0	0	5	5	0	0	0	5
Not remarkable	5	0	0	4	5	0	0	0	5
Ectopic thymus	0	0	0	1	0	0	0	0	0
minimal	0	0	0	1	0	0	0	0	0
Urinary bladder									
Number examined	5	0	0	5	5	0	1	5	5
Not remarkable	4	0	0	5	5	0	0	0	5
Cell infiltration,submucosal	0	0	0	0	0	0	1	0	0
mild	0	0	0	0	0	0	1	0	0
Mineralization,serosal	1	0	0	0	0	0	0	0	0
minimal	1	0	0	0	0	0	0	0	0
Hyperplasia,mucosal	0	0	0	0	0	0	1	0	0
mild	0	0	0	0	0	0	1	0	0
Uterus									
Number examined	-	-	-	-	5	0	0	5	5
Not remarkable	-	-	-	-	5	0	0	5	5

-: Not applicable

Table 10-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Histopathological findings (Recovery period)

Organs Findings	Sex: Dose(mg/kg): Number:	M 0 5	M 1000 5	F 0 5	F 1000 5
Stomach					
Number examined		5	5	5	5
Not remarkable		4	4	4	2
Dilatation,glandular mild		1	0	0	0
Hyperplasia,squamous,limiting ridge minimal		0	1	1	3
		0	1		

Table 11

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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	
0	12	0	0	0	7	5	3.4±0.5
100	12	0	0	0	4	8	3.7±0.5
300	12	0	0	0	7	5	3.4±0.5
1000	12	0	0	0	7	5	3.4±0.5

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Mating and fertility of animals

Dose mg/kg	No. of males	Male			Female			
		Days until copulation Mean±S.D.	Copulation index (%) a)	Insemination index (%) b)	No. of females	Days until copulation Mean±S.D.	Copulation index (%) a)	Fertility index (%) c)
0	12	2.4±1.1	12/12(100.0)	12/12(100.0)	12	2.4±1.1	12/12(100.0)	12/12(100.0)
100	12	3.1±1.0	12/12(100.0)	12/12(100.0)	12	3.1±1.0	12/12(100.0)	12/12(100.0)
300	12	2.5±1.2	12/12(100.0)	11/12( 91.7)	12	2.5±1.2	12/12(100.0)	11/12( 91.7)
1000	12	2.8±1.5	12/12(100.0)	11/12( 91.7)	12	2.8±1.5	12/12(100.0)	11/12( 91.7)

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

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

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

No significant difference in any treated groups from control group.

Table 13

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Delivery data on dams

Dose mg/kg		No. of pregnant females	No. of females with live pups	Delivery index % a)	Gestation period	No. of corpora lutea	No. of implan- tation sites	Implan- tation index % b)	No. of stillborn pups (%c)	No. of liveborn pups	Live birth index % d)
0	Total	12	12	100.0	22.1 0.4	205	188	92.2 6.8	1	173	99.4 1.9
	Mean					17.1	15.7		( 0.6)	14.4	
	S.D.					2.7	2.1		( 1.9)	2.1	
100	Total	12	12	100.0	22.2 0.4	197	193	97.9 4.1	5	177	97.3 4.6
	Mean					16.4	16.1		( 2.8)	14.8	
	S.D.					1.4	1.6		( 4.6)	2.0	
300	Total	11	11	100.0	22.1 0.4	198	183	92.8 9.7	3	172	98.6 4.8
	Mean					18.0	16.6		( 1.4)	15.6	
	S.D.					1.6	1.9		( 4.8)	1.6	
1000	Total	11	11	100.0	22.1 0.4	188	170	90.9 15.1	3	157	98.4 3.8
	Mean					17.1	15.5		( 1.6)	14.3	
	S.D.					2.2	2.9		( 3.8)	2.5	

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

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

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

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

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 diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

External examination of liveborn pups

Dose mg/kg	No. of dams	No. of males	No. of females	Sex ratio a)	Body weight(g)		External b) abnor- malities(%)c)
					Male	Female	
0	12	Total	83	90	0.48		0
		Mean	6.9	7.5		6.5	( 0.0)
		S.D.	2.5	2.5		0.6	( 0.0)
100	12	Total	95	82	0.54		0
		Mean	7.9	6.8		6.5	( 0.0)
		S.D.	1.2	1.7		0.3	( 0.0)
300	11	Total	94	78	0.55		0
		Mean	8.5	7.1		6.4	( 0.0)
		S.D.	2.2	2.5		0.6	( 0.0)
1000	11	Total	73	84	0.46		0
		Mean	6.6	7.6		6.5	( 0.0)
		S.D.	2.6	1.8		0.6	( 0.0)

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

b): No. of liveborn pups with external abnormalities

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

No significant difference in any treated groups from control group.

Table 15

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## 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	173	171
	Mean		14.4	14.3
	S.D.		2.1	2.1
100	Total	12	177	173
	Mean		14.8	14.4
	S.D.		2.0	1.8
300	Total	11	172	158
	Mean		15.6	14.4
	S.D.		1.6	1.9
1000	Total	11	157	156
	Mean		14.3	14.2
	S.D.		2.5	2.6

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

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

DT: Dunnnett-type rank test

Table 16

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Body weight of pups

Dose mg/kg	Male		Female		
	0	4	0	4a)	
0	No. Mean S.D.	12 6.5 0.6	12 10.0 1.2	12 6.1 0.5	12 9.4 1.1
100	No. Mean S.D.	12 6.5 0.3	12 9.9 0.8	12 6.2 0.3	12 9.2 0.7
300	No. Mean S.D.	11 6.4 0.6	11 9.4 1.4	11 6.0 0.6	11 9.0 1.4
1000	No. Mean S.D.	11 6.5 0.6	11 9.8 1.7	11 6.2 0.5	11 9.1 1.6

Unit: g

No.: No. of dams

a): Day after birth

No significant difference in any treated groups from control group.

Table 17

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Gross pathological findings in pups on day 4 after birth

	Dose (mg/kg)	0	100	300	1000
<b>Male</b>					
No. of pups examined		81	91	86	73
No. of pups with abnormal findings		0	3	0	0
Thymic remnant in neck		0	3	0	0
<b>Female</b>					
No. of pups examined		90	82	72	83
No. of pups with abnormal findings		0	1	0	0
Thymic remnant in neck		0	1	0	0

## Appendix 1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in male rats (Main group)

Dose (mg/kg): 0

Animal number	Day of administration					
	1-7	8-14	15-21	22-28	29-35	36-42
1001	-	-	-	-	-	-
1002	-	-	-	-	-	-
1003	-	-	-	-	-	-
1004	-	-	-	-	-	-
1005	-	-	-	-	-	-
1006	-	-	-	-	-	-
1007	-	-	-	-	-	-
1008	-	-	-	-	-	-
1009	-	-	-	-	-	-
1010	-	-	-	-	-	-
1011	-	-	-	-	-	-
1012	-	-	-	-	-	-

-: No abnormal findings

## Appendix 2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in male rats (Main group)

Dose (mg/kg): 100

Animal number	Day of administration					
	1-7	8-14	15-21	22-28	29-35	36-42
2001	-	-	-	-	-	-
2002	-	-	-	-	-	-
2003	-	-	-	-	-	-
2004	-	-	-	-	-	-
2005	-	-	-	-	-	-
2006	-	-	-	-	-	-
2007	-	-	-	-	-	-
2008	-	-	-	-	-	-
2009	-	-	-	-	-	-
2010	-	-	-	-	-	-
2011	-	-	-	-	-	-
2012	-	-	-	-	-	-

-: No abnormal findings

## Appendix 3

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in male rats (Main group)

Dose (mg/kg): 300

Animal number	Day of administration					
	1-7	8-14	15-21	22-28	29-35	36-42
3001	-	-	-	-	-	-
3002	-	-	-	-	-	-
3003	-	-	-	-	-	-
3004	-	-	-	-	-	-
3005	-	-	-	-	-	-
3006	-	-	-	-	-	-
3007	-	-	-	-	-	-
3008	-	-	-	-	-	-
3009	-	-	-	-	-	-
3010	-	-	-	-	-	-
3011	-	-	-	-	-	-
3012	-	-	-	-	-	-

-: No abnormal findings

## Appendix 4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in male rats (Main group)

Dose (mg/kg): 1000

Animal number	Day of administration					
	1-7	8-14	15-21	22-28	29-35	36-42
4001	-	-	-	-	-	-
4002	-	-	-	"	-	-
4003	-	-	-	-	-	-
4004	-	-	-	"	-	-
4005	-	-	-	-	-	-
4006	-	-	-	"	-	"
4007	-	"	-	-	-	-
4008	-	-	-	-	-	-
4009	-	-	-	-	-	"
4010	"	-	-	"	-	-
4011	-	"	-	"	"	-
4012	-	"	-	-	-	-

-: No abnormal findings

## Appendix 5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

## Appendix 6

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 100

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

## Appendix 7

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 300

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

## Appendix 8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

## Appendix 9

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in dams during the gestation period (Main group)

Dose (mg/kg): 0

Dam number	Administration																					
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd

a): Day of gestation

-: No abnormal findings

sd: Spontaneous delivery

## Appendix 10

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in dams during the gestation period (Main group)

Dose (mg/kg): 100

Dam number	Administration																					
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd

a): Day of gestation

-: No abnormal findings

sd: Spontaneous delivery

## Appendix 11

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in dams during the gestation period (Main group)

Dose (mg/kg): 300

Dam number	Administration																					
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3106	Non-pregnant																					
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd

a): Day of gestation

-: No abnormal findings

sd: Spontaneous delivery

## Appendix 12

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in dams during the gestation period (Main group)

Dose (mg/kg): 1000

Dam number	Administration																						
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22a)
4101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4107	Non-pregnant																						
4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	sd	

a): Day of gestation

-: No abnormal findings

sd: Spontaneous delivery

## Appendix 13

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in dams during the lactation period (Main group)

Dose (mg/kg): 0

Dam number	Administration				
	0	1	2	3	4a)
1101	-	-	-	-	-
1102	-	-	-	-	-
1103	-	-	-	-	-
1104	-	-	-	-	-
1105	-	-	-	-	-
1106	-	-	-	-	-
1107	-	-	-	-	-
1108	-	-	-	-	-
1109	-	-	-	-	-
1110	-	-	-	-	-
1111	-	-	-	-	-
1112	-	-	-	-	-

a): Day of lactation

-: No abnormal findings

## Appendix 14

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in dams during the lactation period (Main group)

Dose (mg/kg): 100

Dam number	Administration				
	0	1	2	3	4a)
2101	-	-	-	-	-
2102	-	-	-	-	-
2103	-	-	-	-	-
2104	-	-	-	-	-
2105	-	-	-	-	-
2106	-	-	-	-	-
2107	-	-	-	-	-
2108	-	-	-	-	-
2109	-	-	-	-	-
2110	-	-	-	-	-
2111	-	-	-	-	-
2112	-	-	-	-	-

a): Day of lactation

-: No abnormal findings

## Appendix 15

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in dams during the lactation period (Main group)

Dose (mg/kg): 300

Dam number	Administration				
	0	1	2	3	4a)
3101	-	-	-	-	-
3102	-	-	-	-	-
3103	-	-	-	-	-
3104	-	-	-	-	-
3105	-	-	-	-	-
3106	Non-pregnant				
3107	-	-	-	-	-
3108	-	-	-	-	-
3109	-	-	-	-	-
3110	-	-	-	-	-
3111	-	-	-	-	-
3112	-	-	-	-	-

a): Day of lactation

-: No abnormal findings

## Appendix 16

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in dams during the lactation period (Main group)

Dose (mg/kg): 1000

Dam number	Administration				
	0	1	2	3	4a)
4101	-	-	-	-	-
4102	-	-	-	-	-
4103	-	-	-	-	-
4104	-	-	-	-	-
4105	-	-	-	-	-
4106	-	-	-	-	-
4107	Non-pregnant				
4108	-	-	-	-	-
4109	-	-	-	-	-
4110	-	-	-	-	-
4111	-	-	-	-	-
4112	-	-	-	-	-

a): Day of lactation

-: No abnormal findings

## Appendix 17

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in male rats (Recovery group, administration period)

Dose (mg/kg): 0

Animal number	Day of administration					
	1-7	8-14	15-21	22-28	29-35	36-42
1013	-	-	-	-	-	-
1014	-	-	-	-	-	-
1015	-	-	-	-	-	-
1016	-	-	-	-	-	-
1017	-	-	-	-	-	-

-: No abnormal findings

## Appendix 18

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in male rats (Recovery group, administration period)

Dose (mg/kg): 1000

Animal number	Day of administration					
	1-7	8-14	15-21	22-28	29-35	36-42
4013	-	-	-	-	-	-
4014	-	-	-	-	-	-
4015	-	-	-	-	-	-
4016	-	-	-	-	-	-
4017	-	-	-	-	-	-

-: No abnormal findings

## Appendix 19

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in female rats (Recovery group, administration period)

Dose (mg/kg): 0

Animal number	Day of administration					
	1-7	8-14	15-21	22-28	29-35	36-42
1113	-	-	-	-	-	-
1114	-	-	-	-	-	-
1115	-	-	-	-	-	-
1116	-	-	-	-	-	-
1117	-	-	-	-	-	-

-: No abnormal findings

## Appendix 20

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in female rats (Recovery group, administration period)

Dose (mg/kg): 1000

Animal number	Day of administration					
	1-7	8-14	15-21	22-28	29-35	36-42
4113	-	-	-	-	-	-
4114	-	-	-	-	-	-
4115	-	-	-	-	-	-
4116	-	-	-	-	-	-
4117	-	-	-	-	-	-

-: No abnormal findings

## Appendix 21

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in male rats (Recovery group, recovery period)

Dose (mg/kg): 0

Animal number	Day of recovery													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1013	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1014	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1015	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1016	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1017	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

## Appendix 22

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in male rats (Recovery group, recovery period)

Dose (mg/kg): 1000

Animal number	Day of recovery													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4013	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4014	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4015	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4016	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4017	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

## Appendix 23

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in female rats (Recovery group, recovery period)

Dose (mg/kg): 0

Animal number	Day of recovery													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1114	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1115	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1116	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1117	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

## Appendix 24

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual clinical signs in female rats (Recovery group, recovery period)

Dose (mg/kg): 1000

Animal number	Day of recovery													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4114	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4115	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4116	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4117	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

## Appendix 25

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 26

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 27

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 28

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 29

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 30

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 31

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 32

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 33

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 34

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 35

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 36

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 37

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattend, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 38

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattend, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 39

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in male rats: home cage observations  
(Main group. Week 4 of administration)

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattend, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 40

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 41

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 42

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 43

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 44

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 45

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 46

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 47

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 48

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattend, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 49

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 50

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 51

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 52

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 53

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 54

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 55

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 56

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 57

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in female rats: home cage observations  
(Main group. Day 1 of gestation)

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 58

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 59

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Posture a)	N	N	N	N	N		N	N	N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 60

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	NP	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 61

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 62

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 63

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Posture a)	N	N	N	N	N		N	N	N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 64

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	NP	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 65

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 66

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 67

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Posture a)	N	N	N	N	N		N	N	N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0	0	0

a) N: Normal, F: Flattend, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 68

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
							NP					
Posture a)	N	N	N	N	N	N		N	N	N	N	N
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 69

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 70

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 71

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Posture a)	N	N	N	N	N		N	N	N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 72

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
						NP						
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 73

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 74

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 75

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Posture a)	N	N	N	N	N		N	N	N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 76

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7 NP	8	9	10	11	12
Posture a)	N	N	N	N	N	N		N	N	N	N	N
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

NP: Non-pregnant

## Appendix 77

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 78

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 79

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattend, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 80

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 81

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in male rats: home cage observations  
(Recovery group. Week 3 of administration)

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 82

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 83

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in male rats: home cage observations  
(Recovery group. Week 4 of administration)

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 84

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 85

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 86

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 87

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 88

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattend, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 89

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 90

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 91

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 92

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 93

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 94

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 95

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 96

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 97

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 98

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 99

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 100

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 101

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 102

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 103

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 104

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 105

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 106

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 107

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 108

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

## Appendix 109

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacration h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	1	0	0	1
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 110

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	1	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	1	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 111

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	1	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacration h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	2	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 112

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 113

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	1	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	1	0	0	0	0	2	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	2	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 114

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	1	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	1	1	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	1	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 115

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	1	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	2	0	0	0	0	1	0	1	0	2	0	0
Reactivity to handling n)	1	1	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 116

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	1	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	1	0	0	1	0	0	0	0	2	0	0
Reactivity to handling n)	0	0	0	0	1	0	0	0	0	2	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 117

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	1	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	1	0	0	0	1	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 118

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	1	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 119

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	1	0	0	0	0	0	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 120

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	1	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 121

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 122

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	1	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 123

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	1	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 124

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacration h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	1	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 125

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	1	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	-0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 126

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	1	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	1	1	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile. 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 127

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	1	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 128

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 129

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	1	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 130

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	1	0	1	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	2	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	1	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 131

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	1	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	1	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	1	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 132

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	1	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacration h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	1	1	0	0	0	1	0	0	0
Reactivity to handling n)	0	0	0	0	1	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 133

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	1	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 134

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	1	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	1	0	0	0	0	0	0
Reactivity to handling n)	0	1	0	0	0	0	0	0	0	0	1	1

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 135

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	1	0	0	0	0	1	0	1	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	1	1	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	1	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 136

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	1	1	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	1	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	1	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 137

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 138

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	1	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 139

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	1	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 140

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	1	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 141

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 142

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacration h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 143

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in female rats: in-the-hand observations  
(Main group. Day 1 of gestation)

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0		1	0	0	0	0	0
Fur condition b)	0	0	0	0	0		0	0	0	0	0	0
Skin c)	0	0	0	0	0		0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0		0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0		0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0		0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0		0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0		0	0	0	0	0	0
Piloerection i)	0	0	0	0	0		0	0	0	0	0	0
Pupil size j)	0	0	0	0	0		0	0	0	0	0	0
Salivation k)	0	0	0	0	0		0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0		0	0	0	0	0	0
Vocalization m)	0	0	0	0	0		0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0		1	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 144

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	1	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	2	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 145

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	1	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 146

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	1	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 147

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0		0	0	0	0	0	0
Fur condition b)	0	0	0	0	0		0	0	0	0	0	0
Skin c)	0	0	0	0	0		0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0		0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0		0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0		0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0		0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0		0	0	0	0	0	0
Piloerection i)	0	0	0	0	0		0	0	0	0	0	0
Pupil size j)	0	0	0	0	0		0	0	0	0	0	0
Salivation k)	0	0	0	0	0		0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0		0	0	0	0	0	0
Vocalization m)	0	0	0	0	0		0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0		0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 148

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)												
	1	2	3	4	5	6	7	NP	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0		1	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0		0	0	0	0	0	0
Skin c)	0	0	0	0	0	0		0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0		0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0		0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0		0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0		0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0		0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0		0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0		0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0		0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0		0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0		2	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0		0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 149

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 150

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	1
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 151

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0		0	0	0	0	0	0
Fur condition b)	0	0	0	0	0		0	0	0	0	0	0
Skin c)	0	0	0	0	0		0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0		0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0		0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0		0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0		0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0		0	0	0	0	0	0
Piloerection i)	0	0	0	0	0		0	0	0	0	0	0
Pupil size j)	0	0	0	0	0		0	0	0	0	0	0
Salivation k)	0	0	0	0	0		0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0		0	0	0	0	0	0
Vocalization m)	1	0	0	0	0		0	0	0	0	0	0
Reactivity to handling n)	1	0	0	0	0		0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 152

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)												
	1	2	3	4	5	6	7	NP	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0			0	0	0	0	0
Fur condition b)	0	0	0	0	0	0			0	0	0	0	0
Skin c)	0	0	0	0	0	0			0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0			0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0			0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0			0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0			0	0	0	0	0
Lacration h)	0	0	0	0	0	0			0	0	0	0	0
Piloerection i)	0	0	0	0	0	0			0	0	0	0	0
Pupil size j)	0	0	0	0	0	0			0	0	0	0	0
Salivation k)	0	0	0	0	0	0			0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0			0	0	0	0	0
Vocalization m)	0	0	0	0	0	0			1	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0			1	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 153

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacration h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	1	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 154

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in female rats: in-the-hand observations  
(Main group. Day 20 of gestation)

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 155

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)												
	1	2	3	4	5	6	NP	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0			0	0	0	0	0	0
Fur condition b)	0	0	0	0	0			0	0	0	0	0	0
Skin c)	0	0	0	0	0			0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0			0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0			0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0			0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0			0	0	0	0	0	0
Lacration h)	0	0	0	0	0			0	0	0	0	0	0
Piloerection i)	0	0	0	0	0			0	0	0	0	0	0
Pupil size j)	0	0	0	0	0			0	0	0	0	0	0
Salivation k)	0	0	0	0	0			0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0			0	0	0	0	0	0
Vocalization m)	0	0	0	0	0			0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0			0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 156

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)												
	1	2	3	4	5	6	7	NP	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0			0	0	0	0	0
Fur condition b)	0	0	0	0	0	0			0	0	0	0	0
Skin c)	0	0	0	0	0	0			0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0			0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0			0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0			0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0			0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0			0	0	0	0	0
Piloerection i)	0	0	0	0	0	0			0	0	0	0	0
Pupil size j)	0	0	0	0	0	0			0	0	0	0	0
Salivation k)	0	0	0	0	0	0			0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0			0	0	0	0	0
Vocalization m)	0	0	0	0	0	0			1	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0			0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 157

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 158

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 159

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0		0	0	0	0	0	0
Fur condition b)	0	0	0	0	0		0	0	0	0	0	0
Skin c)	0	0	0	0	0		0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0		0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0		0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0		0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0		0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0		0	0	0	0	0	0
Piloerection i)	0	0	0	0	0		0	0	0	0	0	0
Pupil size j)	0	0	0	0	0		0	0	0	0	0	0
Salivation k)	0	0	0	0	0		0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0		0	0	0	0	0	0
Vocalization m)	0	0	0	0	0		0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0		0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 160

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7 NP	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0		0	0	0	0	0
Fur condition b)	0	0	0	0	0	0		0	0	0	0	0
Skin c)	0	0	0	0	0	0		0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0		0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0		0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0		0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0		0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0		0	0	0	0	0
Piloerection i)	0	0	0	0	0	0		0	0	0	0	0
Pupil size j)	0	0	0	0	0	0		0	0	0	0	0
Salivation k)	0	0	0	0	0	0		0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0		0	0	0	0	0
Vocalization m)	0	0	0	0	0	0		0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0		0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

NP: Non-pregnant

## Appendix 161

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in male rats: in-the-hand observations  
(Recovery group. Week 1 of administration)

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 162

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 163

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	1	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile. 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 164

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	1	1	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 165

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis. 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 166

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	2	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 167

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Ease of removal from cage a)	1	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	1	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 168

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	1	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 169

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	2	0	0	0	0
Reactivity to handling n)	1	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 170

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	1	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile. 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 171

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacration h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 172

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 173

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in male rats: in-the-hand observations  
(Recovery group. Week 1 of recovery)

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 174

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	1	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 175

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 176

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	1	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 177

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Ease of removal from cage a)	0	1	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	1	0	0
Reactivity to handling n)	0	1	1	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 178

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 179

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 180

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 181

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 182

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 183

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in female rats: in-the-hand observations  
(Recovery group. Week 4 of administration)

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacration h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	1	1	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 184

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 185

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacration h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	1	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 186

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	1	0
Reactivity to handling n)	0	0	1	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 187

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacration h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 188

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4118-4117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 189

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	1	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 190

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual detailed clinical signs in female rats: in-the-hand observations  
(Recovery group. Week 1 of recovery)

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 191

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	1	1	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 192

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

b) 0: Normal, 1: Slight, unkempt fur, 2: Moderate, 3: Marked

c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

d) 0: Absent, 1: Present

e) 0: Absent, 1: Present

f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

h) 0: Normal, 1: Present

i) 0: Absent, 1: Present

j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

k) 0: None, 1: Slight, 2: Moderate, 3: Marked

l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked

m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

## Appendix 193

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	5	3	6	2	6	6	2	4	3	6	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	2	1	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 194

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	7	2	6	4	2	3	3	3	5	5	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 195

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	1	4	4	3	4	5	3	5	4	2	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 196

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	10	3	2	4	1	1	3	1	8	3	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 197

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	U	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	1	4	6	3	3	5	0	3	5	4	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	1	0	1	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 198

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	U	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	5	2	7	5	3	6	1	3	3	3	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 199

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	U	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	0	0	4	2	4	4	5	0	5	2	1	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	1	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 200

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	U	0	0	0	0	U	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	1	3	5	2	5	1	0	4	2	4	4	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	1	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 201

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	U	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	0	4	4	3	5	0	2	4	4	4	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	1	1	0	0	0	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 202

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	5	2	3	4	6	6	4	0	6	2	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	1	1	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 203

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	2	3	3	4	1	7	1	6	5	2	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 204

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	4	7	3	4	1	0	2	4	1	4	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 205

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	3	3	5	3	6	2	4	5	6	2	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	1	0	0	1	1	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 206

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	6	2	5	4	5	5	1	2	3	2	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	2	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 207

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	3	4	2	5	1	5	3	3	2	2	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	1	0	1	0	0	0	2	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 208

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	3	6	5	2	2	1	5	0	8	6	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	2	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 209

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	3	4	3	6	6	1	4	4	3	2	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	1	1	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 210

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	8	6	1	5	2	4	3	3	1	5	5	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	1	2	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 211

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	5	4	2	3	2	4	3	4	7	3	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	1	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 212

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	4	6	3	3	2	2	3	0	4	7	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1	0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 213

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	4	4	5	6	3	4	3	5	4	2	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 214

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	U	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	8	7	1	3	3	6	8	5	0	2	5	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	1	0	0	0	0	2	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 215

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	2	6	6	5	1	2	1	1	6	3	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	1	0	0	0	0	0	2	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 216

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	5	5	4	6	5	2	4	2	2	6	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	1	0	0	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 217

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	9	4	5	4	5	6	3	7	8	5	1	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 218

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	6	1	4	6	2	12	6	7	6	4	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 219

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	9	4	5	0	6	10	5	5	6	9	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 220

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	4	4	8	8	8	9	6	7	2	7	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 221

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	8	4	6	6	5	4	5	10	8	7	4	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 222

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	10	2	7	8	3	11	10	5	4	6	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 223

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	U	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	3	6	5	0	9	4	1	5	10	7	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 224

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	5	5	7	8	7	8	8	7	3	10	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattend, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 225

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	5	8	4	9	5	5	8	8	6	8	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 226

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	8	7	6	6	5	15	6	7	8	7	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 227

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)												
	1	2	3	4	5	6	NP	7	8	9	10	11	12
Arousal a)	0	0	0	0	0			0	0	0	0	0	0
Convulsion b)	0	0	0	0	0			0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0			0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0			0	0	0	0	0	0
Gait e)	0	0	0	0	0			0	0	0	0	0	0
Posture f)	N	N	N	N	N			N	N	N	N	N	N
Grooming g)	0	0	0	0	0			0	0	0	0	0	0
Rearing	6	9	6	6	5			10	4	6	7	5	6
Defecation count	0	0	0	0	0			1	0	0	0	0	0
Urination h)	0	0	0	0	0			0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 228

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7 NP	8	9	10	11	12
Arousal a)	0	0	0	0	0	0		0	0	0	0	0
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0		0	0	0	0	0
Gait e)	0	0	0	0	0	0		0	0	0	0	0
Posture f)	N	N	N	N	N	N		N	N	N	N	N
Grooming g)	0	0	0	0	0	0		0	0	0	0	0
Rearing	5	6	5	11	8	5		8	8	4	7	7
Defecation count	0	0	0	0	0	0		0	0	0	0	0
Urination h)	0	0	0	0	0	0		0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 229

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	7	8	7	5	5	5	5	7	7	4	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 230

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	11	6	6	9	6	9	7	7	6	6	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 231

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)												
	1	2	3	4	5	6	NP	7	8	9	10	11	12
Arousal a)	0	0	0	0	0		0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0		0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0		0	0	0	0	0	0	0
Gait e)	0	0	0	0	0		0	0	0	0	0	0	0
Posture f)	N	N	N	N	N		N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0		0	0	0	0	0	0	0
Rearing	8	7	10	6	3		4	11	5	8	3	6	
Defecation count	0	0	0	0	0		0	0	0	0	0	0	0
Urination h)	0	0	0	0	0		0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 232

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7 NP	8	9	10	11	12
Arousal a)	0	0	0	0	0	0		0	0	0	0	0
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0		0	0	0	0	0
Gait e)	0	0	0	0	0	0		0	0	0	0	0
Posture f)	N	N	N	N	N	N		N	N	N	N	N
Grooming g)	0	0	0	0	0	0		0	0	0	0	0
Rearing	5	6	5	5	8	6		7	8	3	6	8
Defecation count	0	0	0	0	0	0		0	0	0	0	0
Urination h)	0	0	0	0	0	0		0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 233

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	6	5	4	4	3	4	5	6	4	5	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 234

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	7	4	6	10	6	5	7	5	5	4	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 235

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diaminium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)												
	1	2	3	4	5	6	NP	7	8	9	10	11	12
Arousal a)	0	0	0	0	0			0	0	0	0	0	0
Convulsion b)	0	0	0	0	0			0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0			0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0			0	0	0	0	0	0
Gait e)	0	0	0	0	0			0	0	0	0	0	0
Posture f)	N	N	N	N	N			N	N	N	N	N	N
Grooming g)	0	0	0	0	0			0	0	0	0	0	0
Rearing	6	8	7	7	6			5	5	4	8	6	3
Defecation count	0	0	0	0	0			0	0	0	0	0	0
Urination h)	0	0	0	0	0			0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 236

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7 NP	8	9	10	11	12
Arousal a)	0	0	0	0	0	0		0	0	0	0	0
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0		0	0	0	0	0
Gait e)	0	0	0	0	0	0		0	0	0	0	0
Posture f)	N	N	N	N	N	N		N	N	N	N	N
Grooming g)	0	0	0	0	0	0		0	0	0	0	0
Rearing	4	4	4	9	7	4		5	6	3	4	9
Defecation count	0	0	0	0	0	0		0	0	0	0	0
Urination h)	0	0	0	0	0	0		0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattend, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 237

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	8	6	6	6	5	8	6	6	8	3	5	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 238

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	8	6	5	9	7	6	6	5	4	5	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 239

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)												
	1	2	3	4	5	6	NP	7	8	9	10	11	12
Arousal a)	0	0	0	0	0			0	0	0	0	0	0
Convulsion b)	0	0	0	0	0			0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0			0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0			0	0	0	0	0	0
Gait e)	0	0	0	0	0			0	0	0	0	0	0
Posture f)	N	N	N	N	N			N	N	N	N	N	N
Grooming g)	0	0	0	0	0			0	0	0	0	0	0
Rearing	1	5	7	4	4			5	4	5	6	4	4
Defecation count	0	0	0	0	0			0	0	0	0	0	0
Urination h)	0	0	0	0	0			1	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 240

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7 NP	8	9	10	11	12
Arousal a)	0	0	0	0	0	0		0	0	0	0	0
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0		0	0	0	0	0
Gait e)	0	0	0	0	0	0		0	0	0	0	0
Posture f)	N	N	N	N	N	N		N	N	N	N	N
Grooming g)	0	0	0	0	0	0		0	0	0	0	0
Rearing	4	4	7	7	6	3		5	8	4	5	6
Defecation count	0	0	0	0	0	0		0	0	0	0	0
Urination h)	0	0	0	0	0	0		0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 241

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	11	8	8	4	7	5	7	12	10	8	5	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 242

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	9	7	7	10	8	8	10	7	6	6	10
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 243

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6 NP	7	8	9	10	11	12
Arousal a)	0	0	0	0	0		0	0	0	0	0	0
Convulsion b)	0	0	0	0	0		0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0		0	0	0	0	0	0
Gait e)	0	0	0	0	0		0	0	0	0	0	0
Posture f)	N	N	N	N	N		N	N	N	N	N	N
Grooming g)	0	0	0	0	0		0	0	0	0	0	0
Rearing	6	8	8	7	6		6	6	8	6	6	6
Defecation count	0	0	0	0	0		0	0	0	0	0	0
Urination h)	0	0	0	0	0		0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location. 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 244

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4112)												
	1	2	3	4	5	6	7	NP	8	9	10	11	12
Arousal a)	0	0	0	0	0	0		0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0		0	0	0	0	0	0
Gait e)	0	0	0	0	0	0		0	0	0	0	0	0
Posture f)	N	N	N	N	N	N		N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0		0	0	0	0	0	0
Rearing	8	10	12	9	5	7		8	11	6	8	7	
Defecation count	0	0	0	0	0	0		0	0	0	0	0	0
Urination h)	0	0	0	0	0	0		0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

NP: Non-pregnant

## Appendix 245

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	3	0	3	2	6
Defecation count	0	0	0	0	0
Urination h)	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 246

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	2	5	3	2	1
Defecation count	0	0	0	2	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 247

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	U	U	0	U	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	0	0	3	0	6
Defecation count	0	0	0	0	0
Urination h)	0	0	1	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 248

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	3	5	5	3	2
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 249

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	U	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	0	3	4	0	5
Defecation count	0	0	0	0	0
Urination h)	0	0	2	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 250

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	3	5	6	3	5
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 251

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	U	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	0	0	5	0	8
Defecation count	0	0	0	0	0
Urination h)	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 252

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	3	7	6	5	5
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 253

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	U	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	0	1	6	0	7
Defecation count	0	0	0	0	0
Urination h)	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 254

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	3	4	3	3	3
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	2

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 255

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	1	4	6	0	9
Defecation count	0	0	0	0	0
Urination h)	0	0	2	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 256

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	5	3	5	3	4
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	2

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 257

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	2	3	7	1	9
Defecation count	0	0	0	0	0
Urination h)	0	1	2	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 258

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	6	4	6	3	4
Defecation count	0	0	0	0	0
Urination h)	0	0	1	0	2

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 259

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	4	5	5	2	8
Defecation count	0	0	0	0	0
Urination h)	0	0	2	0	1

a) -2: Unconscious/semi-conscious. -1: Reduced awareness. 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 260

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	6	4	6	4	6
Defecation count	0	0	0	0	0
Urination h)	0	0	1	0	2

a) -2: Unconscious/semi-conscious. -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 261

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	6	3	7	5	10
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious. -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 262

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	5	7	2	3	8
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 263

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	3	5	7	4	13
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 264

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	6	11	5	3	13
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 265

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	9	5	6	6	11
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 266

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	6	12	8	4	15
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 267

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	9	4	5	6	8
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 268

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	5	6	4	4	7
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 269

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	12	5	5	9	9
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 270

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	6	6	5	5	11
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 271

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	10	4	7	7	9
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 272

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	5	9	7	4	10
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 273

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	5	4	8	5	9
Defecation count	0	0	0	0	0
Urination h)	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 274

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	6	7	6	4	7
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 275

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	7	7	8	9	9
Defecation count	0	0	0	0	0
Urination h)	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 276

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	7	7	6	7	8
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

d) 0: None, 1: Minor, 2: Moderate, 3: Severe

e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

f) N: Normal, F: Flattened, H: Hunched

g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)

h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

## Appendix 277

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1001-1005)				
	1	2	3	4	5
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	68	105	58	63	75

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 278

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2001-2005)				
	1	2	3	4	5
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	78	103	75	89	78

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormal/fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormal/fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 279

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3001-3005)				
	1	2	3	4	5
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	77	103	74	87	80

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 280

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4001-4005)				
	1	2	3	4	5
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	105	60	68	80	73

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 281

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1103-1109)				
	3	4	5	7	9
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	57	68	27	99	37

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 282

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Parameter	Animal number (2106-2110)				
	6	7	8	9	10
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	61	66	66	62	58

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 283

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Parameter	Animal number (3101-3111)				
	1	4	7	9	11
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	118	58	54	108	57

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 284

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4101-4111)				
	1	3	6	10	11
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	58	89	58	45	50

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 285

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	36	109	65	76	58

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 286

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	79	98	62	96	94

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 287

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	64	91	64	69	16

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 288

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	50	56	84	50	44

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 289

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1013-1017)				
	13	14	15	16	17
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	73	100	92	97	64

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 290

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual manipulative test of male rats (Recovery group. Week 2 of recovery)

Dose (mg/kg) : 1000

Parameter	Animal number (4013-4017)				
	13	14	15	16	17
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	79	114	83	88	97

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 291

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Parameter	Animal number (1113-1117)				
	13	14	15	16	17
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	76	92	79	76	53

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

## Appendix 292

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Parameter	Animal number (4113-4117)				
	13	14	15	16	17
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	62	70	72	59	59

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

e) P: Pass, both. F: Failed, neither. L: Left pupil responds. R: Right pupil responds

## Appendix 293

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Fore limb g	Hind limb g
1001	1213	898
1002	848	877
1003	858	689
1004	946	881
1005	810	580
Mean	935	785
S.D.	163	143

## Appendix 294

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Animal number	Fore limb g	Hind limb g
2001	965	1005
2002	950	450
2003	927	596
2004	1375	1048
2005	958	728
Mean	1035	765
S.D.	191	258

Appendix 295

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Animal number	Fore limb g	Hind limb g
3001	1307	1128
3002	925	726
3003	1036	932
3004	982	1002
3005	979	1070
Mean	1046	972
S.D.	151	156

## Appendix 296

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Fore limb g	Hind limb g
4001	1507	1275
4002	984	798
4003	992	857
4004	997	1002
4005	936	1032
Mean	1083	993
S.D.	238	186

## Appendix 297

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Fore limb g	Hind limb g
1103	1510	956
1104	1424	635
1105	1318	799
1107	1424	821
1109	1173	1009
Mean	1370	844
S.D.	129	147

## Appendix 298

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Animal number	Fore limb g	Hind limb g
2106	1260	644
2107	1148	735
2108	1266	744
2109	1531	883
2110	1186	705
Mean	1278	742
S.D.	150	88

## Appendix 299

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Animal number	Fore limb g	Hind limb g
3101	1264	861
3104	1579	795
3107	1600	915
3109	1441	939
3111	1634	794
Mean	1504	861
S.D.	153	67

## Appendix 300

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Fore limb g	Hind limb g
4101	1477	689
4103	1277	689
4106	1226	793
4110	935	561
4111	1339	817
Mean	1251	710
S.D.	200	102

## Appendix 301

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Fore limb g	Hind limb g
1013	1479	778
1014	1436	1056
1015	1526	1002
1016	1620	900
1017	1418	887
Mean	1496	925
S.D.	81	108

## Appendix 302

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diaminium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Fore limb g	Hind limb g
4013	1229	874
4014	1668	927
4015	1354	913
4016	2018	1022
4017	1434	887
Mean	1541	925
S.D.	311	58

## Appendix 303

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Fore limb g	Hind limb g
1113	1138	708
1114	1342	732
1115	1136	962
1116	1021	810
1117	1115	841
Mean	1150	811
S.D.	117	101

## Appendix 304

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Fore limb g	Hind limb g
4113	1170	765
4114	1137	840
4115	1020	932
4116	1125	770
4117	1455	736
Mean	1181	809
S.D.	163	79

## Appendix 305

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Fore limb g	Hind limb g
1013	1363	849
1014	1829	970
1015	1765	1119
1016	1721	1004
1017	1506	828
Mean	1637	954
S.D.	195	119

## Appendix 306

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Fore limb g	Hind limb g
4013	1611	785
4014	1831	1186
4015	1719	974
4016	1695	1081
4017	1818	928
Mean	1735	991
S.D.	91	152

Appendix 307

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Fore limb g	Hind limb g
1113	1182	788
1114	1159	757
1115	1237	908
1116	1286	839
1117	1305	890
Mean	1234	836
S.D.	63	65

## Appendix 308

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Fore limb g	Hind limb g
4113	1315	593
4114	1502	1077
4115	872	875
4116	1210	880
4117	1288	801
Mean	1237	845
S.D.	231	174

## Appendix 309

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1001	415	12	21	156	10	79	693
1002	382	204	47	15	3	15	666
1003	395	368	212	39	41	53	1108
1004	508	319	4	48	362	29	1270
1005	410	331	143	94	22	5	1005
Mean	422	247	85	70	88	36	948
S.D.	50	145	89	56	154	30	263

## Appendix 310

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
2001	487	251	200	196	0	3	1137
2002	452	378	74	12	3	2	921
2003	412	310	157	192	171	9	1251
2004	442	380	215	47	8	0	1092
2005	406	366	297	297	256	200	1822
Mean	440	337	189	149	88	43	1245
S.D.	33	56	82	117	119	88	344

## Appendix 311

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
3001	441	355	387	321	210	213	1927
3002	372	244	127	63	49	0	855
3003	392	277	92	209	5	8	983
3004	427	144	115	66	63	307	1122
3005	318	72	54	14	72	255	785
Mean	390	218	155	135	80	157	1134
S.D.	49	111	133	127	77	143	461

## Appendix 312

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Interval (minutes)						Total(0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
4001	336	258	190	19	59	20	882
4002	389	277	170	173	36	300	1345
4003	454	290	68	75	3	5	895
4004	458	108	46	12	24	8	656
4005	354	273	76	28	176	100	1007
Mean	398	241	110	61	60	87	957
S.D.	56	75	65	67	68	125	252

Appendix 313

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1103	420	362	109	250	229	78	1448
1104	265	42	25	9	17	1	359
1105	329	82	13	20	9	7	460
1107	450	300	225	218	132	332	1657
1109	385	312	230	288	211	102	1528
Mean	370	220	120	157	120	104	1090
S.D.	74	146	105	132	104	135	627

## Appendix 314

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Animal number	Interval (minutes)						Total(0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
2106	419	218	254	208	127	97	1323
2107	168	63	115	55	215	3	619
2108	407	304	260	135	161	301	1568
2109	142	58	28	5	14	12	259
2110	295	216	30	5	2	261	809
Mean	286	172	137	82	104	135	916
S.D.	129	108	115	88	93	139	530

Appendix 315

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Animal number	Interval (minutes)						Total(0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
3101	288	15	20	7	22	19	371
3104	137	27	21	169	42	16	412
3107	444	329	313	300	316	294	1996
3109	259	11	0	6	31	0	307
3111	351	344	358	233	302	221	1809
Mean	296	145	142	143	143	110	979
S.D.	114	175	177	133	152	137	846

## Appendix 316

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Interval (minutes)						Total(0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
4101	194	165	235	236	187	198	1215
4103	366	35	15	20	18	4	458
4106	305	274	232	216	196	223	1446
4110	215	52	26	175	165	136	769
4111	281	69	7	41	16	12	426
Mean	272	119	103	138	116	115	863
S.D.	70	100	119	100	91	102	455

## Appendix 317

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Interval (minutes)						Total(0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
1013	421	307	387	368	197	40	1720
1014	390	331	135	23	11	8	898
1015	396	254	139	35	1	16	841
1016	460	246	37	220	6	7	976
1017	439	208	2	48	12	16	725
Mean	421	269	140	139	45	17	1032
S.D.	29	49	151	151	85	13	395

## Appendix 318

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4013	470	357	275	172	199	5	1478
4014	399	324	161	134	41	64	1123
4015	435	339	115	141	16	13	1059
4016	414	205	18	91	5	23	756
4017	494	397	370	260	101	26	1648
Mean	442	324	188	160	72	26	1213
S.D.	39	72	138	63	80	23	354

Appendix 319

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1113	392	285	248	0	0	5	930
1114	338	309	259	110	37	32	1085
1115	365	284	69	4	0	1	723
1116	400	385	9	10	162	22	988
1117	238	111	59	1	0	50	459
Mean	347	275	129	25	40	22	837
S.D.	65	100	116	48	70	20	249

## Appendix 320

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4113	424	219	5	4	7	90	749
4114	350	50	13	109	32	18	572
4115	322	253	13	2	3	30	623
4116	371	296	324	319	301	251	1862
4117	433	309	284	358	159	19	1562
Mean	380	225	128	158	100	82	1074
S.D.	48	104	162	171	129	99	596

Appendix 321

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1013	401	391	313	287	373	313	2078
1014	486	374	322	316	320	320	2138
1015	457	408	363	346	273	117	1964
1016	408	393	316	353	288	72	1830
1017	477	433	413	317	340	132	2112
Mean	446	400	345	324	319	191	2024
S.D.	39	22	43	26	40	117	127

Appendix 322

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Interval (minutes)						Total(0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
4013	446	369	288	221	273	148	1745
4014	394	342	350	355	185	47	1673
4015	399	377	324	401	323	286	2110
4016	379	222	87	35	112	70	905
4017	483	409	321	326	273	352	2164
Mean	420	344	274	268	233	181	1719
S.D.	43	72	107	146	84	134	504

## Appendix 323

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1113	453	348	347	297	284	386	2115
1114	352	328	349	290	224	212	1755
1115	386	279	219	60	23	271	1238
1116	390	364	355	296	63	3	1471
1117	243	125	93	190	218	343	1212
Mean	365	289	273	227	162	243	1558
S.D.	77	97	115	104	113	150	380

## Appendix 324

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4113	407	254	339	239	57	6	1302
4114	283	80	355	116	95	262	1191
4115	470	427	403	335	335	335	2305
4116	329	265	57	109	333	284	1377
4117	373	338	311	286	291	240	1839
Mean	372	273	293	217	222	225	1603
S.D.	72	128	136	101	135	128	464

## Appendix 325

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of male rats (Main group)

Dose (mg/kg): 0

Animal number	Pre-mating period					Mating period				Post-mating period				Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42a)	
1001	405	421	434	451	467	466	473	488	505	514	528	539	540	135
1002	398	410	423	436	444	451	461	466	479	490	503	497	503	105
1003	393	412	430	440	460	459	476	487	500	522	536	541	541	148
1004	379	393	407	423	440	454	466	469	490	504	513	521	526	147
1005	371	386	413	420	435	438	455	463	470	478	492	484	486	115
1006	393	403	414	436	458	461	476	486	500	512	528	526	530	137
1007	404	417	435	449	467	470	484	501	521	536	546	554	562	158
1008	439	458	472	488	505	508	523	540	556	562	579	581	586	147
1009	404	418	434	442	464	475	495	507	515	529	540	545	565	161
1010	418	440	468	479	500	500	530	541	568	586	603	608	622	204
1011	400	408	429	441	460	469	482	492	508	524	542	546	558	158
1012	381	396	419	428	439	445	456	466	482	491	504	512	525	144
Mean	398.8	413.5	431.5	444.4	461.6	466.3	481.4	492.2	507.8	520.7	534.5	537.8	545.3	146.6
S.D.	18.2	20.0	20.2	20.6	22.2	20.7	24.1	26.6	29.5	30.6	31.9	34.2	36.6	24.7

Unit: g

a): Day of administration

## Appendix 326

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of male rats (Main group)

Dose (mg/kg): 100

Animal number	Pre-mating period					Mating period				Post-mating period				Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42a)	
2001	393	403	421	432	448	452	471	479	495	504	521	515	517	124
2002	383	402	412	420	441	440	460	471	493	498	509	526	521	138
2003	384	392	407	420	431	437	452	458	477	487	505	511	519	135
2004	430	446	463	480	499	448	480	496	509	521	543	545	540	110
2005	405	422	429	443	446	451	465	471	484	492	506	508	506	101
2006	423	440	468	490	513	528	549	561	583	595	613	623	630	207
2007	389	407	420	432	452	458	476	490	502	507	518	524	527	138
2008	410	425	445	464	486	478	498	512	536	543	551	571	569	159
2009	400	413	434	444	458	473	481	499	512	523	535	540	555	155
2010	381	387	402	413	433	442	451	460	472	482	488	492	494	113
2011	405	420	439	446	459	471	491	500	516	511	536	534	534	129
2012	400	421	443	458	476	482	498	509	522	537	549	558	570	170
Mean	400.3	414.8	431.9	445.2	461.8	463.3	481.0	492.2	508.4	516.7	531.2	537.3	540.2	139.9
S.D.	15.5	17.8	20.9	24.1	26.2	25.5	26.7	28.3	30.1	31.1	32.4	34.9	36.8	29.4

Unit: g

a): Day of administration

## Appendix 327

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of male rats (Main group)

Dose (mg/kg): 300

Animal number	Pre-mating period					Mating period				Post-mating period				Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42a)	
3001	407	411	426	435	445	451	458	468	490	490	508	507	510	103
3002	379	400	416	426	435	434	449	449	462	470	479	483	487	108
3003	398	410	418	425	430	423	439	445	455	467	481	476	483	85
3004	405	413	430	443	455	457	471	483	497	513	526	524	537	132
3005	405	427	448	456	472	478	498	508	525	534	552	553	565	160
3006	384	391	402	419	429	432	449	460	475	488	496	503	508	124
3007	381	398	422	439	448	460	478	489	502	509	525	531	535	154
3008	402	408	423	432	444	452	458	468	484	490	508	510	516	114
3009	390	404	431	454	478	493	507	520	542	555	571	578	591	201
3010	430	435	458	466	479	473	490	493	508	512	526	540	545	115
3011	396	407	425	438	441	444	460	477	490	499	508	513	506	110
3012	381	385	403	408	421	429	443	445	458	476	484	484	491	110
Mean	396.5	407.4	425.2	436.8	448.1	452.2	466.7	475.4	490.7	500.3	513.7	516.8	522.8	126.3
S.D.	14.8	13.9	16.1	16.5	19.4	21.4	22.2	24.3	26.5	26.1	28.2	30.3	32.8	31.5

Unit: g

a): Day of administration

## Appendix 328

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of male rats (Main group)

Dose (mg/kg): 1000

Animal number	Pre-mating period					Mating period				Post-mating period				Gain 1-42
	1	4	8	11	15	18	22	25	29	32	36	39	42a)	
4001	393	409	428	444	455	460	477	495	512	520	527	525	528	135
4002	412	419	445	454	467	481	495	503	517	526	539	542	556	144
4003	377	388	399	410	417	426	431	434	452	460	474	476	480	103
4004	394	410	435	445	466	454	472	484	504	522	525	536	543	149
4005	415	429	442	460	480	478	493	511	517	532	545	538	553	138
4006	413	429	445	459	477	480	492	502	509	516	531	534	538	125
4007	385	394	406	420	425	437	449	464	470	477	492	496	503	118
4008	385	398	409	421	432	428	453	466	482	491	505	514	514	129
4009	427	443	465	479	490	504	508	523	546	559	569	584	593	166
4010	406	428	440	458	476	472	489	499	519	526	533	547	552	146
4011	387	404	408	420	426	435	444	459	476	482	489	496	502	115
4012	404	421	441	448	466	464	477	481	503	514	534	540	549	145
Mean	399.8	414.3	430.3	443.2	456.4	459.9	473.3	485.1	500.6	510.4	521.9	527.3	534.3	134.4
S.D.	15.2	16.6	20.3	21.0	25.0	24.6	24.0	25.5	25.9	27.7	26.9	28.6	30.6	17.4

Unit: g

a): Day of administration

Appendix 329

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of administration					Gain 1-15
	1	4	8	11	15	
1101	239	246	256	263	271	32
1102	234	233	244	241	251	17
1103	241	254	263	272	278	37
1104	245	256	268	270	281	36
1105	243	256	270	274	279	36
1106	250	253	266	266	268	18
1107	231	243	248	257	267	36
1108	246	242	257	272	280	34
1109	230	235	237	252	260	30
1110	272	279	289	301	310	38
1111	257	267	283	289	303	46
1112	246	267	276	290	297	51
Mean	244.5	252.6	263.1	270.6	278.8	34.3
S.D.	11.7	13.7	15.6	16.9	17.4	9.7

Unit: g

## Appendix 330

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 100

Animal number	Day of administration					Gain 1-15
	1	4	8	11	15	
2101	254	249	264	275	284	30
2102	239	247	254	256	267	28
2103	244	248	264	262	264	20
2104	255	260	271	271	282	27
2105	235	240	242	246	260	25
2106	234	245	256	255	268	34
2107	220	238	247	257	264	44
2108	253	264	274	278	285	32
2109	260	268	282	290	298	38
2110	237	245	260	264	268	31
2111	253	258	269	277	288	35
2112	258	265	274	279	289	31
Mean	245.2	252.3	263.1	267.5	276.4	31.3
S.D.	12.2	10.3	11.8	12.8	12.5	6.2

Unit: g

## Appendix 331

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 300

Animal number	Day of administration					Gain 1-15
	1	4	8	11	15	
3101	253	258	268	274	283	30
3102	245	253	262	266	278	33
3103	246	248	260	260	260	14
3104	256	276	279	295	303	47
3105	258	264	280	284	291	33
3106	245	263	275	281	289	44
3107	237	234	245	258	271	34
3108	219	220	231	230	233	14
3109	240	238	251	260	267	27
3110	246	248	253	262	267	21
3111	255	255	271	283	294	39
3112	244	247	255	253	258	14
Mean	245.3	250.3	260.8	267.2	274.5	29.2
S.D.	10.5	14.9	14.7	17.4	19.3	11.5

Unit: g

## Appendix 332

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of administration					Gain 1-15
	1	4	8	11	15	
4101	229	243	246	251	258	29
4102	273	276	291	296	301	28
4103	230	228	233	247	253	23
4104	253	260	265	274	281	28
4105	242	245	254	253	260	18
4106	236	248	255	264	271	35
4107	251	254	266	265	271	20
4108	250	251	259	261	269	19
4109	245	243	253	266	274	29
4110	263	270	272	278	280	17
4111	235	238	248	259	268	33
4112	231	241	250	255	258	27
Mean	244.8	249.8	257.7	264.1	270.3	25.5
S.D.	13.8	13.6	14.7	13.5	13.1	6.0

Unit: g

## Appendix 333

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of dams during the gestation period (Main group)

Dose (mg/kg): 0

Dam number	Administration							Gain 0-20
	0	4	7	11	14	17	20a)	
1101	273	299	308	332	351	381	432	159
1102	266	294	302	328	348	376	425	159
1103	281	298	312	334	353	380	420	139
1104	280	309	315	343	354	384	439	159
1105	285	304	313	328	347	383	420	135
1106	283	305	313	332	344	373	415	132
1107	270	284	298	315	330	356	399	129
1108	285	309	324	340	356	388	440	155
1109	260	284	295	318	336	361	404	144
1110	314	334	350	365	378	405	448	134
1111	312	339	353	379	403	431	484	172
1112	298	333	350	367	384	423	475	177
Mean	283.9	307.7	319.4	340.1	357.0	386.8	433.4	149.5
S.D.	16.9	18.6	20.6	20.1	21.0	22.6	25.9	16.2

Unit: g

a): Day of gestation

## Appendix 334

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of dams during the gestation period (Main group)

Dose (mg/kg): 100

Dam number	Administration							Gain 0-20
	0	4	7	11	14	17	20a)	
2101	285	305	319	338	356	392	435	150
2102	285	323	329	357	366	398	436	151
2103	275	297	308	331	344	376	415	140
2104	297	329	344	374	390	430	478	181
2105	271	302	311	336	346	377	412	141
2106	270	306	329	354	374	408	438	168
2107	266	288	296	320	330	356	395	129
2108	291	321	331	347	365	389	427	136
2109	301	329	341	369	394	436	490	189
2110	269	295	305	331	345	369	428	159
2111	288	302	316	330	344	372	426	138
2112	294	315	324	344	365	400	460	166
Mean	282.7	309.3	321.1	344.3	359.9	391.9	436.7	154.0
S.D.	12.1	13.7	14.6	16.5	19.5	24.2	27.3	18.9

Unit: g

a): Day of gestation

## Appendix 335

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of dams during the gestation period (Main group)

Dose (mg/kg): 300

Dam number	Administration							Gain 0-20
	0	4	7	11	14	17	20a)	
3101	283	308	321	336	356	387	434	151
3102	277	306	317	343	364	393	434	157
3103	281	306	311	334	349	390	441	160
3104	299	324	339	352	372	401	448	149
3105	296	315	328	349	370	412	458	162
3106	Non-pregnant							
3107	273	301	324	349	362	396	450	177
3108	253	286	303	327	338	377	427	174
3109	273	288	298	317	339	365	415	142
3110	288	302	315	338	360	390	439	151
3111	296	331	355	385	411	443	492	196
3112	277	297	308	331	344	377	429	152
Mean	281.5	305.8	319.9	341.9	360.5	393.7	442.5	161.0
S.D.	13.3	13.7	16.4	17.7	20.4	20.7	20.3	15.7

Unit: g

a): Day of gestation

Appendix 336

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of dams during the gestation period (Main group)

Dose (mg/kg): 1000

Dam number	Administration							Gain 0-20
	0	4	7	11	14	17	20a)	
4101	262	292	302	317	348	376	429	167
4102	316	342	345	388	399	434	491	175
4103	263	284	300	326	342	375	426	163
4104	284	324	344	368	380	405	431	147
4105	262	290	304	328	341	376	417	155
4106	274	307	322	353	366	404	458	184
4107	Non-pregnant							
4108	277	309	318	344	357	384	429	152
4109	276	307	319	338	358	392	454	178
4110	287	297	308	324	341	370	408	121
4111	267	289	301	324	334	357	402	135
4112	273	290	301	312	330	356	406	133
Mean	276.5	302.8	314.9	338.4	354.2	384.5	431.9	155.5
S.D.	15.6	17.6	16.6	23.3	20.9	23.1	26.6	20.2

Unit: g

a): Day of gestation

## Appendix 337

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of dams during the lactation period (Main group)

Dose (mg/kg): 0

Dam number	Administration		Gain 0-4
	0	4a)	
1101	342	352	10
1102	332	343	11
1103	323	352	29
1104	336	359	23
1105	356	363	7
1106	324	335	11
1107	314	339	25
1108	341	347	6
1109	320	329	9
1110	385	377	-8
1111	387	385	-2
1112	336	382	46
Mean	341.3	355.3	13.9
S.D.	23.7	18.5	14.7

Unit: g

a): Day of lactation

## Appendix 338

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of dams during the lactation period (Main group)

Dose (mg/kg): 100

Dam number	Administration		Gain 0-4
	0	4a)	
2101	339	375	36
2102	337	367	30
2103	341	352	11
2104	370	397	27
2105	325	349	24
2106	368	388	20
2107	278	318	40
2108	341	349	8
2109	379	388	9
2110	309	351	42
2111	342	328	-14
2112	336	359	23
Mean	338.8	360.1	21.3
S.D.	27.4	24.1	15.9

Unit: g

a): Day of lactation

## Appendix 339

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of dams during the lactation period (Main group)

Dose (mg/kg): 300

Dam number	Administration		Gain 0-4
	0	4a)	
3101	344	364	20
3102	360	367	7
3103	294	330	36
3104	354	371	17
3105	373	366	-7
3106	Non-pregnant		
3107	306	342	36
3108	348	349	1
3109	334	354	20
3110	346	352	6
3111	385	384	-1
3112	352	362	10
Mean	345.1	358.3	13.2
S.D.	26.4	14.9	14.2

Unit: g

a): Day of lactation

## Appendix 340

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual body weight of dams during the lactation period (Main group)

Dose (mg/kg): 1000

Dam number	Administration		Gain 0-4
	0	4a)	
4101	342	343	1
4102	385	429	44
4103	326	347	21
4104	363	379	16
4105	343	352	9
4106	358	391	33
4107	Non-pregnant		
4108	354	356	2
4109	343	352	9
4110	340	346	6
4111	339	340	1
4112	308	315	7
Mean	345.5	359.1	13.5
S.D.	19.9	30.5	14.0

Unit: g

a): Day of lactation

## Appendix 341

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of administration												Gain 1-42	
	1	4	8	11	15	18	22	25	29	32	36	39		
1013	422	443	462	480	506	505	528	528	545	559	571	589	588	166
1014	397	407	429	443	460	468	490	499	518	523	535	545	543	146
1015	405	422	441	450	464	473	496	506	515	529	542	551	556	151
1016	384	394	418	433	447	457	471	477	490	494	507	516	512	128
1017	388	404	427	443	459	468	479	485	502	509	516	526	521	133
Mean	399.2	414.0	435.4	449.8	467.2	474.2	492.8	499.0	514.0	522.8	534.2	545.4	544.0	144.8
S.D.	15.1	19.1	17.0	17.9	22.6	18.2	21.9	19.8	20.6	24.3	24.9	28.2	30.1	15.1

Unit: g

## Appendix 342

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of administration												Gain 1-42	
	1	4	8	11	15	18	22	25	29	32	36	39		
4013	379	391	403	413	426	437	456	472	494	500	518	525	525	146
4014	400	408	424	439	445	459	473	481	503	513	524	532	527	127
4015	392	401	417	426	441	448	463	471	483	496	502	508	514	122
4016	410	424	445	462	478	494	509	514	524	536	543	554	553	143
4017	435	450	469	484	501	519	531	547	569	579	596	610	611	176
Mean	403.2	414.8	431.6	444.8	458.2	471.4	486.4	497.0	514.6	524.8	536.6	545.8	546.0	142.8
S.D.	21.1	23.1	25.8	28.4	30.5	34.1	32.2	33.0	33.9	34.1	36.3	39.5	39.1	21.2

Unit: g

## Appendix 343

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of administration												Gain 1-42	
	1	4	8	11	15	18	22	25	29	32	36	39		
1113	230	240	261	265	275	273	280	282	284	294	294	296	300	70
1114	262	273	286	297	310	313	317	330	333	342	345	348	349	87
1115	237	241	254	267	279	279	281	294	300	299	304	299	300	63
1116	248	254	267	267	276	273	281	294	300	292	303	307	309	61
1117	230	237	251	252	261	276	282	284	291	293	296	297	299	69
Mean	241.4	249.0	263.8	269.6	280.2	282.8	288.2	296.8	301.6	304.0	308.4	309.4	311.4	70.0
S.D.	13.7	14.9	13.9	16.5	18.0	17.1	16.1	19.4	18.8	21.4	20.9	22.0	21.4	10.2

Unit: g

## Appendix 344

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of administration												Gain 1-42	
	1	4	8	11	15	18	22	25	29	32	36	39		
4113	252	251	258	265	274	277	287	289	294	288	288	300	306	54
4114	237	237	260	268	280	279	292	300	308	314	323	314	328	91
4115	243	244	251	251	256	267	278	281	289	293	294	292	300	57
4116	258	260	273	268	282	292	295	296	316	319	318	333	332	74
4117	266	276	271	278	279	290	304	320	320	323	318	325	333	67
Mean	251.2	253.6	262.6	266.0	274.2	281.0	291.2	297.2	305.4	307.4	308.2	312.8	319.8	68.6
S.D.	11.6	15.1	9.2	9.7	10.6	10.2	9.6	14.7	13.5	15.9	16.0	17.0	15.6	14.8

Unit: g

## Appendix 345

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of recovery					Gain 1-14
	1	4	8	11	14	
1013	590	592	606	607	616	26
1014	548	552	563	561	565	17
1015	558	559	578	575	582	24
1016	514	519	526	530	535	21
1017	525	526	532	543	543	18
Mean	547.0	549.6	561.0	563.2	568.2	21.2
S.D.	29.8	29.1	33.1	29.9	32.5	3.8

Unit: g

## Appendix 346

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of recovery					Gain 1-14
	1	4	8	11	14	
4013	532	541	546	549	553	21
4014	528	539	550	549	557	29
4015	515	532	541	543	547	32
4016	559	555	570	576	573	14
4017	615	624	640	639	646	31
Mean	549.8	558.2	569.4	571.2	575.2	25.4
S.D.	39.8	37.7	41.0	40.0	40.7	7.7

Unit: g

Appendix 347

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of recovery					Gain 1-14
	1	4	8	11	14	
1113	302	302	306	305	312	10
1114	353	352	353	368	372	19
1115	297	299	301	315	313	16
1116	310	314	314	312	309	-1
1117	288	293	300	306	305	17
Mean	310.0	312.0	314.8	321.2	322.2	12.2
S.D.	25.3	23.6	22.1	26.5	28.0	8.1

Unit: g

Appendix 348

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of recovery					Gain 1-14
	1	4	8	11	14	
4113	305	305	309	301	299	-6
4114	319	325	333	324	332	13
4115	289	299	305	300	304	15
4116	338	326	330	337	344	6
4117	337	339	350	360	370	33
Mean	317.6	318.8	325.4	324.4	329.8	12.2
S.D.	21.0	16.4	18.5	25.3	29.3	14.2

Unit: g

## Appendix 349

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual food consumption of male rats (Main group)

Dose (mg/kg): 0

Animal number	Pre-mating period					Post-mating period			
	1	4	8	11	15	32	36	39	42a)
1001	29	32	28	30	32	30	31	31	30
1002	32	31	29	27	29	27	28	24	29
1003	27	35	29	31	30	33	36	32	32
1004	22	30	26	28	27	30	30	31	31
1005	22	30	28	27	26	28	28	25	32
1006	29	33	29	31	29	34	35	37	37
1007	25	30	30	31	30	33	35	30	36
1008	35	34	31	34	30	30	31	29	32
1009	25	30	32	29	30	32	33	30	37
1010	30	38	38	26	37	32	34	34	38
1011	28	32	31	33	33	33	37	34	39
1012	25	31	32	30	27	29	32	33	36
Mean	27.4	32.2	30.3	29.8	30.0	30.9	32.5	30.8	34.1
S.D.	3.9	2.5	3.0	2.5	3.0	2.2	3.0	3.7	3.4

Unit: g/rat/day

a): Day of administration

## Appendix 350

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of male rats (Main group)

Dose (mg/kg): 100

Animal number	Pre-mating period					Post-mating period			
	1	4	8	11	15	32	36	39	42a)
2001	25	28	27	21	25	27	30	29	28
2002	28	32	29	26	24	31	29	30	31
2003	25	30	28	29	29	34	33	33	37
2004	31	33	31	30	33	33	35	32	32
2005	32	34	30	33	27	31	33	32	32
2006	33	35	37	39	36	35	35	38	38
2007	25	34	29	28	26	30	32	31	33
2008	32	32	31	33	33	34	31	35	36
2009	30	32	34	35	34	34	34	34	39
2010	24	28	29	27	28	28	30	29	29
2011	28	37	32	27	25	26	33	27	31
2012	30	38	35	37	32	33	36	35	38
Mean	28.6	32.8	31.0	30.4	29.3	31.3	32.6	32.1	33.7
S.D.	3.2	3.1	3.0	5.1	4.1	3.0	2.2	3.1	3.8

Unit: g/rat/day

a): Day of administration

## Appendix 351

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of male rats (Main group)

Dose (mg/kg): 300

Animal number	Pre-mating period					Post-mating period			
	1	4	8	11	15	32	36	39	42a)
3001	27	29	30	30	26	28	31	31	32
3002	25	30	28	29	24	30	28	29	31
3003	29	32	28	29	26	26	30	28	31
3004	27	31	31	29	27	29	29	29	36
3005	25	37	32	29	30	29	30	31	32
3006	26	27	25	29	28	32	29	29	31
3007	21	31	29	28	26	30	28	30	34
3008	25	26	27	25	27	29	29	25	31
3009	25	33	33	34	29	33	34	32	40
3010	30	29	28	29	27	27	28	30	30
3011	22	27	27	28	23	26	27	28	27
3012	27	30	27	28	27	29	28	27	32
Mean	25.8	30.2	28.8	28.9	26.7	29.0	29.3	29.1	32.3
S.D.	2.6	3.0	2.3	2.0	1.9	2.1	1.9	1.9	3.3

Unit: g/rat/day

a): Day of administration

Appendix 352

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of male rats (Main group)

Dose (mg/kg): 1000

Animal number	Pre-mating period					Post-mating period			
	1	4	8	11	15	32	36	39	42a)
4001	23	28	28	29	29	28	28	32	31
4002	33	31	30	30	27	29	33	29	35
4003	24	31	25	28	26	26	28	29	32
4004	28	31	36	30	32	33	34	30	33
4005	31	38	32	34	35	33	35	32	39
4006	31	35	33	32	32	29	32	28	35
4007	29	29	25	29	28	28	28	28	30
4008	24	27	23	24	22	27	32	30	31
4009	26	34	32	32	34	35	37	34	35
4010	34	36	32	31	34	33	30	31	34
4011	24	34	27	29	26	31	29	31	33
4012	30	33	30	29	32	31	33	36	35
Mean	28.1	32.3	29.4	29.8	29.8	30.3	31.6	30.8	33.6
S.D.	3.8	3.3	3.9	2.5	4.0	2.8	3.0	2.4	2.5

Unit: g/rat/day

a): Day of administration

Appendix 353

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of administration				
	1	4	8	11	15
1101	18	22	23	23	23
1102	19	21	20	19	18
1103	17	26	21	22	20
1104	16	24	22	17	22
1105	16	23	23	22	22
1106	18	21	23	19	17
1107	13	22	21	22	22
1108	21	17	19	24	23
1109	17	22	16	21	22
1110	18	25	24	22	22
1111	18	25	24	26	26
1112	12	24	24	28	23
Mean	16.9	22.7	21.7	22.1	21.7
S.D.	2.5	2.4	2.4	3.0	2.4

Unit: g/rat/day

Appendix 354

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 100

Animal number	Day of administration				
	1	4	8	11	15
2101	20	21	21	21	24
2102	19	23	23	19	22
2103	19	22	23	20	17
2104	25	28	30	21	25
2105	19	22	23	19	17
2106	17	25	25	25	25
2107	12	21	22	23	23
2108	16	25	23	23	25
2109	22	27	24	26	24
2110	14	21	21	20	19
2111	22	20	20	22	22
2112	20	23	23	21	26
Mean	18.8	23.2	23.2	21.7	22.4
S.D.	3.6	2.6	2.6	2.2	3.1

Unit: g/rat/day

## Appendix 355

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 300

Animal number	Day of administration				
	1	4	8	11	15
3101	19	25	23	21	22
3102	19	23	20	21	24
3103	19	21	20	20	16
3104	15	25	21	24	24
3105	19	25	24	23	24
3106	12	24	21	22	22
3107	21	16	16	21	22
3108	13	19	19	16	14
3109	21	16	16	20	21
3110	16	19	17	19	20
3111	22	22	21	28	27
3112	17	20	21	16	15
Mean	17.8	21.3	19.9	20.9	20.9
S.D.	3.2	3.3	2.5	3.3	4.0

Unit: g/rat/day

## Appendix 356

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of administration				
	1	4	8	11	15
4101	11	20	18	19	19
4102	20	25	22	19	22
4103	18	14	15	20	18
4104	18	24	22	24	25
4105	21	23	21	25	20
4106	12	20	20	21	20
4107	20	24	24	23	24
4108	20	23	23	23	25
4109	18	18	14	24	22
4110	21	22	20	19	19
4111	18	16	16	22	20
4112	14	19	21	22	21
Mean	17.6	20.7	19.7	21.8	21.3
S.D.	3.4	3.4	3.2	2.1	2.4

Unit: g/rat/day

## Appendix 357

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of dams during the gestation period (Main group)

Dose (mg/kg): 0

Dam number	Administration						
	1	4	7	11	14	17	20a)
1101	18	25	28	29	29	27	28
1102	25	28	27	30	29	24	24
1103	15	25	26	26	29	28	21
1104	24	25	24	30	22	28	27
1105	21	23	23	22	27	30	30
1106	22	20	23	24	22	24	22
1107	23	22	28	27	28	27	27
1108	27	26	27	27	25	26	23
1109	21	23	22	26	23	27	25
1110	25	23	25	24	24	27	28
1111	23	27	29	30	31	31	27
1112	26	30	31	31	32	32	31
Mean	22.5	24.8	26.1	27.2	26.8	27.6	26.1
S.D.	3.4	2.8	2.7	2.9	3.5	2.5	3.1

Unit: g/rat/day

a): Day of gestation

## Appendix 358

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of dams during the gestation period (Main group)

Dose (mg/kg): 100

Dam number	Administration						
	1	4	7	11	14	17	20a)
2101	15	23	25	23	25	30	27
2102	28	30	28	30	29	31	25
2103	20	27	31	28	29	33	30
2104	31	33	29	32	30	33	31
2105	25	27	28	27	26	32	24
2106	25	29	34	31	32	38	29
2107	21	25	22	27	25	26	25
2108	25	24	26	26	27	26	25
2109	26	26	32	35	35	40	31
2110	23	25	24	27	28	26	26
2111	23	21	21	23	21	23	14
2112	23	26	27	27	26	30	29
Mean	23.8	26.3	27.3	28.0	27.8	30.7	26.3
S.D.	4.0	3.2	3.9	3.5	3.6	5.0	4.6

Unit: g/rat/day

a): Day of gestation

Appendix 359

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of dams during the gestation period (Main group)

Dose (mg/kg): 300

Dam number	Administration						
	1	4	7	11	14	17	20a)
3101	18	22	26	29	29	32	25
3102	24	25	26	29	31	33	29
3103	25	25	24	26	27	32	23
3104	24	27	28	29	27	28	24
3105	21	27	28	29	28	31	29
3106	Non-pregnant						
3107	25	26	30	31	25	28	26
3108	25	25	30	26	25	28	27
3109	23	23	19	26	24	26	24
3110	24	24	26	24	24	31	22
3111	25	29	29	37	32	37	28
3112	21	19	23	21	20	27	25
Mean	23.2	24.7	26.3	27.9	26.5	30.3	25.6
S.D.	2.3	2.7	3.3	4.1	3.4	3.2	2.4

Unit: g/rat/day

a): Day of gestation

## Appendix 360

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of dams during the gestation period (Main group)

Dose (mg/kg): 1000

Dam number	Administration						
	1	4	7	11	14	17	20a)
4101	21	25	26	28	32	28	24
4102	25	25	26	33	27	33	27
4103	26	25	23	29	23	26	24
4104	26	28	31	33	29	31	26
4105	23	26	30	28	28	33	29
4106	25	27	26	33	33	33	27
4107	Non-pregnant						
4108	25	27	26	29	24	29	30
4109	20	25	23	30	22	27	23
4110	17	20	21	21	23	25	24
4111	24	22	23	26	24	24	22
4112	23	26	26	23	26	29	24
Mean	23.2	25.1	25.5	28.5	26.5	28.9	25.5
S.D.	2.8	2.3	3.0	4.0	3.7	3.3	2.5

Unit: g/rat/day

a): Day of gestation

## Appendix 361

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of dams during the lactation period (Main group)

Dose (mg/kg): 0

Dam number	Administration	
	2	4a)
1101	26	48
1102	29	44
1103	28	51
1104	29	44
1105	25	41
1106	19	43
1107	31	40
1108	14	37
1109	24	39
1110	27	49
1111	30	41
1112	39	55
Mean	26.8	44.3
S.D.	6.2	5.4

Unit: g/rat/day

a): Day of lactation

## Appendix 362

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of dams during the lactation period (Main group)

Dose (mg/kg): 100

Dam number	Administration	
	2	4a)
2101	49	58
2102	28	48
2103	27	44
2104	41	58
2105	30	40
2106	29	47
2107	30	41
2108	28	43
2109	27	48
2110	32	49
2111	21	42
2112	24	50
Mean	30.5	47.3
S.D.	7.5	6.0

Unit: g/rat/day

a): Day of lactation

## Appendix 363

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of dams during the lactation period (Main group)

Dose (mg/kg): 300

Dam number	Administration	
	2	4a)
3101	21	53
3102	35	49
3103	16	48
3104	24	43
3105	20	38
3106	Non-pregnant	
3107	30	47
3108	27	45
3109	30	51
3110	32	47
3111	34	42
3112	26	49
Mean	26.8	46.5
S.D.	6.1	4.3

Unit: g/rat/day

a): Day of lactation

## Appendix 364

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual food consumption of dams during the lactation period (Main group)

Dose (mg/kg): 1000

Dam number	Administration	
	2	4a)
4101	27	44
4102	34	52
4103	30	44
4104	28	43
4105	26	47
4106	32	52
4107	Non-pregnant	
4108	27	42
4109	26	43
4110	26	39
4111	26	40
4112	23	32
Mean	27.7	43.5
S.D.	3.1	5.7

Unit: g/rat/day

a): Day of lactation

## Appendix 365

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of administration								
	1	4	8	11	15	32	36	39	42
1013	30	35	30	29	31	29	28	39	34
1014	28	30	29	30	29	31	30	34	30
1015	27	32	30	30	28	32	32	32	36
1016	24	28	28	29	29	29	31	31	30
1017	24	32	29	31	29	29	28	32	30
Mean	26.6	31.4	29.2	28.8	29.2	30.0	29.8	33.6	32.0
S.D.	2.6	2.6	0.8	0.8	1.1	1.4	1.8	3.2	2.8

Unit: g/rat/day

## Appendix 366

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of administration								
	1	4	8	11	15	32	36	39	42
4013	26	27	25	25	26	29	30	28	31
4014	28	29	27	28	26	33	31	33	29
4015	28	30	29	29	28	30	29	32	30
4016	33	36	33	33	34	35	34	33	37
4017	32	38	30	34	32	31	38	33	39
Mean	29.4	32.0	28.8	29.8	29.2	31.6	32.4	31.8	33.2
S.D.	3.0	4.7	3.0	3.7	3.6	2.4	3.6	2.2	4.5

Unit: g/rat/day

Appendix 367

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of administration								
	1	4	8	11	15	32	36	39	42
1113	10	19	20	21	23	19	18	24	21
1114	22	27	26	27	27	25	26	23	24
1115	16	17	18	23	25	20	21	18	19
1116	15	22	20	21	19	17	26	19	22
1117	16	20	23	18	18	22	23	19	23
Mean	15.8	21.0	21.4	22.0	22.4	20.6	22.8	20.6	21.8
S.D.	4.3	3.8	3.1	3.3	3.8	3.0	3.4	2.7	1.9

Unit: g/rat/day

Appendix 368

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of administration								
	1	4	8	11	15	32	36	39	42
4113	19	17	14	20	19	18	14	20	23
4114	20	19	20	25	24	24	25	21	28
4115	19	23	22	18	16	22	24	8	25
4116	18	22	22	19	23	24	22	25	25
4117	17	21	19	20	14	21	15	22	25
Mean	18.6	20.4	19.4	20.4	19.2	21.8	20.0	19.2	25.2
S.D.	1.1	2.4	3.3	2.7	4.3	2.5	5.1	6.5	1.8

Unit: g/rat/day

Appendix 369

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of recovery				
	1	4	8	11	14
1013	35	25	26	28	28
1014	30	26	29	29	31
1015	31	32	38	34	36
1016	22	28	28	30	29
1017	25	25	27	32	29
Mean	28.6	27.2	29.6	30.6	30.6
S.D.	5.1	2.9	4.8	2.4	3.2

Unit: g/rat/day

Appendix 370

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of recovery				
	1	4	8	11	14
4013	28	32	28	29	29
4014	26	28	29	30	30
4015	27	33	32	31	33
4016	30	33	33	34	34
4017	29	36	38	36	38
Mean	28.0	32.4	32.0	32.0	32.8
S.D.	1.6	2.9	3.9	2.9	3.6

Unit: g/rat/day

Appendix 371

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 0

Animal number	Day of recovery				
	1	4	8	11	14
1113	20	19	20	18	24
1114	20	20	21	29	31
1115	16	15	16	22	22
1116	21	21	21	21	14
1117	15	20	21	23	23
Mean	18.4	19.0	19.8	22.6	22.8
S.D.	2.7	2.3	2.2	4.0	6.1

Unit: g/rat/day

Appendix 372

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg): 1000

Animal number	Day of recovery				
	1	4	8	11	14
4113	17	19	21	19	16
4114	19	23	26	23	22
4115	11	21	25	23	25
4116	23	21	23	20	25
4117	22	20	21	24	26
Mean	18.4	20.8	23.2	21.8	22.8
S.D.	4.8	1.5	2.3	2.2	4.1

Unit: g/rat/day

## Appendix 373

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual urinalysis of male rats (Week 6 of administration)

Dose (mg/kg) : 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
1001	8.5	+	+	-	-	-	+-	Y
1002	7.0	+	+-	-	-	-	+-	Y
1003	8.0	++	+-	-	-	-	+-	Y
1004	8.5	++	-	-	-	-	+-	Y
1005	7.0	+	+-	-	-	-	+-	Y
1006	7.5	-	-	-	++	-	+-	Y
1007	8.0	++	-	-	-	-	+-	Y
1008	8.0	+	+-	-	+	-	+-	Y
1009	8.5	++	-	-	-	-	+-	Y
1010	8.0	++	-	-	-	-	+-	Y
1011	8.0	++	-	-	-	-	+-	Y
1012	8.0	-	-	-	-	-	+-	Y
1013	9.0	++	+-	-	-	-	+-	Y
1014	8.0	-	-	-	-	-	+-	Y
1015	7.0	+	+	-	++	-	+-	Y
1016	8.5	++	-	-	-	-	+-	Y
1017	8.5	+	+-	-	-	-	+-	Y

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
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			

Appendix 374

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 6 of administration)

Dose (mg/kg) : 0

Animal number	URINE SEDIMENT					CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
1001	-	-	++	-	-	+	-
1002	-	-	++	-	-	++	-
1003	-	-	++	-	-	+	-
1004	-	-	++	-	-	+	-
1005	-	-	++	-	-	++	-
1006	-	-	++	-	-	+	-
1007	-	-	++	-	-	+	-
1008	-	-	++	-	-	+	-
1009	-	-	++	-	-	++	-
1010	-	-	++	-	-	++	-
1011	-	-	++	-	-	++	-
1012	-	-	++	-	-	++	-
1013	-	-	++	-	-	++	-
1014	-	-	++	-	-	+	-
1015	-	-	++	-	-	++	-
1016	-	-	++	-	-	++	-
1017	-	-	++	-	-	-	-

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

## Appendix 375

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual water intake and urinalysis (Week 6 of administration)

Sex : Male

Dose (mg/kg) : 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
1001	41	14.8	1930
1002	39	17.9	1512
1003	38	17.6	2110
1004	56	29.1	1304
1005	36	12.3	2272
1006	58	24.9	1972
1007	44	18.7	2170
1008	51	26.5	1496
1009	57	31.2	1218
1010	59	34.2	1304
1011	52	23.2	1558
1012	66	31.8	1288
1013	61	31.5	1284
1014	54	27.9	1502
1015	39	15.1	2288
1016	39	14.4	2564
1017	42	14.0	2308
Mean	49	22.7	1769
S.D.	10	7.5	451

## Appendix 376

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 6 of administration)

Dose (mg/kg) : 100

Animal number	pH	1) Protein	2) Ketone body	3) Glucose	4) Occult blood	5) Bilirubin	6) Urobilinogen	7) Color
2001	8.5	+	+	-	-	-	+-	Y
2002	7.5	+-	-	-	-	-	+-	Y
2003	8.5	+-	-	-	-	-	+-	Y
2004	8.0	+-	-	-	-	-	+-	Y
2005	6.5	+-	+-	-	+-	-	+-	Y
2006	7.5	+-	+-	-	+-	-	+-	Y
2007	8.5	+	+-	-	-	-	+-	Y
2008	8.0	+-	-	-	-	-	+-	Y
2009	7.5	-	-	-	-	-	+-	Y
2010	7.5	+	+	-	-	-	+-	Y
2011	8.5	+-	-	-	-	-	+-	Y
2012	7.5	+	+	-	+-	-	+-	Y

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
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			

Appendix 377

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 6 of administration)

Dose (mg/kg) : 100

Animal number	URINE SEDIMENT					CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
2001	-	-	++	-	-	+	-
2002	-	-	++	-	-	++	-
2003	-	-	++	-	-	+	-
2004	-	-	++	-	-	+	-
2005	-	-	++	-	-	-	-
2006	-	-	++	-	-	+	-
2007	-	-	++	-	-	++	-
2008	-	-	++	-	-	+	-
2009	-	-	++	-	-	-	-
2010	-	-	++	-	-	++	-
2011	-	-	++	-	-	++	-
2012	-	-	++	-	-	++	-

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

Appendix 378

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual water intake and urinalysis (Week 6 of administration)

Sex : Male

Dose (mg/kg) : 100

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
2001	41	20.0	1494
2002	49	26.5	1558
2003	52	23.0	1706
2004	48	19.6	2008
2005	45	21.4	1782
2006	62	26.4	1554
2007	42	16.8	1936
2008	48	20.1	1872
2009	72	40.7	1136
2010	41	14.5	2534
2011	26	12.9	2226
2012	37	12.4	2604
Mean	47	21.2	1868
S.D.	12	7.7	431

## Appendix 379

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 6 of administration)

Dose (mg/kg) : 300

Animal number	pH	1) Protein	2) Ketone body	3) Glucose	4) Occult blood	5) Bilirubin	6) Urobilinogen	7) Color
3001	6.5	+-	+-	-	++	-	+-	Y
3002	6.0	+-	+-	-	-	-	+-	Y
3003	7.0	+-	-	-	-	-	+-	Y
3004	6.5	+-	+-	-	-	-	+-	Y
3005	6.5	+-	+-	-	-	-	+-	Y
3006	7.5	+-	-	-	-	-	+-	Y
3007	8.5	+-	-	-	++	-	+-	Y
3008	6.5	+-	-	-	++	-	+-	Y
3009	8.5	+	+-	-	++	-	+-	Y
3010	7.0	+-	+-	-	-	-	+-	Y
3011	8.0	-	-	-	-	-	+-	Y
3012	8.5	+-	-	-	-	-	+-	Y

- 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  
 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

## Appendix 380

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 6 of administration)

Dose (mg/kg) : 300

Animal number	URINE SEDIMENT						CRYSTALLIZATION
	RBC	WBC	SEC	SREC	Cast	PS	
3001	-	-	++	-	-	-	-
3002	-	-	++	-	-	-	-
3003	-	-	++	-	-	+	-
3004	-	-	++	-	-	-	-
3005	-	-	++	-	-	++	-
3006	-	-	++	-	-	+	-
3007	-	-	++	-	-	-	-
3008	-	-	++	-	-	++	-
3009	-	-	++	-	-	++	-
3010	-	-	++	-	-	++	-
3011	-	-	++	-	-	-	-
3012	-	-	++	-	-	++	-

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

## Appendix 381

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual water intake and urinalysis (Week 6 of administration)

Sex : Male

Dose (mg/kg) : 300

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
3001	40	12.9	2322
3002	40	19.6	1804
3003	46	13.2	1960
3004	45	21.5	1776
3005	47	15.0	2064
3006	49	24.0	1600
3007	45	25.7	1752
3008	50	15.7	1788
3009	42	20.8	1656
3010	58	37.4	1140
3011	36	15.6	2168
3012	35	9.2	2484
Mean	44	19.2	1876
S.D.	6	7.5	357

## Appendix 382

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual urinalysis of male rats (Week 6 of administration)

Dose (mg/kg) : 1000

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Billi-rubin	6) Urobi-linogen	7) Color
4001	6.5	+	++	-	-	-	+	Y
4002	6.5	+-	-	-	-	-	+-	Y
4003	6.5	+-	-	-	-	-	+-	Y
4004	6.5	+	++	-	-	-	++	Y
4005	6.5	+	++	-	++	-	+-	Y
4006	6.5	+-	++	-	-	-	++	Y
4007	6.5	+-	-	-	-	-	++	Y
4008	6.0	+-	-	-	-	-	++	Y
4009	7.0	+-	++	-	-	-	++	Y
4010	6.5	+	++	-	++	-	++	Y
4011	6.0	+	++	-	-	-	++	Y
4012	6.5	+-	-	-	-	-	++	Y
4013	7.0	+	-	-	-	-	++	Y
4014	7.5	+-	-	-	-	-	++	Y
4015	6.0	+-	++	-	-	-	++	Y
4016	6.5	+	-	-	-	-	++	Y
4017	6.0	-	-	-	-	-	++	Y

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
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			

Appendix 383

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 6 of administration)

Dose (mg/kg) : 1000

Animal number	URINE SEDIMENT						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO	
4001	-	-	++	-	-	-	-	-
4002	-	-	+-	-	-	-	-	-
4003	-	-	+-	-	-	-	-	-
4004	-	-	+-	-	-	-	-	-
4005	-	-	++	-	-	-	-	-
4006	-	-	+-	-	-	-	-	-
4007	-	-	+-	-	-	++	-	-
4008	-	-	+-	-	-	-	-	-
4009	-	-	++	-	-	++	-	-
4010	++	-	+-	-	-	-	-	-
4011	-	-	+-	-	-	-	-	-
4012	-	-	+	-	-	-	-	-
4013	-	-	+-	-	-	-	-	-
4014	-	-	+-	-	-	++	-	-
4015	-	-	+-	-	-	-	-	-
4016	-	-	+-	-	-	-	-	-
4017	-	-	+-	-	-	-	-	-

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

Appendix 384

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual water intake and urinalysis (Week 6 of administration)

Sex : Male

Dose (mg/kg) : 1000

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
4001	41	11.9	2478
4002	54	33.8	1528
4003	46	16.2	1916
4004	37	17.2	2196
4005	41	25.6	1638
4006	48	24.3	1802
4007	41	14.6	2092
4008	35	17.2	1952
4009	48	18.4	2158
4010	38	15.8	2222
4011	30	15.5	2154
4012	58	27.2	1414
4013	47	24.2	1692
4014	50	21.0	1468
4015	53	16.9	1298
4016	52	19.6	1988
4017	65	31.1	1676
Mean	46	20.6	1863
S.D.	9	6.1	333

## Appendix 385

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual urinalysis of male rats (Week 2 of recovery)

Dose (mg/kg) : 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
1013	8.0	-	-	-	++	-	++	Y
1014	8.0	+-	+-	-	-	-	+-	Y
1015	7.5	+	+	-	++	-	+-	Y
1016	8.5	+	+-	-	-	-	+-	Y
1017	8.5	++	+	-	-	-	+	Y

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
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			

Appendix 386

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 2 of recovery)

Dose (mg/kg) : 0

Animal number	URINE SEDIMENT						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO	
1013	-	-	++	-	-	++	-	
1014	-	-	++	-	-	+	-	
1015	-	-	++	-	-	++	-	
1016	-	-	++	-	-	+	-	
1017	-	-	++	-	-	+	-	

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

## Appendix 387

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual water intake and urinalysis (Week 2 of recovery)

Sex : Male

Dose (mg/kg) : 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
1013	70	31.7	1302
1014	69	27.7	1340
1015	51	16.1	2138
1016	36	12.5	2606
1017	39	12.8	2376
Mean	53	20.2	1952
S.D.	16	8.9	600

## Appendix 388

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 2 of recovery)

Dose (mg/kg) : 1000

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
4013	8.5	+	-	-	-	-	+-	Y
4014	7.5	+	++	-	-	-	+	Y
4015	8.0	+-	++	-	-	-	+-	Y
4016	8.0	+	++	-	++	-	+-	Y
4017	8.0	-	-	-	-	-	+-	Y
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		
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					

Appendix 389

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual urinalysis of male rats (Week 2 of recovery)

Dose (mg/kg) : 1000

Animal number	URINE SEDIMENT					CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4013	-	-	++	-	-	+	-
4014	-	-	++	-	-	++	-
4015	-	-	++	-	-	++	-
4016	+	-	++	-	-	++	-
4017	-	-	++	-	-	++	-

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

## Appendix 390

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual water intake and urinalysis (Week 2 of recovery)

Sex : Male

Dose (mg/kg) : 1000

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
4013	40	21.7	1756
4014	45	18.7	1706
4015	48	20.4	1678
4016	49	20.2	1964
4017	65	26.7	1518
Mean	49	21.5	1724
S.D.	9	3.1	161

## Appendix 391

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diaminium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual hematology (Week 6 of administration)

Sex : Male

Dose mg/kg	Animal number	RBC $\times 10^4/\mu\text{L}$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let $\times 10^4/\mu\text{L}$	PT s	APTT s	Fibri- nogen mg/dL
0	1001	903	16.7	44.0	48.7	18.5	38.0	2.1	102.7	12.8	19.5	295
	1002	901	15.9	42.3	47.0	17.7	37.6	1.9	117.6	16.1	26.5	368
	1003	876	16.8	43.7	49.9	19.2	38.5	1.5	103.2	15.5	26.8	285
	1004	913	17.0	45.6	50.0	18.6	37.3	1.6	134.9	14.2	26.5	276
	1005	920	17.0	45.4	49.4	18.5	37.5	1.7	105.9	14.8	28.9	266
	Mean	903	16.7	44.2	49.0	18.5	37.8	1.8	112.9	14.7	25.6	298
100	S.D.	17	0.5	1.4	1.2	0.5	0.5	0.2	13.7	1.3	3.6	41
	2001	936	16.9	44.9	48.0	18.1	37.7	1.7	117.5	14.0	21.3	300
	2002	913	16.5	42.6	46.7	18.1	38.7	2.1	114.6	14.9	18.9	326
	2003	908	16.4	43.5	48.0	18.1	37.6	2.4	118.1	16.7	26.3	337
	2004	879	16.4	42.4	48.2	18.6	38.6	1.3	117.9	14.9	23.2	248
	2005	956	17.3	44.9	47.0	18.1	38.4	1.3	89.7	15.5	19.6	296
300	Mean	918	16.7	43.7	47.6	18.2	38.2	1.8	111.6	15.2	21.9	301
	S.D.	29	0.4	1.2	0.7	0.2	0.5	0.5	12.3	1.0	3.0	34
	3001	915	16.3	42.6	46.6	17.8	38.2	1.7	108.2	14.4	26.9	295
	3002	932	17.2	45.4	48.8	18.5	37.9	1.5	107.9	16.0	21.0	291
	3003	868	16.3	42.9	49.4	18.8	38.0	1.7	103.7	17.7	25.1	299
	3004	971	16.4	43.4	44.7	16.9	37.8	1.9	121.7	15.0	21.8	322
1000	3005	850	16.5	43.6	51.2	19.4	37.8	1.9	106.7	12.9	20.2	281
	Mean	907	16.5	43.6	48.1	18.3	37.9	1.7	109.6	15.2	23.0	298
	S.D.	49	0.4	1.1	2.5	1.0	0.2	0.2	7.0	1.8	2.9	15
	4001	937	17.5	46.8	50.0	18.6	37.3	1.1	101.7	17.9	28.4	304
	4002	876	16.7	44.7	51.0	19.0	37.3	1.9	107.5	13.6	22.2	268
	4003	889	16.9	44.9	50.5	19.0	37.6	1.3	137.2	15.9	23.7	290
4004	4004	925	16.5	43.2	46.7	17.8	38.2	1.3	107.2	13.9	20.6	285
	4005	951	16.6	44.3	46.6	17.5	37.6	1.7	118.3	14.3	21.5	316
	Mean	916	16.8	44.8	49.0	18.4	37.6	1.5	114.4	15.1	23.3	293
S.D.	S.D.	32	0.4	1.3	2.1	0.7	0.4	0.3	14.1	1.8	3.1	18

## Appendix 392

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual hematology (Week 6 of administration)

Sex : Male

Dose mg/kg	Animal number	WBC		Differential leukocyte counts (%)					Differential leukocyte counts ( $\times 10^3/\mu\text{L}$ )					
		$\times 10^3/\mu\text{L}$	X10 <sup>3</sup> /μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.
0	1001	138.5	75.7	20.6	1.0	0.5	1.5	0.8	104.8	28.5	1.4	0.7	2.0	1.1
	1002	104.2	71.3	23.9	1.6	0.5	2.2	0.5	74.3	24.9	1.7	0.5	2.3	0.6
	1003	86.5	82.8	13.2	0.7	0.6	2.4	0.3	71.6	11.4	0.6	0.5	2.1	0.3
	1004	101.4	80.3	15.8	1.2	0.5	1.6	0.6	81.5	16.0	1.2	0.5	1.7	0.6
	1005	68.9	67.4	27.8	2.5	0.5	1.7	0.2	46.5	19.2	1.7	0.3	1.2	0.1
	Mean	99.9	75.5	20.3	1.4	0.5	1.9	0.5	75.7	20.0	1.3	0.5	1.9	0.5
100	S.D.	25.7	6.3	5.9	0.7	0.0	0.4	0.2	20.9	6.8	0.5	0.1	0.4	0.4
	2001	164.8	88.9	8.2	0.7	0.5	1.3	0.4	146.5	13.4	1.2	0.9	2.2	0.6
	2002	117.5	74.6	21.0	1.5	0.5	1.7	0.5	87.7	24.7	1.8	0.6	2.0	0.6
	2003	112.3	83.9	11.7	0.8	0.5	1.6	1.5	94.2	13.2	0.9	0.5	1.8	1.7
	2004	83.1	71.1	22.7	2.3	0.4	3.1	0.3	59.1	18.8	1.9	0.3	2.6	0.3
	2005	102.3	69.9	25.0	2.0	0.4	2.4	0.4	71.5	25.5	2.0	0.4	2.5	0.4
300	Mean	116.0	77.7	17.7	1.5	0.5	2.0	0.6	91.8	19.1	1.6	0.5	2.2	0.7
	S.D.	30.3	8.3	7.3	0.7	0.1	0.7	0.5	33.5	5.9	0.5	0.2	0.3	0.6
	3001	111.9	78.4	16.9	1.4	0.3	2.3	0.6	87.8	18.9	1.5	0.4	2.6	0.7
	3002	95.7	77.8	17.7	0.9	0.5	2.7	0.4	74.4	16.9	0.9	0.5	2.6	0.4
	3003	83.9	80.4	13.6	1.0	0.6	3.1	1.2	67.5	11.4	0.8	0.5	2.6	1.0
	3004	95.1	67.3	26.9	0.7	0.4	4.2	0.5	64.0	25.6	0.6	0.4	4.0	0.5
1000	3005	84.2	71.0	24.3	1.9	0.3	2.1	0.3	59.8	20.5	1.6	0.3	1.8	0.3
	Mean	94.2	75.0	19.9	1.2	0.4	2.9	0.6	70.7	18.7	1.1	0.4	2.7	0.6
	S.D.	11.4	5.6	5.5	0.5	0.1	0.8	0.4	11.0	5.2	0.4	0.1	0.8	0.3
	4001	97.1	80.1	15.8	0.8	0.6	2.3	0.4	77.8	15.4	0.8	0.5	2.2	0.4
	4002	154.2	81.0	15.3	0.8	0.6	1.9	0.4	124.9	23.7	1.2	0.9	2.9	0.6
	4003	84.0	83.8	12.7	1.2	0.4	1.6	0.3	70.4	10.7	1.0	0.4	1.3	0.2
4000	4004	93.1	78.5	17.0	0.6	0.6	2.8	0.4	73.1	15.8	0.6	0.6	2.6	0.4
	4005	82.7	65.9	28.4	1.6	0.3	2.9	0.9	54.5	23.5	1.4	0.3	2.4	0.8
	Mean	102.2	77.9	17.8	1.0	0.5	2.3	0.5	80.1	17.8	1.0	0.5	2.3	0.5
	S.D.	29.7	7.0	6.1	0.4	0.1	0.6	0.2	26.5	5.6	0.3	0.2	0.6	0.2

LUC : Large unstained cells

## Appendix 393

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual hematology (Day 4 of lactation)

Sex : Female

Dose mg/kg	Animal number	RBC $\times 10^4/\mu\text{L}$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let $\times 10^4/\mu\text{L}$	PT s	APTT s	Fibri- nogen mg/dL
0	1103	735	14.0	38.5	52.4	19.0	36.2	6.7	139.3	11.3	13.2	320
	1104	763	14.8	39.3	51.5	19.4	37.6	4.5	158.0	11.8	15.2	319
	1105	768	14.3	38.1	49.6	18.6	37.4	3.7	127.0	12.7	20.4	236
	1107	769	14.5	38.8	50.5	18.9	37.4	3.9	126.9	12.7	20.7	302
	1109	740	14.6	39.1	52.8	19.7	37.3	6.5	168.6	13.5	18.4	306
	Mean	755	14.4	38.8	51.4	19.1	37.2	5.1	144.0	12.4	17.6	297
	S.D.	16	0.3	0.5	1.3	0.4	0.6	1.4	18.7	0.9	3.3	35
100	2106	792	15.1	40.2	50.7	19.1	37.6	5.8	147.3	12.4	19.0	273
	2107	746	15.0	41.6	55.7	20.1	36.0	6.2	130.4	10.0	11.4	263
	2108	705	13.7	36.3	51.5	19.5	37.8	5.8	134.1	12.1	19.2	323
	2109	706	14.4	38.9	55.1	20.4	37.0	6.3	139.4	12.9	17.9	309
	2110	757	14.8	39.3	51.9	19.5	37.6	5.3	121.9	13.7	19.1	261
	Mean	741	14.6	39.3	53.0	19.7	37.2	5.9	134.6	12.2	17.3	286
	S.D.	37	0.6	2.0	2.3	0.5	0.7	0.4	9.5	1.4	3.4	28
300	3101	759	14.7	40.1	52.8	19.3	36.6	6.1	146.8	13.0	15.8	486
	3104	690	13.4	37.0	53.6	19.5	36.3	6.1	152.9	10.7	13.3	290
	3107	722	14.1	38.5	53.4	19.5	36.5	7.6	142.5	13.6	19.5	366
	3109	778	15.5	42.1	54.1	19.9	36.8	6.2	132.6	13.6	17.9	272
	3111	890	16.3	43.7	49.1	18.3	37.4	2.4	107.9	12.5	16.8	320
	Mean	768	14.8	40.3	52.6	19.3	36.7	5.7	136.5	12.7	16.7	347
	S.D.	76	1.1	2.7	2.0	0.6	0.4	1.9	17.6	1.2	2.3	86
1000	4101	749	14.6	39.5	52.6	19.5	37.0	5.2	141.8	11.6	15.6	269
	4103	817	14.8	40.3	49.3	18.2	36.9	3.2	129.0	13.5	20.6	298
	4106	770	15.3	42.1	54.7	19.9	36.4	6.9	130.1	12.4	18.8	297
	4110	705	13.4	36.5	51.8	19.1	36.8	5.1	140.8	12.3	17.9	257
	4111	817	15.5	41.3	50.5	18.9	37.5	4.5	160.3	12.8	19.1	316
	Mean	772	14.7	39.9	51.8	19.1	36.9	5.0	140.4	12.5	18.4	287
	S.D.	48	0.8	2.2	2.1	0.6	0.4	1.3	12.6	0.7	1.8	24

## Appendix 394

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual hematology (Day 4 of lactation)

Sex : Female

Dose mg/kg	Animal number	WBC $\times 10^2/\mu\text{L}$	Differential leukocyte counts (%)					Differential leukocyte counts ( $\times 10^2/\mu\text{L}$ )						
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	
0	1103	112.9	73.6	22.3	0.5	0.3	2.6	0.6	83.2	25.2	0.6	0.4	2.9	0.6
	1104	120.6	62.0	32.9	0.7	0.4	3.2	0.7	74.8	39.7	0.8	0.5	3.9	0.9
	1105	83.8	64.2	31.4	1.4	0.3	2.3	0.4	53.8	26.3	1.2	0.2	2.0	0.3
	1107	108.0	54.4	41.7	1.1	0.2	2.4	0.2	58.8	45.1	1.2	0.2	2.5	0.3
	1109	181.0	63.4	31.6	0.7	0.5	2.9	1.0	114.7	57.2	1.2	0.8	5.3	1.8
	Mean	121.3	63.5	32.0	0.9	0.3	2.7	0.6	77.1	38.7	1.0	0.4	3.3	0.8
100	S.D.	36.1	6.8	6.9	0.4	0.1	0.4	0.3	24.2	13.4	0.3	0.2	1.3	0.6
	2106	101.0	61.0	33.8	0.9	0.3	3.6	0.4	61.6	34.1	0.9	0.3	3.6	0.5
	2107	137.7	66.3	28.6	1.0	0.3	3.3	0.6	91.3	39.3	1.4	0.4	4.6	0.8
	2108	127.9	69.8	27.4	0.6	0.3	1.3	0.7	89.3	35.0	0.8	0.3	1.6	0.9
	2109	161.6	47.4	50.2	0.6	0.2	1.4	0.3	76.5	81.1	0.9	0.4	2.2	0.4
	2110	108.7	55.6	39.7	0.3	0.2	3.2	1.0	60.4	43.2	0.4	0.3	3.4	1.0
300	Mean	127.4	60.0	35.9	0.7	0.3	2.6	0.6	75.8	46.5	0.9	0.3	3.1	0.7
	S.D.	24.1	8.9	9.4	0.3	0.1	1.1	0.3	14.7	19.7	0.4	0.1	1.2	0.3
	3101	86.0	62.6	32.3	1.9	0.3	2.6	0.4	53.8	27.7	1.6	0.2	2.2	0.4
	3104	101.7	67.2	27.6	0.6	0.2	3.7	0.6	68.4	28.1	0.6	0.2	3.8	0.6
	3107	116.4	66.1	28.7	0.5	0.3	3.5	0.9	77.0	33.4	0.6	0.4	4.0	1.0
	3109	106.0	75.8	19.6	0.9	0.4	2.7	0.6	80.3	20.7	1.0	0.4	2.9	0.7
1000	3111	124.8	52.6	42.2	0.8	0.4	3.6	0.4	65.7	52.7	1.0	0.5	4.5	0.5
	Mean	107.0	64.9	30.1	0.9	0.3	3.2	0.6	69.0	32.5	1.0	0.3	3.5	0.6
	S.D.	14.8	8.4	8.2	0.6	0.1	0.5	0.2	10.4	12.2	0.4	0.1	0.9	0.2
	4101	146.2	59.2	36.5	0.9	0.3	2.7	0.3	86.6	53.4	1.4	0.5	3.9	0.5
	4103	152.8	75.5	20.3	0.3	0.3	2.5	1.1	115.4	31.0	0.4	0.5	3.8	1.7
	4106	163.8	61.6	34.9	0.5	0.4	2.2	0.4	100.9	57.1	0.9	0.6	3.6	0.7
4110	84.6	42.1	54.1	1.3	0.2	2.1	0.2	35.6	45.7	1.1	0.2	1.8	0.2	
	4111	203.5	65.2	31.0	0.3	0.4	2.3	0.8	132.6	63.1	0.7	0.7	4.8	1.7
	Mean	150.2	60.7	35.4	0.7	0.3	2.4	0.6	94.2	50.1	0.9	0.5	3.6	1.0
	S.D.	42.9	12.1	12.2	0.4	0.1	0.2	0.4	36.9	12.4	0.4	0.2	1.1	0.7

LUC : Large unstained cells

## Appendix 395

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual hematology (Day 14 of recovery)

Sex : Male

Dose mg/kg	Animal number	RBC $\times 10^4/\mu\text{L}$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let $\times 10^4/\mu\text{L}$	PT s	APTT s	Fibri- nogen mg/dL
0	1013	890	16.2	43.9	49.3	18.2	36.9	2.3	124.1	14.3	25.0	276
	1014	917	16.7	44.2	48.1	18.2	37.8	2.2	111.2	13.5	17.8	339
	1015	938	16.1	43.2	46.1	17.2	37.4	1.9	115.3	14.2	19.5	314
	1016	899	16.2	42.5	47.3	18.1	38.2	1.7	118.1	14.4	21.6	231
	1017	936	16.8	44.1	47.1	18.0	38.1	1.7	112.1	17.2	27.3	335
	Mean	916	16.4	43.6	47.6	17.9	37.7	2.0	116.2	14.7	22.2	298
1000	S.D.	22	0.3	0.7	1.2	0.4	0.5	0.3	5.2	1.4	3.9	45
	4013	924	16.5	43.6	47.2	17.8	37.7	1.2	114.8	14.5	25.3	238
	4014	912	17.1	46.1	50.5	18.7	37.0	2.2	104.8	14.0	21.4	265
	4015	943	16.8	44.9	47.6	17.8	37.5	1.3	105.1	15.5	22.4	292
	4016	929	16.3	42.9	46.2	17.6	38.1	2.1	134.2	15.3	27.7	333
	4017	920	16.6	43.7	47.5	18.0	38.0	2.4	131.5	14.4	17.3	336
	Mean	926	16.7	44.2	47.8	18.0	37.7	1.8	118.1	14.7	22.8	293
	S.D.	12	0.3	1.3	1.6	0.4	0.4	0.6	14.1	0.6	4.0	43

## Appendix 396

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual hematology (Day 14 of recovery)

Sex : Male

Dose mg/kg	Animal number	WBC $\times 10^3/\mu\text{L}$	Differential leukocyte counts (%)					Differential leukocyte counts ( $\times 10^2/\mu\text{L}$ )						
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	1013	138.1	83.5	13.2	0.7	0.5	1.7	0.5	115.3	18.2	0.9	0.7	2.3	0.6
	1014	99.1	72.4	23.9	0.8	0.3	2.1	0.5	71.8	23.7	0.8	0.3	2.1	0.5
	1015	104.6	78.3	16.4	2.1	0.5	2.3	0.4	81.9	17.2	2.2	0.5	2.4	0.5
	1016	61.4	79.8	17.3	1.4	0.2	1.0	0.3	48.9	10.6	0.9	0.1	0.6	0.2
	1017	80.5	84.4	11.2	2.0	0.2	1.6	0.5	68.0	9.0	1.6	0.2	1.3	0.4
	Mean	96.7	79.7	16.4	1.4	0.3	1.7	0.4	77.2	15.7	1.3	0.4	1.7	0.4
1000	S.D.	28.7	4.8	4.9	0.7	0.2	0.5	0.1	24.4	6.0	0.6	0.2	0.8	0.2
	4013	138.2	89.4	7.1	0.7	0.5	1.7	0.7	123.6	9.8	1.0	0.7	2.3	1.0
	4014	148.9	72.7	23.5	1.2	0.4	1.9	0.4	108.3	34.9	1.7	0.6	2.8	0.6
	4015	81.7	83.2	12.8	1.3	0.5	1.9	0.2	68.0	10.4	1.1	0.4	1.6	0.2
	4016	73.8	81.7	15.2	1.5	0.2	1.1	0.2	60.3	11.3	1.1	0.2	0.8	0.2
	4017	122.8	79.3	17.0	0.6	0.4	2.1	0.5	97.4	20.9	0.8	0.5	2.6	0.6
	Mean	113.1	81.3	15.1	1.1	0.4	1.7	0.4	91.5	17.5	1.1	0.5	2.0	0.5
	S.D.	33.7	6.1	6.0	0.4	0.1	0.4	0.2	26.8	10.8	0.3	0.2	0.8	0.3

LUC : Large unstained cells

## Appendix 397

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual hematology (Day 14 of recovery)

Sex : Female

Dose mg/kg	Animal number	RBC $\times 10^4/\mu\text{L}$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticu- locyte %	Plate- let $\times 10^4/\mu\text{L}$	PT s	APTT s	Fibri- nogen mg/dL
0	1113	870	16.0	41.8	48.0	18.4	38.4	1.8	124.3	12.0	19.5	224
	1114	755	15.4	39.6	52.4	20.4	38.9	2.2	103.5	12.0	17.6	229
	1115	814	15.8	40.3	49.5	19.4	39.1	1.6	134.8	13.5	20.3	212
	1116	821	15.8	40.8	49.7	19.3	38.8	1.3	104.7	12.1	17.7	224
	1117	822	16.0	42.2	51.3	19.4	37.9	1.0	116.5	12.5	16.9	255
	Mean	816	15.8	40.9	50.2	19.4	38.6	1.6	116.8	12.4	18.4	229
1000	S.D.	41	0.2	1.1	1.7	0.7	0.5	0.5	13.3	0.6	1.4	16
	4113	801	15.0	39.0	48.7	18.7	38.5	1.1	114.6	12.9	18.9	179
	4114	825	15.9	41.3	50.1	19.3	38.6	1.1	103.0	13.0	15.4	232
	4115	849	16.3	42.7	50.2	19.2	38.1	1.4	112.1	12.9	24.9	207
	4116	873	16.7	44.0	50.3	19.1	37.9	1.9	130.0	12.7	16.6	233
	4117	852	16.2	42.9	50.4	19.0	37.8	2.0	118.8	12.8	20.5	219
	Mean	840	16.0	42.0	49.9	19.1	38.2	1.5	115.7	12.9	19.3	214
	S.D.	28	0.6	1.9	0.7	0.2	0.4	0.4	9.9	0.1	3.7	22

## Appendix 398

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual hematology (Day 14 of recovery)

Sex : Female

Dose mg/kg	Animal number	WBC $\times 10^3/\mu\text{L}$	Differential leukocyte counts (%)					Differential leukocyte counts ( $\times 10^2/\mu\text{L}$ )						
			Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	1113	66.3	73.9	23.4	0.8	0.2	1.3	0.4	49.0	15.5	0.5	0.1	0.9	0.3
	1114	69.8	73.8	21.3	1.3	0.3	2.5	0.7	51.5	14.9	0.9	0.2	1.8	0.5
	1115	64.4	70.8	25.6	1.6	0.3	1.4	0.3	45.6	16.5	1.0	0.2	0.9	0.2
	1116	69.6	72.7	24.0	0.9	0.2	1.8	0.4	50.5	16.7	0.6	0.1	1.2	0.3
	1117	47.6	81.3	15.7	1.3	0.4	0.9	0.4	38.7	7.5	0.6	0.2	0.4	0.2
	Mean	63.5	74.5	22.0	1.2	0.3	1.6	0.4	47.1	14.2	0.7	0.2	1.0	0.3
	S.D.	9.2	4.0	3.8	0.3	0.1	0.6	0.2	5.2	3.8	0.2	0.1	0.5	0.1
1000	4113	55.1	80.9	15.2	2.0	0.2	1.4	0.4	44.6	8.4	1.1	0.1	0.7	0.2
	4114	42.6	69.3	27.2	1.5	0.1	1.6	0.3	29.5	11.6	0.6	0.0	0.7	0.1
	4115	42.4	77.1	18.1	2.5	0.2	1.4	0.6	32.7	7.7	1.1	0.1	0.6	0.3
	4116	41.6	74.7	20.0	1.6	0.2	2.9	0.6	31.0	8.3	0.7	0.1	1.2	0.3
	4117	48.6	72.9	22.4	2.5	0.3	1.4	0.5	35.5	10.9	1.2	0.2	0.7	0.2
	Mean	46.1	75.0	20.6	2.0	0.2	1.7	0.5	34.7	9.4	0.9	0.1	0.8	0.2
	S.D.	5.8	4.4	4.5	0.5	0.1	0.7	0.1	6.0	1.7	0.3	0.1	0.2	0.1

LUC : Large unstained cells

## Appendix 399

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual blood chemistry (Week 6 of administration)

Sex : Male

Dose mg/kg	Animal number	AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	1001	78	39	58	1	455	48	37	81	0.1	136
	1002	68	26	66	1	427	50	59	83	0.0	137
	1003	67	23	52	1	328	63	32	101	0.1	135
	1004	92	34	77	1	344	47	28	75	0.0	133
	1005	68	24	44	1	363	41	13	66	0.1	131
	Mean	75	29	59	1	383	50	34	81	0.1	134
100	S.D.	11	7	13	0	55	8	17	13	0.1	2
	2001	69	33	68	1	594	56	38	93	0.1	160
	2002	86	35	49	0	444	45	31	77	0.1	129
	2003	70	36	72	0	498	39	33	69	0.1	148
	2004	66	26	49	1	313	33	38	64	0.1	147
	2005	71	39	51	1	457	38	24	65	0.1	128
300	Mean	72	34	58	1	461	42	33	74	0.1	142
	S.D.	8	5	11	1	102	9	6	12	0.0	14
	3001	71	40	68	0	330	40	35	71	0.1	164
	3002	65	30	40	1	304	46	15	72	0.1	139
	3003	79	33	41	0	371	37	25	70	0.1	147
	3004	81	41	66	1	461	42	17	64	0.1	125
1000	3005	80	40	62	1	370	57	37	89	0.1	136
	Mean	75	37	55	1	367	44	26	73	0.1	142
	S.D.	7	5	14	1	60	8	10	9	0.0	15
	4001	63	30	57	1	339	38	25	61	0.1	161
	4002	76	32	56	1	448	59	32	94	0.1	162
	4003	61	28	43	1	378	38	20	68	0.1	133
4000	4004	68	32	51	1	365	48	57	89	0.1	159
	4005	60	37	47	1	372	50	58	89	0.1	165
	Mean	66	32	51	1	380	47	38	80	0.1	156
	S.D.	7	3	6	0	41	9	18	15	0.0	13

## Appendix 400

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual blood chemistry (Week 6 of administration)

Sex : Male

Dose mg/kg	Animal number	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	1001	15	0.24	145	4.8	106	9.6	6.7	6.4	2.8	0.78
	1002	18	0.31	144	5.0	108	9.0	6.0	6.0	2.6	0.76
	1003	13	0.21	144	4.9	109	9.5	6.3	6.1	2.8	0.85
	1004	16	0.25	145	4.8	107	9.9	6.6	6.5	2.9	0.81
	1005	17	0.27	144	4.8	109	9.3	6.7	5.9	2.7	0.84
	Mean	16	0.26	144	4.9	108	9.5	6.5	6.2	2.8	0.81
100	S.D.	2	0.04	1	0.1	1	0.3	0.3	0.3	0.1	0.04
	2001	16	0.27	143	4.8	108	9.4	6.7	5.8	2.6	0.81
	2002	13	0.25	143	4.9	106	9.3	6.6	5.7	2.7	0.90
	2003	17	0.32	142	5.0	106	9.9	7.4	6.4	2.9	0.83
	2004	12	0.22	145	4.5	108	9.5	5.9	6.0	2.8	0.88
	2005	14	0.19	145	4.4	108	9.4	6.3	6.4	2.9	0.83
300	Mean	14	0.25	144	4.7	107	9.5	6.6	6.1	2.8	0.85
	S.D.	2	0.05	1	0.3	1	0.2	0.6	0.3	0.1	0.04
	3001	17	0.19	143	4.9	106	9.4	6.3	6.2	2.7	0.77
	3002	17	0.24	142	4.9	109	9.3	6.7	5.7	2.6	0.84
	3003	11	0.26	145	4.5	111	9.6	6.7	5.9	2.8	0.90
	3004	15	0.21	143	5.1	110	9.3	6.4	6.1	2.8	0.85
1000	3005	14	0.24	144	4.6	108	9.5	5.6	6.2	2.9	0.88
	Mean	15	0.23	143	4.8	109	9.4	6.3	6.0	2.8	0.85
	S.D.	2	0.03	1	0.2	2	0.1	0.5	0.2	0.1	0.05
	4001	15	0.31	144	4.7	106	9.4	6.5	6.2	2.7	0.77
	4002	14	0.24	143	4.4	108	9.4	6.4	5.9	2.7	0.84
	4003	13	0.21	144	4.8	109	9.8	6.0	6.1	2.9	0.91
1000	4004	14	0.27	146	4.7	106	9.8	6.8	5.8	2.7	0.87
	4005	11	0.17	143	4.9	108	9.7	6.0	6.1	2.8	0.85
	Mean	13	0.24	144	4.7	107	9.6	6.3	6.0	2.8	0.85
	S.D.	2	0.05	1	0.2	1	0.2	0.3	0.2	0.1	0.05

## Appendix 401

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual blood chemistry (Day 4 of lactation)

Sex : Female

Dose mg/kg	Animal number	AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	1103	88	76	62	1	295	48	26	88	0.1	154
	1104	60	36	58	1	169	66	30	113	0.1	140
	1105	69	39	45	1	186	41	22	78	0.0	138
	1107	96	53	58	1	282	34	36	83	0.0	136
	1109	92	45	59	1	240	53	13	95	0.1	149
	Mean	81	50	56	1	234	48	25	91	0.1	143
100	S.D.	16	16	7	0	56	12	9	14	0.1	8
	2106	68	48	58	1	194	66	32	114	0.1	150
	2107	76	53	49	1	157	47	33	88	0.1	139
	2108	79	51	44	1	207	58	24	103	0.1	129
	2109	69	40	66	1	207	68	43	127	0.1	139
	2110	73	37	43	0	349	40	40	89	0.1	133
300	Mean	73	46	52	1	223	56	34	104	0.1	138
	S.D.	5	7	10	0	73	12	7	17	0.0	8
	3101	89	59	58	1	208	38	12	71	0.1	120
	3104	66	51	52	1	240	75	74	143	0.1	162
	3107	104	59	65	0	388	46	21	86	0.0	135
	3109	75	46	73	1	172	83	50	137	0.1	135
1000	3111	257	195	58	2	275	46	22	86	0.1	138
	Mean	118	82	61	1	257	58	36	105	0.1	138
	S.D.	79	63	8	1	83	20	26	33	0.0	15
	4101	95	74	66	1	181	34	43	72	0.1	147
	4103	66	42	61	1	166	43	59	104	0.1	136
	4106	79	44	66	1	203	66	38	123	0.1	149
	4110	68	40	41	1	150	58	40	116	0.1	152
	4111	125	86	56	2	436	73	37	135	0.1	140
	Mean	87	57	58	1	227	55	43	110	0.1	145
	S.D.	24	21	10	0	118	16	9	24	0.0	7

## Appendix 402

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual blood chemistry (Day 4 of lactation)

Sex : Female

Dose mg/kg	Animal number	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	1103	17	0.26	141	4.5	108	9.9	6.7	6.6	3.1	0.89
	1104	14	0.31	143	4.1	109	10.5	7.4	6.9	3.2	0.86
	1105	15	0.31	141	3.8	108	9.4	5.6	5.7	2.7	0.90
	1107	15	0.37	141	4.8	109	9.7	6.6	6.3	2.9	0.85
	1109	16	0.34	143	4.4	108	10.3	9.8	6.7	3.1	0.86
	Mean	15	0.32	142	4.3	108	10.0	7.2	6.4	3.0	0.87
100	S.D.	1	0.04	1	0.4	1	0.4	1.6	0.5	0.2	0.02
	2106	12	0.23	141	4.2	109	10.4	6.8	6.7	3.0	0.81
	2107	16	0.28	143	4.4	112	10.2	7.2	6.0	2.8	0.88
	2108	15	0.30	140	4.4	109	9.6	5.3	6.2	2.9	0.88
	2109	15	0.27	142	3.8	107	10.2	7.1	6.6	3.0	0.83
	2110	17	0.29	140	4.5	109	9.4	7.3	5.5	2.7	0.96
300	Mean	15	0.27	141	4.3	109	10.0	6.7	6.2	2.9	0.87
	S.D.	2	0.03	1	0.3	2	0.4	0.8	0.5	0.1	0.06
	3101	18	0.27	142	4.8	109	10.1	7.9	6.4	2.8	0.78
	3104	16	0.28	140	4.6	104	10.9	8.2	6.6	3.1	0.89
	3107	20	0.28	142	4.8	107	9.8	8.1	6.5	2.9	0.81
	3109	14	0.25	144	4.6	111	10.2	6.7	6.2	3.0	0.94
1000	3111	19	0.33	144	5.0	108	10.2	8.7	6.5	2.9	0.81
	Mean	17	0.28	142	4.8	108	10.2	7.9	6.4	2.9	0.85
	S.D.	2	0.03	2	0.2	3	0.4	0.7	0.2	0.1	0.07
	4101	20	0.34	141	4.5	107	10.5	7.8	6.2	2.9	0.88
	4103	16	0.25	140	4.9	109	10.2	7.5	6.7	3.1	0.86
	4106	16	0.32	142	4.0	106	10.0	7.0	6.7	3.1	0.86
	4110	13	0.30	143	3.8	110	9.6	4.8	6.2	2.9	0.88
	4111	17	0.31	141	4.4	108	10.2	8.0	6.5	3.1	0.91
	Mean	16	0.30	141	4.3	108	10.1	7.0	6.5	3.0	0.88
	S.D.	3	0.03	1	0.4	2	0.3	1.3	0.3	0.1	0.02

## Appendix 403

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual blood chemistry (Day 14 of recovery)

Sex : Male

Dose mg/kg	Animal number	AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	1013	55	25	62	1	462	46	27	81	0.1	138
	1014	62	27	49	1	354	61	36	91	0.1	136
	1015	57	29	48	1	397	36	41	68	0.1	168
	1016	68	30	53	1	260	58	10	83	0.1	141
	1017	62	34	60	1	356	60	65	99	0.1	122
	Mean	61	29	54	1	366	52	36	84	0.1	141
1000	S.D.	5	3	6	0	74	11	20	12	0.0	17
	4013	67	30	53	1	404	44	30	76	0.1	143
	4014	56	29	45	1	290	53	26	84	0.1	137
	4015	79	40	55	1	319	47	34	81	0.1	130
	4016	65	33	64	1	313	56	40	85	0.1	149
	4017	61	31	52	1	356	65	82	105	0.1	141
	Mean	66	33	54	1	336	53	42	86	0.1	140
	S.D.	9	4	7	0	45	8	23	11	0.0	7

## Appendix 404

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual blood chemistry (Day 14 of recovery)

Sex : Male

Dose mg/kg	Animal number	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	1013	18	0.31	145	4.2	104	10.0	6.6	6.9	2.9	0.73
	1014	13	0.24	144	4.9	109	9.7	6.5	6.3	2.8	0.80
	1015	14	0.20	144	4.1	107	9.8	6.0	6.4	2.8	0.78
	1016	17	0.26	144	4.6	107	9.3	6.5	6.2	2.8	0.82
	1017	15	0.24	146	4.2	108	9.6	5.3	6.4	2.9	0.83
	Mean	15	0.25	145	4.4	107	9.7	6.2	6.4	2.8	0.79
1000	S.D.	2	0.04	1	0.3	2	0.3	0.5	0.3	0.1	0.04
	4013	17	0.29	144	4.4	107	9.6	5.8	6.3	2.9	0.85
	4014	15	0.25	145	4.0	108	9.8	5.5	6.1	2.7	0.79
	4015	15	0.23	146	4.3	108	10.0	6.1	6.3	2.8	0.80
	4016	13	0.20	145	4.7	108	9.9	5.9	6.3	2.8	0.80
	4017	15	0.24	147	4.2	108	10.2	6.0	6.2	2.8	0.82
	Mean	15	0.24	145	4.3	108	9.9	5.9	6.2	2.8	0.81
	S.D.	1	0.03	1	0.3	0	0.2	0.2	0.1	0.1	0.02

## Appendix 405

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual blood chemistry (Day 14 of recovery)

Sex : Female

Dose mg/kg	Animal number	AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	$\gamma$ -GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili- rubin mg/dL	Glucose mg/dL
0	1113	55	18	54	2	216	64	13	119	0.1	146
	1114	64	34	61	1	157	63	23	116	0.1	146
	1115	74	32	58	2	207	56	12	100	0.1	152
	1116	129	54	93	3	170	89	16	149	0.1	139
	1117	62	27	44	1	197	60	11	116	0.1	146
	Mean	77	33	62	2	189	66	15	120	0.1	146
1000	S.D.	30	13	18	1	25	13	5	18	0.0	5
	4113	67	32	54	1	110	55	15	112	0.1	143
	4114	60	23	49	2	236	48	8	88	0.1	111
	4115	67	41	50	1	109	66	24	131	0.1	139
	4116	67	121	52	2	150	53	14	102	0.1	135
	4117	66	31	70	2	287	48	11	89	0.1	152
	Mean	65	50	55	2	178	54	14	104	0.1	136
	S.D.	3	40	9	1	80	7	6	18	0.0	15

## Appendix 406

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual blood chemistry (Day 14 of recovery)

Sex : Female

Dose mg/kg	Animal number	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	1113	15	0.33	144	3.7	111	9.7	4.6	6.7	3.1	0.86
	1114	16	0.26	145	3.7	111	10.2	5.4	6.8	3.3	0.94
	1115	20	0.33	145	3.9	113	9.7	4.9	6.5	3.1	0.91
	1116	16	0.29	145	4.2	110	10.2	5.2	6.9	3.4	0.97
	1117	19	0.30	144	4.6	112	10.0	4.6	6.9	3.2	0.86
	Mean	17	0.30	145	4.0	111	10.0	4.9	6.8	3.2	0.91
1000	S.D.	2	0.03	1	0.4	1	0.3	0.4	0.2	0.1	0.05
	4113	16	0.24	143	4.2	110	10.0	4.8	6.3	3.2	1.03
	4114	16	0.28	142	4.2	111	9.8	5.0	6.2	2.9	0.88
	4115	17	0.26	142	4.3	111	10.1	4.5	7.1	3.4	0.92
	4116	20	0.29	146	3.8	113	10.0	5.0	6.6	3.2	0.94
	4117	17	0.30	146	4.9	115	9.7	5.1	6.6	3.1	0.89
	Mean	17	0.27	144	4.3	112	9.9	4.9	6.6	3.2	0.93
	S.D.	2	0.02	2	0.4	2	0.2	0.2	0.4	0.2	0.06

## Appendix 407

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 0

Animal number	Body weight g	Brain		Thyroid (R)		Thyroid (L)		Thyroid (R+L)		Thymus		Heart		Liver	
		g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)											
Absolute	1001	504	2.11	11.1	13.1	24.2	284	1.55	12.56						
	1002	473	2.20	10.9	10.0	20.9	180	1.43	12.20						
	1003	510	2.08	13.6	12.3	25.9	317	1.54	13.04						
	1004	492	2.00	9.9	9.4	19.3	328	1.45	12.37						
	1005	458	2.18	13.2	12.2	25.4	295	1.29	10.31						
	Mean	487	2.11	11.7	11.4	23.1	281	1.45	12.10						
Relative	S.D.	22	0.08	1.6	1.6	2.9	59	0.10	1.05						
	1001		0.42	2.2	2.6	4.8	56	0.31	2.49						
	1002		0.47	2.3	2.1	4.4	38	0.30	2.58						
	1003		0.41	2.7	2.4	5.1	62	0.30	2.56						
	1004		0.41	2.0	1.9	3.9	67	0.29	2.51						
	1005		0.48	2.9	2.7	5.5	64	0.28	2.25						
	Mean		0.44	2.4	2.3	4.7	57	0.30	2.48						
	S.D.		0.03	0.4	0.3	0.6	12	0.01	0.13						

## Appendix 408

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 0

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)	
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	
Absolute	1001	0.71	1.48	1.72	3.20	37	42	79
	1002	0.88	1.78	5.33	7.11	25	28	53
	1003	0.74	1.89	2.04	3.93	34	40	74
	1004	0.81	1.57	1.63	3.20	34	36	70
	1005	0.68	1.45	1.52	2.97	26	28	54
	Mean	0.76	1.63	2.45	4.08	31	35	66
Relative	S.D.	0.08	0.19	1.62	1.73	5	7	12
	1001	0.14	0.29	0.34	0.63	7	8	16
	1002	0.19	0.38	1.13	1.50	5	6	11
	1003	0.15	0.37	0.40	0.77	7	8	15
	1004	0.16	0.32	0.33	0.65	7	7	14
	1005	0.15	0.32	0.33	0.65	6	6	12
	Mean	0.16	0.34	0.51	0.84	6	7	14
	S.D.	0.02	0.04	0.35	0.37	1	1	2

## Appendix 409

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 0

	Animal number	Body weight g	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)
Absolute	1001	504	1.70	1.70	3.40	652	614	1266
	1002	473	1.98	1.99	3.97	611	592	1203
	1003	510	1.66	1.63	3.29	625	639	1264
	1004	492	1.67	1.65	3.32	627	620	1247
	1005	458	1.80	1.76	3.56	707	663	1370
	1006	509	1.67	1.67	3.34	607	606	1213
	1007	528	1.86	1.93	3.79	679	660	1339
	1008	550	1.80	1.81	3.61	723	710	1433
	1009	518	1.88	1.90	3.78	690	652	1342
	1010	581	1.68	1.68	3.36	686	661	1347
	1011	512	1.61	1.59	3.20	576	573	1149
	1012	481	1.82	1.83	3.65	828	722	1550
		Mean	510	1.76	3.52	668	643	1310
		S.D.	33	0.11	0.24	68	45	111
Relative	1001		0.34	0.34	0.67	120	122	251
	1002		0.42	0.42	0.84	129	125	254
	1003		0.33	0.32	0.65	123	125	248
	1004		0.34	0.34	0.67	127	126	253
	1005		0.39	0.38	0.78	154	145	299
	1006		0.33	0.33	0.66	119	119	238
	1007		0.35	0.37	0.72	129	125	254
	1008		0.33	0.33	0.66	131	129	261
	1009		0.36	0.37	0.73	133	126	259
	1010		0.29	0.29	0.58	118	114	232
	1011		0.31	0.31	0.63	113	112	224
	1012		0.38	0.38	0.76	172	150	322
		Mean	0.35	0.35	0.70	131	127	258
		S.D.	0.04	0.04	0.07	16	11	27

## Appendix 410

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 100

Animal number	Body weight g	Brain	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus	Heart	Liver
		g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	2001	491	2.18	12.7	11.0	23.7	284	1.47
	2002	495	2.22	12.3	12.6	24.9	343	1.59
	2003	488	2.16	15.6	11.8	27.4	355	1.46
	2004	519	2.11	11.8	7.2	19.0	292	1.48
	2005	480	2.27	10.2	9.5	19.7	269	1.38
	Mean	495	2.19	12.5	10.4	22.9	309	1.48
Relative	S.D.	15	0.06	2.0	2.1	3.5	38	0.08
	2001		0.44	2.6	2.2	4.8	58	0.30
	2002		0.45	2.5	2.5	5.0	69	0.32
	2003		0.44	3.2	2.4	5.6	73	0.30
	2004		0.41	2.3	1.4	3.7	56	0.29
	2005		0.47	2.1	2.0	4.1	56	0.29
	Mean		0.44	2.5	2.1	4.6	62	0.30
	S.D.		0.02	0.4	0.4	0.8	8	0.01

## Appendix 411

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 100

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	2001	0.82	1.60	1.60	3.20	27	29
	2002	0.93	1.67	1.85	3.52	29	30
	2003	0.72	1.49	1.55	3.04	29	31
	2004	0.64	1.69	1.83	3.52	32	29
	2005	0.80	1.80	1.95	3.75	30	35
	Mean	0.78	1.65	1.76	3.41	29	31
Relative	S.D.	0.11	0.11	0.17	0.28	2	2
	2001	0.17	0.33	0.33	0.65	5	6
	2002	0.19	0.34	0.37	0.71	6	6
	2003	0.15	0.31	0.32	0.62	6	6
	2004	0.12	0.33	0.35	0.68	6	6
	2005	0.17	0.38	0.41	0.78	6	7
	Mean	0.16	0.34	0.36	0.69	6	6
	S.D.	0.03	0.03	0.04	0.06	0	1

## Appendix 412

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 100

Animal number	Body weight g	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)
Absolute	2001	491	1.60	1.63	3.23	651	630
	2002	495	1.58	1.56	3.14	632	569
	2003	488	1.71	1.70	3.41	723	666
	2004	519	1.89	1.79	3.68	699	682
	2005	480	1.83	1.82	3.65	740	602
	2006	590	2.10	2.02	4.12	729	685
	2007	499	1.55	1.58	3.13	673	668
	2008	536	1.51	1.48	2.99	626	587
	2009	518	1.26	1.33	2.59	549	587
	2010	471	1.57	1.59	3.16	642	646
	2011	505	1.64	1.63	3.27	618	632
	2012	534	1.82	1.80	3.62	700	698
Mean		511	1.67	1.66	3.33	665	638
S.D.		32	0.22	0.18	0.40	56	44
Relative	2001		0.33	0.33	0.66	133	128
	2002		0.32	0.32	0.63	128	115
	2003		0.35	0.35	0.70	148	136
	2004		0.36	0.34	0.71	135	131
	2005		0.38	0.38	0.76	154	125
	2006		0.36	0.34	0.70	124	116
	2007		0.31	0.32	0.63	135	134
	2008		0.28	0.28	0.56	117	110
	2009		0.24	0.26	0.50	106	113
	2010		0.33	0.34	0.67	136	137
	2011		0.32	0.32	0.65	122	125
	2012		0.34	0.34	0.68	131	131
Mean			0.33	0.33	0.65	131	125
S.D.			0.04	0.03	0.07	13	9
							256
							21

## Appendix 413

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual organ weight of male rats (Main group)

Dose (mg/kg): 300

Animal number	Body weight g	Brain		Thyroid (R)		Thyroid (L)		Thyroid (R+L)		Thymus		Heart		Liver	
		g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)											
Absolute	3001	479	2.21	11.7	9.6	21.3	248	1.52	13.13						
	3002	455	2.02	11.3	9.7	21.0	304	1.27	11.20						
	3003	457	2.09	10.2	9.1	19.3	198	1.30	11.31						
	3004	499	2.20	10.6	11.2	21.8	297	1.43	12.15						
	3005	526	2.01	18.2	14.1	32.3	392	1.38	14.20						
	Mean	483	2.11	12.4	10.7	23.1	288	1.38	12.40						
	S.D.	30	0.10	3.3	2.0	5.2	72	0.10	1.27						
Relative	3001		0.46	2.4	2.0	4.4	52	0.32	2.74						
	3002		0.44	2.5	2.1	4.6	67	0.28	2.46						
	3003		0.46	2.2	2.0	4.2	43	0.28	2.47						
	3004		0.44	2.1	2.2	4.4	60	0.29	2.43						
	3005		0.38	3.5	2.7	6.1	75	0.26	2.70						
	Mean		0.44	2.5	2.2	4.7	59	0.29	2.56						
	S.D.		0.03	0.6	0.3	0.8	13	0.02	0.15						

## Appendix 414

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 300

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	3001	0.75	1.66	1.82	3.48	30	32
	3002	0.68	1.55	1.50	3.05	28	29
	3003	0.67	1.46	1.56	3.02	31	31
	3004	1.08	1.76	1.85	3.61	39	35
	3005	1.06	1.61	1.64	3.25	30	35
	Mean	0.85	1.61	1.67	3.28	32	32
Relative	S.D.	0.21	0.11	0.16	0.26	4	6
	3001	0.16	0.35	0.38	0.73	6	7
	3002	0.15	0.34	0.33	0.67	6	6
	3003	0.15	0.32	0.34	0.66	7	7
	3004	0.22	0.35	0.37	0.72	8	7
	3005	0.20	0.31	0.31	0.62	6	7
	Mean	0.18	0.33	0.35	0.68	7	7
	S.D.	0.03	0.02	0.03	0.05	1	1

## Appendix 415

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 300

Animal number	Body weight g	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)
Absolute	3001	479	1.65	1.64	3.29	626	651
	3002	455	1.83	1.82	3.65	710	701
	3003	457	1.28	1.30	2.58	646	633
	3004	499	1.96	1.95	3.91	714	682
	3005	526	1.62	1.66	3.28	699	718
	3006	474	1.57	1.56	3.13	643	641
	3007	504	1.76	1.72	3.48	736	675
	3008	481	1.74	1.70	3.44	675	655
	3009	557	1.69	1.68	3.37	691	666
	3010	505	1.72	1.69	3.41	704	641
	3011	475	1.63	1.67	3.30	637	585
	3012	459	1.52	1.57	3.09	565	592
Mean		489	1.66	1.66	3.33	671	653
S.D.		31	0.17	0.15	0.32	48	39
Relative	3001		0.34	0.34	0.69	131	136
	3002		0.40	0.40	0.80	156	154
	3003		0.28	0.28	0.56	141	139
	3004		0.39	0.39	0.78	143	137
	3005		0.31	0.32	0.62	133	137
	3006		0.33	0.33	0.66	136	135
	3007		0.35	0.34	0.69	146	134
	3008		0.36	0.35	0.72	140	136
	3009		0.30	0.30	0.61	124	120
	3010		0.34	0.33	0.68	139	127
	3011		0.34	0.35	0.69	134	123
	3012		0.33	0.34	0.67	123	129
Mean			0.34	0.34	0.68	137	134
S.D.			0.03	0.03	0.07	9	9

## Appendix 416

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 1000

Animal number	Body weight g	Brain		Thyroid (R)		Thyroid (L)		Thyroid (R+L)		Thymus		Heart	Liver
		g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)							
Absolute	4001	498	2.10	10.2	10.6	20.8	283	1.45	12.60				
	4002	517	2.03	8.6	10.7	19.3	261	1.42	13.58				
	4003	443	2.06	9.6	11.9	21.5	319	1.40	11.77				
	4004	514	2.09	15.7	14.2	29.9	242	1.56	12.82				
	4005	517	2.02	13.2	15.1	28.3	372	1.46	15.16				
	Mean	498	2.06	11.5	12.5	24.0	295	1.46	13.19				
	S.D.	32	0.04	2.9	2.1	4.8	52	0.06	1.28				
Relative	4001		0.42	2.0	2.1	4.2	57	0.29	2.53				
	4002		0.39	1.7	2.1	3.7	50	0.27	2.63				
	4003		0.47	2.2	2.7	4.9	72	0.32	2.66				
	4004		0.41	3.1	2.8	5.8	47	0.30	2.49				
	4005		0.39	2.6	2.9	5.5	72	0.28	2.93				
	Mean		0.42	2.3	2.5	4.8	60	0.29	2.65				
	S.D.		0.03	0.5	0.4	0.9	12	0.02	0.17				

## Appendix 417

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 1000

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	4001	0.87	1.60	1.54	3.14	43	44
	4002	0.76	1.60	1.71	3.31	29	29
	4003	0.66	1.58	1.75	3.33	34	32
	4004	0.83	1.71	1.69	3.40	38	41
	4005	0.82	1.77	1.90	3.67	29	33
	Mean	0.79	1.65	1.72	3.37	35	36
Relative	S.D.	0.08	0.08	0.13	0.19	6	6
	4001	0.17	0.32	0.31	0.63	9	9
	4002	0.15	0.31	0.33	0.64	6	6
	4003	0.15	0.36	0.40	0.75	8	7
	4004	0.16	0.33	0.33	0.66	7	8
	4005	0.16	0.34	0.37	0.71	6	6
	Mean	0.16	0.33	0.35	0.68	7	7
	S.D.	0.01	0.02	0.04	0.05	1	1

## Appendix 418

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Main group)

Dose (mg/kg): 1000

Animal number	Body weight g	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	
Absolute	4001	498	1.62	1.59	3.21	648	658	1306
	4002	517	1.65	1.73	3.38	654	651	1305
	4003	443	1.59	1.61	3.20	646	622	1268
	4004	514	1.50	1.52	3.02	657	670	1327
	4005	517	1.86	1.81	3.67	718	704	1422
	4006	502	1.63	1.64	3.27	683	681	1384
	4007	474	1.38	1.28	2.66	470	449	919
	4008	486	1.83	1.85	3.68	671	668	1339
	4009	549	1.61	1.60	3.21	719	660	1379
	4010	519	1.71	1.69	3.40	705	666	1371
	4011	469	1.68	1.74	3.42	606	600	1206
	4012	511	1.72	1.77	3.49	674	664	1338
Mean		500	1.65	1.65	3.30	654	641	1295
S.D.		28	0.13	0.15	0.28	67	66	131
Relative	4001		0.33	0.32	0.64	130	132	262
	4002		0.32	0.33	0.65	126	126	252
	4003		0.36	0.36	0.72	146	140	286
	4004		0.29	0.30	0.59	128	130	258
	4005		0.36	0.35	0.71	139	136	275
	4006		0.32	0.33	0.65	136	136	272
	4007		0.29	0.27	0.56	99	95	194
	4008		0.38	0.38	0.76	138	137	276
	4009		0.29	0.29	0.58	131	120	251
	4010		0.33	0.33	0.66	136	128	264
	4011		0.36	0.37	0.73	129	128	257
	4012		0.34	0.35	0.68	132	130	262
Mean			0.33	0.33	0.66	131	128	259
S.D.			0.03	0.03	0.06	11	12	23

## Appendix 419

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Main group)

Dose (mg/kg): 0

Animal number	Body weight g	Brain	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus	Heart	Liver
		g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	1103	301	2.08	8.4	9.3	17.7	178	0.93
	1104	323	2.05	11.6	10.1	21.7	185	1.12
	1105	317	2.01	8.5	8.6	17.1	246	1.01
	1107	298	2.02	8.0	8.7	16.7	246	9.72
	1109	292	1.98	11.3	10.6	21.9	272	0.98
	Mean	306	2.03	9.6	9.5	19.0	225	10.16
	S.D.	13	0.04	1.7	0.9	2.6	42	0.57
Relative	1103		0.69	2.8	3.1	5.9	0.31	3.43
	1104		0.63	3.6	3.1	6.7	57	0.35
	1105		0.63	2.7	2.7	5.4	78	0.32
	1107		0.68	2.7	2.9	5.6	83	0.31
	1109		0.68	3.9	3.6	7.5	93	0.34
	Mean		0.66	3.1	3.1	6.2	74	3.32
	S.D.		0.03	0.6	0.3	0.9	16	0.10

## Appendix 420

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Main group)

Dose (mg/kg): 0

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	1103	0.62	1.02	1.02	2.04	45	45
	1104	0.70	1.02	0.97	1.99	37	46
	1105	0.61	1.02	1.09	2.11	40	51
	1107	0.58	1.01	1.06	2.07	46	52
	1109	0.60	1.03	0.93	1.96	51	52
	Mean	0.62	1.02	1.01	2.03	44	49
Relative	S.D.	0.05	0.01	0.07	0.06	5	3
	1103	0.21	0.34	0.34	0.68	15	15
	1104	0.22	0.32	0.30	0.62	11	14
	1105	0.19	0.32	0.34	0.67	13	16
	1107	0.19	0.34	0.36	0.60	15	17
	1109	0.21	0.35	0.32	0.67	17	18
	Mean	0.20	0.33	0.33	0.67	14	16
	S.D.	0.01	0.01	0.02	0.03	2	2
							31
							4

## Appendix 421

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Main group)

Dose (mg/kg): 100

Animal number	Body weight g	Brain	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus	Heart	Liver
		g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	2106	329	1.96	8.2	7.5	15.7	256	0.97
	2107	281	1.94	7.9	4.8	12.7	196	0.94
	2108	316	1.89	9.7	7.3	17.0	172	1.04
	2109	338	1.99	8.4	10.0	18.4	191	1.03
	2110	312	1.95	10.1	8.3	18.4	229	0.93
	Mean	315	1.95	8.9	7.6	16.4	209	0.98
Relative	S.D.	22	0.04	1.0	1.9	2.4	33	1.46
	2106		0.60	2.5	2.3	4.8	78	0.29
	2107		0.69	2.8	1.7	4.5	70	0.33
	2108		0.60	3.1	2.3	5.4	54	0.33
	2109		0.59	2.5	3.0	5.4	57	0.30
	2110		0.63	3.2	2.7	5.9	73	0.30
Mean		0.62	2.8	2.4	5.2	66	0.31	3.29
	S.D.	0.04	0.3	0.5	0.6	10	0.02	0.30

## Appendix 422

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Main group)

Dose (mg/kg): 100

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	2106	0.60	1.17	1.14	2.31	43	41
	2107	0.56	0.96	0.97	1.93	31	38
	2108	0.58	0.99	0.98	1.97	36	40
	2109	0.87	1.19	1.15	2.34	50	55
	2110	0.56	1.14	1.13	2.27	39	44
	Mean	0.63	1.09	1.07	2.16	40	44
Relative	S.D.	0.13	0.11	0.09	0.20	7	7
	2106	0.18	0.36	0.35	0.70	13	12
	2107	0.20	0.34	0.35	0.69	11	14
	2108	0.18	0.31	0.31	0.62	11	13
	2109	0.26	0.35	0.34	0.69	15	16
	2110	0.18	0.37	0.36	0.73	13	14
	Mean	0.20	0.35	0.34	0.69	13	14
	S.D.	0.03	0.02	0.02	0.04	2	1
							27
							3

## Appendix 423

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Main group)

Dose (mg/kg): 300

Animal number	Body weight g	Brain		Thyroid (R)		Thyroid (L)		Thyroid (R+L)		Thymus		Heart	Liver
		g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)						
Absolute	3101	316	2.04	7.0	6.3	13.3	111	1.04	9.63				
	3104	328	1.93	9.8	8.0	17.8	169	0.93	11.11				
	3107	300	1.96	7.8	6.8	14.6	172	1.07	10.32				
	3109	308	2.00	6.0	8.8	14.8	296	1.13	10.93				
	3111	340	1.96	7.9	5.9	13.8	264	1.01	11.11				
	Mean	318	1.98	7.7	7.2	14.9	202	1.04	10.62				
	S.D.	16	0.04	1.4	1.2	1.8	76	0.07	0.64				
Relative	3101		0.65	2.2	2.0	4.2	35	0.33	3.05				
	3104		0.59	3.0	2.4	5.4	52	0.28	3.39				
	3107		0.65	2.6	2.3	4.9	57	0.36	3.44				
	3109		0.65	1.9	2.9	4.8	96	0.37	3.55				
	3111		0.58	2.3	1.7	4.1	78	0.30	3.27				
	Mean		0.62	2.4	2.3	4.7	64	0.33	3.34				
	S.D.		0.04	0.4	0.5	0.5	24	0.04	0.19				

## Appendix 424

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Main group)

Dose (mg/kg): 300

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	3101	0.67	1.04	1.04	2.08	38	43
	3104	0.56	1.00	1.01	2.01	40	39
	3107	0.71	1.17	1.14	2.31	46	50
	3109	0.74	1.05	1.07	2.12	41	43
	3111	0.71	1.59	1.19	2.78	50	51
	Mean	0.68	1.17	1.09	2.26	43	45
Relative	S.D.	0.07	0.24	0.07	0.31	5	5
	3101	0.21	0.33	0.33	0.66	12	14
	3104	0.17	0.30	0.31	0.61	12	12
	3107	0.24	0.39	0.38	0.77	15	17
	3109	0.24	0.34	0.35	0.69	13	14
	3111	0.21	0.47	0.35	0.82	15	15
	Mean	0.21	0.37	0.34	0.71	13	14
	S.D.	0.03	0.07	0.03	0.08	2	2

## Appendix 425

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Main group)

Dose (mg/kg): 1000

	Animal number	Body weight g	Brain g(g/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/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	4101	290	2.02	6.2	6.1	12.3	298	0.92	10.32
	4103	304	1.93	12.1	10.5	22.6	278	1.11	10.50
	4106	332	1.99	8.2	8.7	16.9	209	1.07	12.30
	4110	311	1.94	5.4	6.8	12.2	200	0.90	9.46
	4111	312	1.81	6.9	10.0	16.9	176	0.91	10.02
	Mean	310	1.94	7.8	8.4	16.2	232	0.98	10.52
Relative	S.D.	15	0.08	2.6	1.9	4.3	53	0.10	1.07
	4101		0.70	2.1	2.1	4.2	103	0.32	3.56
	4103		0.63	4.0	3.5	7.4	91	0.37	3.45
	4106		0.60	2.5	2.6	5.1	63	0.32	3.70
	4110		0.62	1.7	2.2	3.9	64	0.29	3.04
	4111		0.58	2.2	3.2	5.4	56	0.29	3.21
	Mean		0.63	2.5	2.7	5.2	75	0.32	3.39
	S.D.		0.05	0.9	0.6	1.4	20	0.03	0.27

## Appendix 426

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Main group)

Dose (mg/kg): 1000

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)	
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	
Absolute	4101	0.64	1.08	1.12	2.20	46	52	98
	4103	0.60	1.06	1.02	2.08	41	42	83
	4106	0.87	1.07	1.06	2.13	49	56	105
	4110	0.55	0.97	1.01	1.98	41	47	88
	4111	0.58	0.99	0.98	1.97	35	38	73
	Mean	0.65	1.03	1.04	2.07	42	47	89
Relative	S.D.	0.13	0.05	0.05	0.10	5	7	13
	4101	0.22	0.37	0.39	0.76	16	18	34
	4103	0.20	0.35	0.34	0.68	13	14	27
	4106	0.26	0.32	0.32	0.64	15	17	32
	4110	0.18	0.31	0.32	0.64	13	15	28
	4111	0.19	0.32	0.31	0.63	11	12	23
	Mean	0.21	0.33	0.34	0.67	14	15	29
	S.D.	0.03	0.03	0.03	0.05	2	2	4

## Appendix 427

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Recovery group)

Dose (mg/kg): 0

Animal number	Body weight g	Brain	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus	Heart	Liver	
		g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)	
Absolute	1013	570	2.06	8.4	11.8	20.2	236	1.71	14.19
	1014	521	2.23	17.8	14.8	32.6	372	1.45	13.58
	1015	552	2.14	13.2	11.4	24.6	307	1.62	15.62
	1016	500	2.17	15.1	14.8	29.9	202	1.29	10.93
	1017	509	2.15	12.7	13.5	26.2	346	1.30	13.88
	Mean	530	2.15	13.4	13.3	26.7	293	1.47	13.64
Relative	S.D.	30	0.06	3.5	1.6	4.8	72	0.19	1.71
	1013		0.36	1.5	2.1	3.5	41	0.30	2.49
	1014		0.43	3.4	2.8	6.3	71	0.28	2.61
	1015		0.39	2.4	2.1	4.5	56	0.29	2.83
	1016		0.43	3.0	3.0	6.0	40	0.26	2.19
	1017		0.42	2.5	2.7	5.1	68	0.26	2.73
	Mean		0.41	2.6	2.5	5.1	55	0.28	2.57
	S.D.		0.03	0.7	0.4	1.1	15	0.02	0.25

## Appendix 428

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Recovery group)

Dose (mg/kg): 0

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	1013	0.68	1.61	1.70	3.31	26	29
	1014	0.86	1.78	1.87	3.65	26	31
	1015	0.90	1.99	1.99	3.98	28	31
	1016	0.68	1.56	1.62	3.18	29	34
	1017	0.82	1.75	1.75	3.50	37	39
	Mean	0.79	1.74	1.79	3.52	28	33
Relative	S.D.	0.10	0.17	0.15	0.31	5	4
	1013	0.12	0.28	0.30	0.58	5	5
	1014	0.17	0.34	0.36	0.70	5	6
	1015	0.16	0.36	0.36	0.72	5	6
	1016	0.14	0.31	0.32	0.64	6	7
	1017	0.16	0.34	0.34	0.69	7	8
	Mean	0.15	0.33	0.34	0.67	6	6
	S.D.	0.02	0.03	0.03	0.06	1	1

## Appendix 429

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Recovery group)

Dose (mg/kg): 0

Animal number	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)
Absolute	1013	1.78	1.79	3.57	666	642
	1014	1.84	1.91	3.75	855	717
	1015	1.75	1.82	3.57	706	692
	1016	1.71	1.75	3.46	701	678
	1017	1.69	1.64	3.33	779	807
	Mean	1.75	1.78	3.54	741	707
	S.D.	0.06	0.10	0.16	76	62
Relative	1013	0.31	0.31	0.63	117	113
	1014	0.35	0.37	0.72	164	138
	1015	0.32	0.33	0.65	128	125
	1016	0.34	0.35	0.69	140	136
	1017	0.33	0.32	0.65	153	159
	Mean	0.33	0.34	0.67	140	134
	S.D.	0.02	0.02	0.04	19	17

## Appendix 430

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Recovery group)

Dose (mg/kg): 1000

Animal number	Body weight g	Brain	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus	Heart	Liver
		g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	4013	514	2.11	15.9	15.2	31.1	257	1.48
	4014	513	2.15	9.1	11.3	20.4	195	1.40
	4015	505	2.20	10.3	10.9	21.2	284	1.45
	4016	536	2.34	12.3	13.4	25.7	287	1.50
	4017	603	2.18	11.9	11.5	23.4	330	1.64
	Mean	534	2.20	11.9	12.5	24.4	271	1.49
	S.D.	40	0.09	2.6	1.8	4.3	50	0.09
Relative	4013		0.41	3.1	3.0	6.1	50	0.29
	4014		0.42	1.8	2.2	4.0	38	0.27
	4015		0.44	2.0	2.2	4.2	56	0.29
	4016		0.44	2.3	2.5	4.8	54	0.28
	4017		0.36	2.0	1.9	3.9	55	0.27
	Mean		0.41	2.2	2.4	4.6	51	0.28
	S.D.		0.03	0.5	0.4	0.9	7	0.01

## Appendix 431

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of male rats (Recovery group)

Dose (mg/kg): 1000

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)	
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	
Absolute	4013	0.79	1.31	1.38	2.70	37	39	76
	4014	1.03	1.71	1.54	3.25	35	32	67
	4015	0.68	1.80	1.80	3.60	30	33	63
	4016	0.81	1.92	1.94	3.86	32	36	68
	4017	0.83	1.71	1.77	3.48	28	31	59
	Mean	0.83	1.69	1.69	3.38	32	34	67
	S.D.	0.13	0.23	0.22	0.44	4	3	6
Relative	4013	0.15	0.25	0.27	0.53	7	8	15
	4014	0.20	0.33	0.30	0.63	7	6	13
	4015	0.13	0.36	0.36	0.71	6	7	12
	4016	0.15	0.36	0.36	0.72	6	7	13
	4017	0.14	0.28	0.29	0.58	5	5	10
	Mean	0.15	0.32	0.32	0.63	6	7	13
	S.D.	0.03	0.05	0.04	0.08	1	1	2

## Appendix 432

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual organ weight of male rats (Recovery group)

Dose (mg/kg): 1000

Animal number	Testis (R)	Testis (L)	Testis (R+L)	Epididymis (R)	Epididymis (L)	Epididymis (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	4013	1.67	1.64	3.31	713	678
	4014	1.52	1.70	3.22	592	662
	4015	1.71	1.71	3.42	729	790
	4016	1.91	1.92	3.83	767	745
	4017	1.64	1.57	3.21	770	726
	Mean	1.69	1.71	3.40	714	720
Relative	S.D.	0.14	0.13	0.26	73	52
	4013	0.32	0.32	0.64	139	132
	4014	0.30	0.33	0.63	115	129
	4015	0.34	0.34	0.68	144	156
	4016	0.36	0.36	0.71	143	139
	4017	0.27	0.26	0.53	128	120
	Mean	0.32	0.32	0.64	134	135
	S.D.	0.03	0.04	0.07	12	13
						269
						24

## Appendix 433

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Recovery group)

Dose (mg/kg): 0

Animal number	Body weight g	Brain	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus	Heart	Liver
		g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	1113	289	2.07	9.7	8.8	18.5	294	0.93
	1114	344	2.07	8.8	9.3	18.1	324	1.11
	1115	290	2.08	7.8	6.3	14.1	292	0.88
	1116	290	2.05	8.3	8.7	17.0	270	0.93
	1117	281	1.97	9.7	6.1	15.8	229	0.90
	Mean	299	2.05	8.9	7.8	16.7	282	0.95
	S.D.	26	0.04	0.8	1.5	1.8	35	0.09
Relative	1113		0.72	3.4	3.0	6.4	102	0.32
	1114		0.60	2.6	2.7	5.3	94	0.32
	1115		0.72	2.7	2.2	4.9	101	0.30
	1116		0.71	2.9	3.0	5.9	93	0.32
	1117		0.70	3.5	2.2	5.6	81	0.32
	Mean		0.69	3.0	2.6	5.6	94	0.32
	S.D.		0.05	0.4	0.4	0.6	8	0.12

## Appendix 434

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Recovery group)

Dose (mg/kg): 0

Animal number	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	Adrenal (R)	Adrenal (L)	Adrenal (R+L)	
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	
Absolute	1113	0.58	0.93	0.89	1.82	34	38	72
	1114	0.74	1.26	1.23	2.49	42	44	86
	1115	0.50	0.91	0.89	1.80	37	33	70
	1116	0.62	0.92	0.91	1.83	33	34	67
	1117	0.47	0.84	0.85	1.69	36	41	77
	Mean	0.58	0.97	0.95	1.93	36	38	74
Relative	S.D.	0.11	0.16	0.16	0.32	4	5	7
	1113	0.20	0.32	0.31	0.63	12	13	25
	1114	0.22	0.37	0.36	0.72	12	13	25
	1115	0.17	0.31	0.31	0.62	13	11	24
	1116	0.21	0.32	0.31	0.63	11	12	23
	1117	0.17	0.30	0.30	0.60	13	15	27
	Mean	0.19	0.32	0.32	0.64	12	13	25
	S.D.	0.02	0.03	0.02	0.05	1	1	1

## Appendix 435

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Recovery group)

Dose (mg/kg): 1000

Animal number	Body weight g	Brain		Thyroid (R)		Thyroid (L)		Thyroid (R+L)		Thymus		Heart		Liver	
		g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)											
Absolute	4113	286	1.96	10.7	9.6	20.3	291	0.93	7.07						
	4114	313	2.04	11.5	10.2	21.7	441	0.94	6.82						
	4115	281	1.88	9.4	7.9	17.3	226	0.96	7.63						
	4116	319	2.03	7.6	8.8	16.4	250	0.87	7.44						
	4117	337	2.02	12.3	10.3	22.6	254	0.93	7.89						
	Mean	307	1.99	10.3	9.4	19.7	292	0.93	7.37						
	S.D.	23	0.07	1.9	1.0	2.7	86	0.03	0.43						
Relative	4113		0.69	3.7	3.4	7.1	102	0.33	2.47						
	4114		0.65	3.7	3.3	6.9	141	0.30	2.18						
	4115		0.67	3.3	2.8	6.2	80	0.34	2.72						
	4116		0.64	2.4	2.8	5.1	78	0.27	2.33						
	4117		0.60	3.6	3.1	6.7	75	0.28	2.34						
	Mean		0.65	3.3	3.1	6.4	95	0.30	2.41						
	S.D.		0.03	0.6	0.3	0.8	28	0.03	0.20						

## Appendix 436

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual organ weight of female rats (Recovery group)

Dose (mg/kg): 1000

	Animal number	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)
Absolute	4113	0.51	1.16	1.23	2.39	36	41	77
	4114	0.54	1.15	1.10	2.25	38	37	75
	4115	0.54	1.09	1.14	2.23	40	39	79
	4116	0.49	1.09	1.10	2.19	33	40	73
	4117	0.66	0.98	1.02	2.00	37	31	68
	Mean	0.55	1.09	1.12	2.21	37	38	74
	S.D.	0.07	0.07	0.08	0.14	3	4	4
Relative	4113	0.18	0.41	0.43	0.84	13	14	27
	4114	0.17	0.37	0.35	0.72	12	12	24
	4115	0.19	0.39	0.41	0.79	14	14	28
	4116	0.15	0.34	0.34	0.69	10	13	23
	4117	0.20	0.29	0.30	0.59	11	9	20
	Mean	0.18	0.36	0.37	0.73	12	12	24
	S.D.	0.02	0.05	0.05	0.10	2	2	3

Appendix 437(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1001 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Mineralization,medullary: minimal

Liver Microgranuloma: minimal

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Heart  
Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum  
Intestine,colon, Intestine,rectum, Lymph node,mesenteric  
Lymph node,submandibular, Lung(bronchus), Parathyroid, Pituitary  
Spinal cord(thoracic), Sciatic nerve, Stomach, Seminal vesicle, Sternum+Marrow  
Testis, Thymus, Thyroid, Urinary bladder

Appendix 438(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1002 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

Kidney Nodule: 2 present, left  
20x10x10mm, 10x10x10mm

Other tissues Not remarkable

Histopathology:

Kidney Regeneration,tubular: minimal, unilateral  
Urinary cast,hyaline: minimal, unilateral  
Cell infiltration,interstitial: minimal, unilateral, mononuclear  
NEPHROBLASTOMA: 1 present, unilateral

Liver Microgranuloma: minimal

Spleen Hematopoiesis,extramedullary: mild

Urinary bladder Mineralization,serosal: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Heart  
Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum  
Intestine,colon, Intestine,rectum, Lymph node,mesenteric  
Lymph node,submandibular, Lung(bronchus), Parathyroid, Pituitary  
Spinal cord(thoracic), Sciatic nerve, Stomach, Seminal vesicle, Sternum+Marrow  
Testis, Thymus, Thyroid

Appendix 439(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1003 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Regeneration,tubular: minimal

Liver Vacuolation,hepatocyte,periportal: minimal  
Microgranuloma: minimal

Lung(bronchus) Mineralization,arterial wall: minimal

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Heart  
Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum  
Intestine,colon, Intestine,rectum, Lymph node,mesenteric  
Lymph node,submandibular, Parathyroid, Pituitary, Spinal cord(thoracic)  
Sciatic nerve, Stomach, Seminal vesicle, Sternum+Marrow, Testis, Thymus, Thyroid  
Urinary bladder

Appendix 440(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1004 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Lung(bronchus) Alveolar macrophage: minimal

Spleen Hematopoiesis, extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Heart  
Intestine, duodenum, Intestine, jejunum, Intestine, ileum, Intestine, cecum  
Intestine, colon, Intestine, rectum, Kidney, Lymph node, mesenteric  
Lymph node, submandibular, Parathyroid, Pituitary, Spinal cord(thoracic)  
Sciatic nerve, Stomach, Seminal vesicle, Sternum+Marrow, Testis, Thymus, Thyroid  
Urinary bladder

Appendix 441(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1005 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Heart Cell infiltration, focal: minimal, mononuclear

Kidney Regeneration, tubular: minimal  
Mineralization, medullary: minimal

Lung(bronchus) Alveolar macrophage: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Intestine, duodenum  
Intestine, jejunum, Intestine, ileum, Intestine, cecum, Intestine, colon  
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular, Liver  
Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve, Spleen, Stomach  
Seminal vesicle, Sternum+Marrow, Testis, Thymus, Thyroid, Urinary bladder

Appendix 442(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1006 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 443(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1007 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present  
1x1mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion, glandular stomach: minimal

Appendix 444(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1008 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 445(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1009 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 446(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1010 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 447(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1011 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 448(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1012 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

Epididymis Focus, yellow: 1 present, right tail, 10x7mm

Other tissues Not remarkable

Histopathology:

Epididymis Granuloma, spermatic: moderate tail

Following tissues : Not remarkable

Stomach

Appendix 449(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 2001 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 450(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2002 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 451(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2003 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 452(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diaminium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 2004 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 453(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2005 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

Epididymis Focus, yellow: 1 present, right tail, 10x8mm

Other tissues Not remarkable

Histopathology:

Epididymis Granuloma, spermatic: mild tail

Following tissues : Not remarkable

Stomach

Appendix 454(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate Individual gross and histopathological findings

Animal No. 2006 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 455(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2007 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

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Appendix 456(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2008 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 457(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2009 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 458(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2010 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 459(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2011 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

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Appendix 460(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2012 Male 100 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

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Appendix 461(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3001 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 462(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3002 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 463(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3003 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 464(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3004 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 465(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3005 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 466(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3006 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 467(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 3007 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 468(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3008 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 469(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diaminium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3009 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 470(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3010 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 471(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3011 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 472(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3012 Male 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 473(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4001 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present  
1.5x1.5mm

Other tissues Not remarkable

Histopathology:

Epididymis Cell infiltration,interstitial: minimal, lymphocytic head

Kidney Regeneration,tubular: minimal  
Mineralization,medullary: minimal  
Cell infiltration,interstitial: minimal, lymphocytic

Liver Microgranuloma: minimal

Lung(bronchus) Alveolar macrophage: mild  
Cell infiltration,alveolar: minimal, inflammatory

Stomach Erosion,glandular stomach: mild  
Hyperplasia,squamous,limiting ridge: minimal

Thyroid Ectopic thymus: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine,duodenum  
Intestine,jejunum, Intestine,ileum, Intestine,cecum, Intestine,colon  
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Parathyroid  
Pituitary, Spinal cord(thoracic), Sciatic nerve, Spleen, Seminal vesicle  
Sternum+Marrow, Testis, Thymus, Urinary bladder

Appendix 474(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4002 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Regeneration,tubular: minimal  
Mineralization,medullary: minimal

Liver Microgranuloma: minimal

Lung(bronchus) Mineralization,arterial wall: minimal

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

( Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Heart,  
Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum  
Intestine,colon, Intestine,rectum, Lymph node,mesenteric  
Lymph node,submandibular, Parathyroid, Pituitary, Spinal cord(thoracic)  
Sciatic nerve, Stomach, Seminal vesicle, Sternum+Marrow, Testis, Thymus, Thyroid  
Urinary bladder

Appendix 475(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4003 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney	Regeneration, tubular: minimal Cell infiltration, interstitial: minimal, lymphocytic
Liver	Microgranuloma: minimal
Lung(bronchus)	Alveolar macrophage: minimal
Spleen	Hematopoiesis, extramedullary: minimal
Stomach	Hyperplasia, squamous, limiting ridge: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Heart  
Intestine, duodenum, Intestine, jejunum, Intestine, ileum, Intestine, cecum  
Intestine, colon, Intestine, rectum, Lymph node, mesenteric  
Lymph node, submandibular, Parathyroid, Pituitary, Spinal cord(thoracic)  
Sciatic nerve, Seminal vesicle, Sternum+Marrow, Testis, Thymus, Thyroid  
Urinary bladder

Appendix 476(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4004 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Regeneration,tubular: minimal  
Mineralization,medullary: minimal

Liver Microgranuloma: minimal

Spleen Hematopoiesis, extramedullary: minimal

Stomach Hyperplasia,squamous,limiting ridge: minimal

Following tissues : Not remarkable

( Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Heart  
Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum  
Intestine,colon, Intestine,rectum, Lymph node,mesenteric  
Lymph node,submandibular, Lung(bronchus), Parathyroid, Pituitary  
Spinal cord(thoracic), Sciatic nerve, Seminal vesicle, Sternum+Marrow, Testis  
Thymus, Thyroid, Urinary bladder

Appendix 477(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4005 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine, cecum Cell infiltration, mucosal: minimal  
eosinophilic/lymphocytic

Kidney Regeneration, tubular: minimal

Liver Microgranuloma: minimal

Spleen Hematopoiesis, extramedullary: minimal

Stomach Hyperplasia, squamous, limiting ridge: mild

Seminal vesicle Cell infiltration, muscle layer: minimal, mononuclear

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Epididymis, Femur+Marrow, Heart  
Intestine, duodenum, Intestine, jejunum, Intestine, ileum, Intestine, colon  
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular  
Lung(bronchus), Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve  
Sternum+Marrow, Testis, Thymus, Thyroid, Urinary bladder

Appendix 478(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4006 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

Appendix 479(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diaminium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4007 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia,squamous,limiting ridge: mild

Appendix 480(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4008 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia,squamous,limiting ridge: minimal

Appendix 481(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4009 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present  
1x1mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion,glandular stomach: minimal  
Hyperplasia,squamous,limiting ridge: minimal

Appendix 482(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4010 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

Appendix 483(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4011 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 484(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4012 Male 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

Appendix 485(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1101 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

Stomach Focus, dark red, glandular stomach: 2 present  
2x2mm, 4x2mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion, glandular stomach: mild

Appendix 486(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1102 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 487(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1103 Female 0 mg/kg Day 44 End of administration period

Gross pathology:

Lung(bronchus) Focus,dark red: 2 present  
1x1mm,1x1mm

Other tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Lung(bronchus) Alveolar macrophage: minimal  
Cell infiltration,alveolar: minimal, inflammatory  
No finding correlating with necropsy data

Pituitary Cell infiltration,anterior,focal: minimal, mononuclear

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine,duodenum  
Intestine,jejunum, Intestine,ileum, Intestine,cecum, Intestine,colon  
Intestine,rectum, Kidney, Lymph node,mesenteric, Lymph node,submandibular  
Parathyroid, Spinal cord(thoracic), Sciatic nerve, Stomach, Sternum+Marrow  
Thymus, Thyroid, Urinary bladder, Uterus

Appendix 488(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1104 Female 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Cell infiltration, interstitial: minimal, lymphocytic

Liver Microgranuloma: minimal

Spleen Hematopoiesis, extramedullary: mild

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine, duodenum  
Intestine, jejunum, Intestine, ileum, Intestine, cecum, Intestine, colon  
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular  
Lung(bronchus), Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve  
Stomach, Sternum+Marrow, Thymus, Thyroid, Urinary bladder, Uterus

Appendix 489(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diaminium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1105 Female 0 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Lung(bronchus) Cell infiltration, alveolar: minimal, inflammatory  
Hemorrhage, alveolar: minimal

Spleen Hematopoiesis, extramedullary: mild

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine, duodenum  
Intestine, jejunum, Intestine, ileum, Intestine, cecum, Intestine, colon  
Intestine, rectum, Kidney, Lymph node, mesenteric, Lymph node, submandibular  
Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve, Stomach  
Sternum+Marrow, Thymus, Thyroid, Urinary bladder, Uterus

Appendix 490(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1106 Female 0 mg/kg Day 46 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 491(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1107 Female 0 mg/kg Day 44 End of administration period

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present  
1x1mm

Other tissues Not remarkable

Histopathology:

Heart Cell infiltration,focal: minimal, mononuclear

Kidney Regeneration,tubular: minimal

Liver Vacuolation,hepatocyte,periportal: minimal

Spleen Hematopoiesis,extramedullary: mild

Stomach Erosion,glandular stomach: mild

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Intestine,duodenum  
Intestine,jejunum, Intestine,ileum, Intestine,cecum, Intestine,colon  
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular  
Lung(bronchus), Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve  
Sternum+Marrow, Thymus, Thyroid, Urinary bladder, Uterus

Appendix 492(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1108 Female 0 mg/kg Day 42 End of administration period

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present  
2x2mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion, glandular stomach: minimal

Appendix 493(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1109 Female 0 mg/kg Day 43 End of administration period

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present  
1x1mm  
Other tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal  
Lung(bronchus) Alveolar macrophage: minimal  
Spleen Hematopoiesis,extramedullary: mild  
Stomach Erosion,glandular stomach: minimal  
healed erosion

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine,duodenum  
Intestine,jejunum, Intestine,ileum, Intestine,cecum, Intestine,colon  
Intestine,rectum, Kidney, Lymph node,mesenteric, Lymph node,submandibular  
Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve, Sternum+Marrow  
Thymus, Thyroid, Urinary bladder, Uterus

Appendix 494(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1110 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 495(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1111 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present  
1x1mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion, glandular stomach: minimal

Appendix 496(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1112 Female 0 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 497(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2101 Female 100 mg/kg Day 46 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 498(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2102 Female 100 mg/kg Day 46 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 499(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2103 Female 100 mg/kg Day 46 End of administration period

Gross pathology:

Stomach Focus, dark red, glandular stomach: 2 present  
3x2mm, 3x2mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion, glandular stomach: mild

Appendix 500(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2104 Female 100 mg/kg Day 46 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 501(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2105 Female 100 mg/kg Day 46 End of administration period

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present  
2x2mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion, glandular stomach: mild

Appendix 502(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2106 Female 100 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

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Appendix 503(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 2107 Female 100 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 504(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2108 Female 100 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 505(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2109 Female 100 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 506(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2110 Female 100 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

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Appendix 507(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2111 Female 100 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 508(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 2112 Female 100 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 509(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3101 Female 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

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Appendix 510(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 3102 Female 300 mg/kg Day 45 End of administration period

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present  
1x1mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion, glandular stomach: mild

Appendix 511(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxyp propane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3103 Female 300 mg/kg Day 46 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 512(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3104 Female 300 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 513(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3105 Female 300 mg/kg Day 45 End of administration period

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present  
1x1mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion,glandular stomach: mild

## Appendix 514(1/1)

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual gross and histopathological findings

Animal No. 3106 Female 300 mg/kg Day 42 End of administration period

Gross pathology:

Urinary bladder                    Thickening,wall:  
    Content,white fluid:  
    0.3ml

Other tissues                      Not remarkable

Histopathology:

Urinary bladder                    Cell infiltration,submucosal: mild, mononuclear  
    Hyperplasia,mucosal: mild

Following tissues : Not remarkable

Stomach

Appendix 515(1/1)

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3107 Female 300 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 518(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3110 Female 300 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 519(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3111 Female 300 mg/kg Day 43 End of administration period

Gross pathology:

Kidney Focus, white: 1 present, right  
10x10mm

Other tissues Not remarkable

Histopathology:

Kidney Regeneration, tubular: minimal, bilateral  
Urinary cast, hyaline: minimal, unilateral  
NEPHROBLASTOMA: 1 present, unilateral

Following tissues : Not remarkable

Stomach

Appendix 520(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 3112 Female 300 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 521(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4101 Female 1000 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Regeneration,tubular: minimal  
Mineralization,medullary: minimal

Liver Vacuolation,hepatocyte,periportal: minimal

Lung(bronchus) Metaplasia,osseous: minimal

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable.

( Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine,duodenum  
Intestine,jejunum, Intestine,ileum, Intestine,cecum, Intestine,colon  
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Parathyroid  
Pituitary, Spinal cord(thoracic), Sciatic nerve, Stomach, Sternum+Marrow, Thymus  
Thyroid, Urinary bladder, Uterus

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Appendix 522(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4102 Female 1000 mg/kg Day 46 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 523(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4103 Female 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Regeneration,tubular: minimal

Spleen Hematopoiesis,extramedullary: mild

Stomach Hyperplasia,squamous,limiting ridge: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine,duodenum  
Intestine,jejunum, Intestine,ileum, Intestine,cecum, Intestine,colon  
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Liver  
Lung(bronchus), Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve  
Sternum+Marrow, Thymus, Thyroid, Urinary bladder, Uterus

Appendix 524(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4104 Female 1000 mg/kg Day 45 End of administration period

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present  
1x5mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion,glandular stomach: mild  
Hyperplasia,squamous,limiting ridge: mild

Appendix 525(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4105 Female 1000 mg/kg Day 46 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

Appendix 526(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4106 Female 1000 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Regeneration,tubular: minimal

Liver Vacuolation,hepatocyte,periportal: minimal  
Microgranuloma: minimal

Spleen Hematopoiesis,extramedullary: mild

Stomach Hyperplasia,squamous,limiting ridge: minimal

Following tissues : Not remarkable

( Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine,duodenum  
Intestine,jejunum, Intestine,ileum, Intestine,cecum, Intestine,colon  
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular  
Lung(bronchus), Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve  
Sternum+Marrow, Thymus, Thyroid, Urinary bladder, Uterus

Appendix 527(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4107 Female 1000 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia,squamous,limiting ridge: minimal

Appendix 528(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4108 Female 1000 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

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Appendix 529(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4109 Female 1000 mg/kg Day 42 End of administration period

Gross pathology:

Stomach Focus,dark red,glandular stomach: 2 present  
1x1mm,1x1mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion,glandular stomach: mild

Appendix 530(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4110 Female 1000 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Lung(bronchus) Alveolar macrophage: minimal

Spleen Hematopoiesis, extramedullary: mild

Stomach Hyperplasia, squamous, limiting ridge: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine, duodenum  
Intestine, jejunum, Intestine, ileum, Intestine, cecum, Intestine, colon  
Intestine, rectum, Kidney, Lymph node, mesenteric, Lymph node, submandibular, Liver  
Parathyroid, Pituitary, Spinal cord(thoracic), Sciatic nerve, Sternum+Marrow  
Thymus, Thyroid, Urinary bladder, Uterus

Appendix 531(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4111 Female 1000 mg/kg Day 43 End of administration period

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present  
2x3mm

Other tissues Not remarkable

Histopathology:

Kidney Regeneration,tubular: minimal

Liver Microgranuloma: minimal

Lung(bronchus) Alveolar macrophage: minimal

Spleen Hematopoiesis,extramedullary: mild

Stomach Erosion,glandular stomach: mild  
Hyperplasia,squamous,limiting ridge: minimal

Following tissues : Not remarkable

Adrenal, Cerebellum, Cerebrum, Femur+Marrow, Heart, Intestine,duodenum  
Intestine,jejunum, Intestine,ileum, Intestine,cecum, Intestine,colon  
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Parathyroid  
Pituitary, Spinal cord(thoracic), Sciatic nerve, Sternum+Marrow, Thymus, Thyroid  
Urinary bladder, Uterus

Appendix 532(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4112 Female 1000 mg/kg Day 48 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 533(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1013 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Dilatation,glandular: mild

Appendix 534(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1014 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 535(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1015 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 536(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1016 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 537(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1017 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 538(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4013 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 539(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4014 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 540(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4015 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

Appendix 541(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4016 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 542(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4017 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 543(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1113 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

Appendix 544(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1114 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 545(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1115 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 546(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 1116 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 547(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 1117 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 548(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross and histopathological findings

Animal No. 4113 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 549(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4114 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

Appendix 550(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4115 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

Appendix 551(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4116 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 552(1/1) A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
Individual gross and histopathological findings

Animal No. 4117 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, limiting ridge: minimal

## Appendix 553

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 0

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14a)	Count of estrus	Mean duration of cycles
1101	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
1102	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
1103	E	M	D	D	P	E	M	D	D	P	E	M	D	D	3	5.0
1104	P	E	M	D	P	E	M	D	P	E	M	D	D	P	3	4.0
1105	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
1106	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
1107	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
1108	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
1109	P	E	M	D	P	E	M	D	D	P	E	M	D	P	3	4.5
1110	E	M	D	D	P	E	E	M	D	D	P	E	M	D	3	5.5
1111	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
1112	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
Mean															3.4	4.3
S.D.															0.5	0.5

P : Proestrus      E : Estrus      M : Metaestrus

a): Day of sampling

## Appendix 554

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 100

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14a)	Count of estrus	Mean duration of cycles
2101	P	E	E	M	D	P	E	E	M	D	P	E	E	M	3	5.0
2102	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
2103	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
2104	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
2105	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
2106	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
2107	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
2108	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
2109	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
2110	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
2111	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
2112	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
Mean															3.7	4.1
S.D.															0.5	0.3

P : Proestrus      E : Estrus      M : Metaestrus

D : Diestrus

a): Day of sampling

## Appendix 555

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 300

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14a)	Count of estrus	Mean duration of cycles
3101	P	E	M	D	P	E	M	D	P	E	M	D	D	D	3	4.5
3102	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
3103	E	M	D	P	E	M	D	P	E	M	D	D	P	E	4	4.3
3104	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
3105	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
3106	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
3107	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
3108	E	M	D	D	P	E	M	D	P	E	M	D	P	E	4	4.3
3109	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
3110	D	P	E	M	D	P	E	M	D	P	E	M	D	D	3	4.0
3111	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
3112	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
Mean															3.4	4.1
S.D.															0.5	0.2

P : Proestrus      E : Estrus      M : Metaestrus      D : Diestrus

a): Day of sampling

## Appendix 556

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

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

Dose (mg/kg) : 1000

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14a)	Count of estrus	Mean duration of cycles
4101	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
4102	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
4103	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
4104	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
4105	M	D	P	E	M	D	P	E	M	D	D	P	E	M	3	4.5
4106	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
4107	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
4108	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
4109	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
4110	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
4111	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
4112	M	D	P	E	M	D	P	E	M	D	P	E	M	D	3	4.0
Mean															3.4	4.0
S.D.															0.5	0.1

P : Proestrus      E : Estrus      M : Metaestrus

D : Diestrus

a): Day of sampling

## Appendix 557

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual mating and fertility of animals

Dose (mg/kg): 0

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
1001	1101	C	3	P
1002	1102	C	4	P
1003	1103	C	2	P
1004	1104	C	1	P
1005	1105	C	3	P
1006	1106	C	4	P
1007	1107	C	2	P
1008	1108	C	1	P
1009	1109	C	1	P
1010	1110	C	3	P
1011	1111	C	3	P
1012	1112	C	2	P

C: Copulated      P: Pregnant

## Appendix 558

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual mating and fertility of animals

Dose (mg/kg): 100

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
2001	2101	C	4	P
2002	2102	C	4	P
2003	2103	C	4	P
2004	2104	C	4	P
2005	2105	C	4	P
2006	2106	C	3	P
2007	2107	C	2	P
2008	2108	C	3	P
2009	2109	C	3	P
2010	2110	C	2	P
2011	2111	C	1	P
2012	2112	C	3	P

C: Copulated      P: Pregnant

## Appendix 559

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual mating and fertility of animals

Dose (mg/kg): 300

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
3001	3101	C	2	P
3002	3102	C	3	P
3003	3103	C	4	P
3004	3104	C	2	P
3005	3105	C	3	P
3006	3106	C	2	NP
3007	3107	C	1	P
3008	3108	C	4	P
3009	3109	C	1	P
3010	3110	C	3	P
3011	3111	C	1	P
3012	3112	C	4	P

C: Copulated

P: Pregnant

NP: Non-pregnant

## Appendix 560

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual mating and fertility of animals

Dose (mg/kg): 1000

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
4001	4101	C	2	P
4002	4102	C	4	P
4003	4103	C	1	P
4004	4104	C	3	P
4005	4105	C	4	P
4006	4106	C	2	P
4007	4107	C	3	NP
4008	4108	C	3	P
4009	4109	C	1	P
4010	4110	C	3	P
4011	4111	C	1	P
4012	4112	C	6	P

C: Copulated

P: Pregnant

NP: Non-pregnant

## Appendix 561

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Delivery data on dams

Dose (mg/kg) : 0

Dam number	Gestation period	No. of corpora lutea	No. of implantation sites	Implantation index % a)	No. of stillborn pups (%)b)	No. of liveborn pups	Live birth index % c)
1101	22.0	15	15	100.0	0( 0.0)	15	100.0
1102	21.5	18	18	100.0	0( 0.0)	18	100.0
1103	22.5	22	18	81.8	0( 0.0)	16	100.0
1104	22.5	20	17	85.0	1( 6.7)	14	93.3
1105	21.5	13	12	92.3	0( 0.0)	12	100.0
1106	22.5	14	14	100.0	0( 0.0)	13	100.0
1107	22.0	15	13	86.7	0( 0.0)	11	100.0
1108	21.5	17	16	94.1	0( 0.0)	16	100.0
1109	22.5	16	14	87.5	0( 0.0)	13	100.0
1110	22.0	20	17	85.0	0( 0.0)	13	100.0
1111	22.5	17	16	94.1	0( 0.0)	15	100.0
1112	22.0	18	18	100.0	0( 0.0)	17	100.0
Total		205	188	1	173		
Mean	22.1	17.1	15.7	92.2	( 0.6)	14.4	99.4
S.D.	0.4	2.7	2.1	6.8	( 1.9)	2.1	1.9

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

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

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

## Appendix 562

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Delivery data on dams

Dose (mg/kg) : 100

Dam number	Gestation period	No. of corpora lutea	No. of implantation sites	Implantation index % a)	No. of stillborn pups (%)b)	No. of liveborn pups	Live birth index % c)
2101	22.5	19	19	100.0	0( 0.0)	18	100.0
2102	22.5	17	17	100.0	1( 6.3)	15	93.8
2103	22.0	15	15	100.0	0( 0.0)	13	100.0
2104	22.5	18	18	100.0	0( 0.0)	17	100.0
2105	22.0	15	14	93.3	0( 0.0)	13	100.0
2106	22.5	16	14	87.5	0( 0.0)	12	100.0
2107	22.0	15	15	100.0	2( 14.3)	12	85.7
2108	22.5	15	15	100.0	0( 0.0)	15	100.0
2109	21.5	17	17	100.0	1( 6.3)	15	93.8
2110	22.0	16	16	100.0	1( 6.3)	15	93.8
2111	21.5	16	16	100.0	0( 0.0)	15	100.0
2112	22.5	18	17	94.4	0( 0.0)	17	100.0
Total		197	193		5	177	
Mean	22.2	16.4	16.1	97.9	( 2.8)	14.8	97.3
S.D.	0.4	1.4	1.6	4.1	( 4.6)	2.0	4.6

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

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

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

## Appendix 563

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Delivery data on dams

Dose (mg/kg) : 300

Dam number	Gestation period	No. of corpora lutea	No. of implantation sites	Implantation index % a)	No. of stillborn pups (%b)	No. of liveborn pups	Live birth index % c)
3101	21.5	19	18	94.7	0( 0.0)	18	100.0
3102	22.5	16	14	87.5	0( 0.0)	12	100.0
3103	22.5	19	19	100.0	3( 15.8)	16	84.2
3104	22.5	18	16	88.9	0( 0.0)	15	100.0
3105	22.5	16	15	93.8	0( 0.0)	15	100.0
3106	<b>Non-pregnant</b>						
3107	22.0	19	18	94.7	0( 0.0)	17	100.0
3108	21.5	17	16	94.1	0( 0.0)	16	100.0
3109	22.0	21	14	66.7	0( 0.0)	14	100.0
3110	22.5	18	18	100.0	0( 0.0)	17	100.0
3111	22.0	19	19	100.0	0( 0.0)	16	100.0
3112	21.5	16	16	100.0	0( 0.0)	16	100.0
Total		198	183	3	172		
Mean	22.1	18.0	16.6	92.8	( 1.4)	15.6	98.6
S.D.	0.4	1.6	1.9	9.7	( 4.8)	1.6	4.8

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

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

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

## Appendix 564

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Delivery data on dams

Dose (mg/kg) : 1000

Dam number	Gestation period	No. of corpora lutea	No. of implantation sites	Implantation index % a)	No. of stillborn pups (%b)	No. of liveborn pups	Live birth index % c)
4101	22.0	17	17	100.0	0( 0.0)	16	100.0
4102	22.0	19	19	100.0	2( 11.8)	15	88.2
4103	22.0	21	15	71.4	0( 0.0)	14	100.0
4104	22.0	17	9	52.9	0( 0.0)	9	100.0
4105	22.5	18	17	94.4	0( 0.0)	14	100.0
4106	22.5	16	15	93.8	0( 0.0)	15	100.0
4107	Non-pregnant						
4108	22.5	13	13	100.0	0( 0.0)	12	100.0
4109	21.5	19	19	100.0	0( 0.0)	19	100.0
4110	21.5	16	15	93.8	0( 0.0)	14	100.0
4111	22.0	15	14	93.3	0( 0.0)	13	100.0
4112	22.5	17	17	100.0	1( 5.9)	16	94.1
Total		188	170		3	157	
Mean	22.1	17.1	15.5	90.9	( 1.6)	14.3	98.4
S.D.	0.4	2.2	2.9	15.1	( 3.8)	2.5	3.8

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

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

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

## Appendix 565

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual external examination of liveborn pups

Dose (mg/kg) : 0

Dam number	No. of males	No. of females	a) Sex ratio	Body weight(g)		External b) abnormalities(%)c)
				Male	Female	
1101	11	4		6.5	5.7	0( 0.0)
1102	11	7		5.9	5.4	0( 0.0)
1103	5	11		6.3	6.1	0( 0.0)
1104	8	6		6.7	6.2	0( 0.0)
1105	8	4		5.8	5.8	0( 0.0)
1106	3	10		7.8	7.2	0( 0.0)
1107	5	6		6.6	6.0	0( 0.0)
1108	7	9		5.9	5.7	0( 0.0)
1109	8	5		6.6	6.1	0( 0.0)
1110	4	9		6.6	6.1	0( 0.0)
1111	6	9		7.2	6.8	0( 0.0)
1112	7	10		6.4	5.8	0( 0.0)
Total	83	90	0.48			0
Mean	6.9	7.5		6.5	6.1	( 0.0)
S.D.	2.5	2.5		0.6	0.5	( 0.0)

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

b): No. of liveborn pups with external abnormalities

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

## Appendix 566

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual external examination of liveborn pups

Dose (mg/kg) : 100

Dam number	No. of males	No. of females	a) Sex ratio	Body weight(g)		External b) abnor- malities(%)c)
				Male	Female	
2101	10	8		6.6	6.6	0( 0.0)
2102	8	7		6.7	6.2	0( 0.0)
2103	9	4		6.4	6.3	0( 0.0)
2104	7	10		6.7	6.6	0( 0.0)
2105	6	7		6.9	6.3	0( 0.0)
2106	6	6		7.0	6.5	0( 0.0)
2107	8	4		6.4	5.9	0( 0.0)
2108	9	6		6.4	6.1	0( 0.0)
2109	8	7		6.3	5.9	0( 0.0)
2110	7	8		5.7	5.7	0( 0.0)
2111	8	7		6.3	5.9	0( 0.0)
2112	9	8		6.8	6.4	0( 0.0)
Total	95	82	0.54			0
Mean	7.9	6.8		6.5	6.2	( 0.0)
S.D.	1.2	1.7		0.3	0.3	( 0.0)

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

b): No. of liveborn pups with external abnormalities

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

## Appendix 567

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual external examination of liveborn pups

Dose (mg/kg) : 300

Dam number	No. of males	No. of females	a) Sex ratio	Body weight(g)		External b) abnormalities(%)c)
				Male	Female	
3101	8	10		5.4	5.1	0( 0.0)
3102	8	4		7.3	7.2	0( 0.0)
3103	11	5		6.6	6.4	0( 0.0)
3104	9	6		7.0	6.7	0( 0.0)
3105	10	5		6.4	6.0	0( 0.0)
3106	Non-pregnant					
3107	9	8		6.4	5.9	0( 0.0)
3108	9	7		5.8	5.4	0( 0.0)
3109	4	10		6.7	6.4	0( 0.0)
3110	6	11		6.5	6.0	0( 0.0)
3111	8	8		6.6	6.0	0( 0.0)
3112	12	4		5.8	5.4	0( 0.0)
Total	94	78	0.55			0
Mean	8.5	7.1		6.4	6.0	( 0.0)
S.D.	2.2	2.5		0.6	0.6	( 0.0)

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

b): No. of liveborn pups with external abnormalities

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

## Appendix 568

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual external examination of liveborn pups

Dose (mg/kg) : 1000

Dam number	No. of males	No. of females	Sex ratio a)	Body weight(g)		External b) abnor- malities(%c)
				Male	Female	
4101	11	5		6.7	6.2	0( 0.0)
4102	7	8		6.1	6.0	0( 0.0)
4103	7	7		6.4	6.1	0( 0.0)
4104	3	6		7.2	6.8	0( 0.0)
4105	8	6		6.5	6.1	0( 0.0)
4106	6	9		7.2	6.9	0( 0.0)
4107	Non-pregnant					
4108	6	6		7.3	6.7	0( 0.0)
4109	11	8		5.8	5.6	0( 0.0)
4110	5	9		5.4	5.4	0( 0.0)
4111	4	9		6.5	6.2	0( 0.0)
4112	5	11		6.3	6.0	0( 0.0)
Total	73	84	0.46			0
Mean	6.6	7.6		6.5	6.2	( 0.0)
S.D.	2.6	1.8		0.6	0.5	( 0.0)

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

b): No. of liveborn pups with external abnormalities

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

## Appendix 569

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual viability index of pups

Dose (mg/kg) : 0

Dam number	No. of live pups		Viability index on day 4 after birth % a)
	Day 0	Day 4	
1101	15	14	93.3
1102	18	18	100.0
1103	16	16	100.0
1104	14	13	92.9
1105	12	12	100.0
1106	13	13	100.0
1107	11	11	100.0
1108	16	16	100.0
1109	13	13	100.0
1110	13	13	100.0
1111	15	15	100.0
1112	17	17	100.0
Total	173	171	
Mean	14.4	14.3	98.9
S.D.	2.1	2.1	2.7

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

## Appendix 570

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual viability index of pups

Dose (mg/kg) : 100

Dam number	No. of live pups		Viability index on day 4 after birth % a)
	Day 0	Day 4	
2101	18	17	94.4
2102	15	15	100.0
2103	13	12	92.3
2104	17	17	100.0
2105	13	13	100.0
2106	12	12	100.0
2107	12	12	100.0
2108	15	15	100.0
2109	15	15	100.0
2110	15	14	93.3
2111	15	15	100.0
2112	17	16	94.1
Total	177	173	
Mean	14.8	14.4	97.8
S.D.	2.0	1.8	3.2

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

Appendix 571

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual viability index of pups

Dose (mg/kg) : 300

Dam number	No. of live pups		Viability index on day 4 after birth % a)
	Day 0	Day 4	
3101	18	17	94.4
3102	12	12	100.0
3103	16	12	75.0
3104	15	15	100.0
3105	15	12	80.0
3106	Non-pregnant		
3107	17	15	88.2
3108	16	16	100.0
3109	14	13	92.9
3110	17	17	100.0
3111	16	15	93.8
3112	16	14	87.5
Total	172	158	
Mean	15.6	14.4	92.0
S.D.	1.6	1.9	8.6

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

## Appendix 572

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammmonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual viability index of pups

Dose (mg/kg) : 1000

Dam number	No. of live pups		Viability index on day 4 after birth % a)
	Day 0	Day 4	
4101	16	16	100.0
4102	15	15	100.0
4103	14	14	100.0
4104	9	9	100.0
4105	14	13	92.9
4106	15	15	100.0
4107	Non-pregnant		
4108	12	12	100.0
4109	19	19	100.0
4110	14	14	100.0
4111	13	13	100.0
4112	16	16	100.0
Total	157	156	
Mean	14.3	14.2	99.4
S.D.	2.5	2.6	2.1

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

## Appendix 573

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual body weight of pups

Dose (mg/kg): 0

Dam number	Male		Female	
	0	4	0	4a)
1101	6.5	11.1	5.7	10.1
1102	5.9	7.9	5.4	6.8
1103	6.3	9.6	6.1	9.3
1104	6.7	10.7	6.2	10.1
1105	5.8	9.0	5.8	9.0
1106	7.8	11.3	7.2	10.5
1107	6.6	11.2	6.0	10.6
1108	5.9	8.1	5.7	8.1
1109	6.6	10.1	6.1	9.8
1110	6.6	11.1	6.1	10.3
1111	7.2	10.7	6.8	9.8
1112	6.4	9.6	5.8	8.6
Mean	6.5	10.0	6.1	9.4
S.D.	0.6	1.2	0.5	1.1

Unit: g

a): Day after birth

## Appendix 574

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual body weight of pups

Dose (mg/kg): 100

Dam number	Male		Female	
	0	4	0	4a)
2101	6.6	9.6	6.6	9.2
2102	6.7	9.0	6.2	8.6
2103	6.4	10.1	6.3	10.1
2104	6.7	9.0	6.6	8.9
2105	6.9	10.7	6.3	9.9
2106	7.0	11.3	6.5	9.9
2107	6.4	10.6	5.9	9.9
2108	6.4	9.9	6.1	9.2
2109	6.3	9.4	5.9	8.5
2110	5.7	9.5	5.7	8.8
2111	6.3	8.8	5.9	7.9
2112	6.8	10.4	6.4	9.5
Mean	6.5	9.9	6.2	9.2
S.D.	0.3	0.8	0.3	0.7

Unit: g

a): Day after birth

## Appendix 575

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual body weight of pups

Dose (mg/kg): 300

Dam number	Male		Female	
	0	4	0	4a)
3101	5.4	7.4	5.1	7.0
3102	7.3	11.6	7.2	11.6
3103	6.6	9.6	6.4	9.3
3104	7.0	11.0	6.7	10.5
3105	6.4	7.5	6.0	7.6
3106	Non-pregnant			
3107	6.4	9.6	5.9	9.0
3108	5.8	8.4	5.4	7.7
3109	6.7	10.7	6.4	10.5
3110	6.5	8.6	6.0	8.3
3111	6.6	10.3	6.0	9.0
3112	5.8	9.2	5.4	8.6
Mean	6.4	9.4	6.0	9.0
S.D.	0.6	1.4	0.6	1.4

Unit: g

a): Day after birth

## Appendix 576

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

## Individual body weight of pups

Dose (mg/kg): 1000

Dam number	Male		Female	
	0	4	0	4a)
4101	6.7	10.6	6.2	9.4
4102	6.1	10.0	6.0	9.7
4103	6.4	10.7	6.1	10.1
4104	7.2	13.0	6.8	12.0
4105	6.5	9.9	6.1	9.2
4106	7.2	9.9	6.9	9.1
4107	Non-pregnant			
4108	7.3	10.9	6.7	10.1
4109	5.8	7.6	5.6	6.6
4110	5.4	8.4	5.4	8.4
4111	6.5	10.0	6.2	9.2
4112	6.3	6.6	6.0	6.4
Mean	6.5	9.8	6.2	9.1
S.D.	0.6	1.7	0.5	1.6

Unit: g

a): Day after birth

## Appendix 577

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally  
with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross pathological findings in pups on day 4 after birth

Dose (mg/kg) : 0

Dam number	No. of pups examined Total ( Male + Female )	Findings
1101	14 ( 10 + 4 )	NAF
1102	18 ( 11 + 7 )	NAF
1103	16 ( 5 + 11 )	NAF
1104	13 ( 7 + 6 )	NAF
1105	12 ( 8 + 4 )	NAF
1106	13 ( 3 + 10 )	NAF
1107	11 ( 5 + 6 )	NAF
1108	16 ( 7 + 9 )	NAF
1109	13 ( 8 + 5 )	NAF
1110	13 ( 4 + 9 )	NAF
1111	15 ( 6 + 9 )	NAF
1112	17 ( 7 + 10 )	NAF

NAF: No abnormal findings

## Appendix 578

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross pathological findings in pups on day 4 after birth

Dose (mg/kg) : 100

Dam number	No. of pups examined			Findings			
	Total ( Male + Female )						
2101	17	(	9	+	8	)	NAF
2102	15	(	8	+	7	)	NAF
2103	12	(	8	+	4	)	NAF
2104	17	(	7	+	10	)	Two males and one female: Thymic remnant in neck
2105	13	(	6	+	7	)	NAF
2106	12	(	6	+	6	)	NAF
2107	12	(	8	+	4	)	NAF
2108	15	(	9	+	6	)	One male: Thymic remnant in neck
2109	15	(	8	+	7	)	NAF
2110	14	(	6	+	8	)	NAF
2111	15	(	8	+	7	)	NAF
2112	16	(	8	+	8	)	NAF

NAF: No abnormal findings

## Appendix 579

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross pathological findings in pups on day 4 after birth

Dose (mg/kg) : 300

Dam number	No. of pups examined Total ( Male + Female )	Findings
3101	17 ( 8 + 9 )	NAF
3102	12 ( 8 + 4 )	NAF
3103	12 ( 9 + 3 )	NAF
3104	15 ( 9 + 6 )	NAF
3105	12 ( 8 + 4 )	NAF
3106	Non-pregnant	
3107	15 ( 8 + 7 )	NAF
3108	16 ( 9 + 7 )	NAF
3109	13 ( 4 + 9 )	NAF
3110	17 ( 6 + 11 )	NAF
3111	15 ( 7 + 8 )	NAF
3112	14 ( 10 + 4 )	NAF

NAF: No abnormal findings

## Appendix 580

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Individual gross pathological findings in pups on day 4 after birth

Dose (mg/kg) : 1000

Dam number	No. of pups examined Total ( Male + Female )	Findings
4101	16 ( 11 + 5 )	NAF
4102	15 ( 7 + 8 )	NAF
4103	14 ( 7 + 7 )	NAF
4104	9 ( 3 + 6 )	NAF
4105	13 ( 8 + 5 )	NAF
4106	15 ( 6 + 9 )	NAF
4107	Non-pregnant	
4108	12 ( 6 + 6 )	NAF
4109	19 ( 11 + 8 )	NAF
4110	14 ( 5 + 9 )	NAF
4111	13 ( 4 + 9 )	NAF
4112	16 ( 5 + 11 )	NAF

NAF: No abnormal findings

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試験責任者陳述書

試験番号 : R-958

試験表題 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate  
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

本試験は以下に示す基準を遵守して実施したものであります。

- 「新規化学物質等に係る試験を実施する試験施設に関する基準について」  
(平成 15 年 11 月 21 日 : 薬食発第 1121003 号、平成 15·11·17 製局第 3 号、  
環保企発第 031121004 号、平成 17 年 4 月 1 日最終改正)

2009 年 5 月 29 日

試験責任者

株式会社ボヅリサーチセンター 御殿場研究所

R-958

### 信頼性保証陳述書

試験番号 : R-958

試験表題 : diammonium hydrogen 2-hydroxypropane-1,2,3-tricarboxylate 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

本試験は以下に示す基準を遵守して実施されたことを保証致します。

- 「新規化学物質等に係る試験を実施する試験施設に関する基準について」  
(平成 15 年 11 月 21 日 : 薬食発第 1121003 号、平成 15·11·17 製局第 3 号、環保企発第 031121004 号、平成 17 年 4 月 1 日最終改正)

なお、調査は下記の通り実施致しました。

2009 年 5 月 29 日  
株式会社ボゾリサーチセンター  
信頼性保証部門責任者

### 試験における調査

調査項目	調査担当者	調査日	試験責任者及び運営管理者への報告日
試験計画書	[REDACTED]	2007年 1月 11日	2007年 1月 11日
コンピュータプロトコール	[REDACTED]	2007年 1月 16日	2007年 1月 17日
作業予定表	[REDACTED]	2007年 1月 16日	2007年 1月 17日

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調査項目	調査担当者	調査日	試験責任者及び運営管理者への報告日
試験計画書変更書（1）		2007年 1月 25日	2007年 1月 26日
調製・被験物質の保存		2007年 1月 26日	2007年 1月 29日
群分け		2007年 1月 29日	2007年 1月 30日
被験液の濃度確認		2007年 1月 29日	2007年 1月 30日
体重・摂餌量測定・投与・一般状態の観察		2007年 1月 30日	2007年 1月 30日
歯垢検査		2007年 1月 31日	2007年 1月 31日
詳細な一般状態の観察		2007年 2月 2日	2007年 2月 3日
交配		2007年 2月 14日	2007年 2月 15日
機能検査・握力測定・自発運動量の測定		2007年 3月 6日	2007年 3月 7日
尿検査（尿量・色調・定性）		2007年 3月 7日	2007年 3月 8日
摂水量測定		2007年 3月 8日	2007年 3月 8日
分娩・授乳観察		2007年 3月 8日	2007年 3月 8日
試験計画書変更書（2）		2007年 3月 12日	2007年 3月 13日
剖検（F1：授乳4日）		2007年 3月 12日	2007年 3月 13日
採血・剖検		2007年 3月 13日	2007年 3月 14日
病理組織学検査（切り出し）		2007年 3月 26日	2007年 3月 26日
試験計画書変更書（3）		2007年 5月 14日	2007年 5月 15日
最終報告書草案・図・表・付表		2007年 8月 1日	
		2007年 8月 2日	
改善確認		2007年 8月 3日	2007年 8月 3日
試験計画書変更書（4）		2007年 8月 3日	2007年 8月 6日
試験計画書変更書（5）		2007年 10月 15日	2007年 10月 16日
		2009年 2月 5日	2009年 2月 6日

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調査項目	調査担当者	調査日	試験責任者及び運営管理者への報告日
生データ		2009年 5月 12日	
		2009年 5月 13日	
		2009年 5月 14日	
		2009年 5月 15日	
		2009年 5月 16日	
		2009年 5月 18日	2009年 5月 19日
改善確認		2009年 5月 22日	2009年 5月 25日
最終報告書		2009年 5月 29日	2009年 5月 29日

### プロセス調査

調査項目	調査担当者	調査日	部門責任者及び運営管理者への報告日
動物入荷		2007年 2月 5日	2007年 2月 6日
検疫・馴化、飼育管理		2007年 2月 5日	2007年 2月 6日
		2007年 2月 13日	2007年 2月 14日
尿検査（沈渣・浸透圧）		2007年 5月 1日	2007年 5月 1日
		2007年 5月 9日	2007年 5月 10日
血液学検査・血液化学検査		2007年 5月 17日	2007年 5月 21日
		2007年 5月 18日	2007年 5月 21日
病理組織学検査 (包埋・薄切・染色)		2007年 5月 8日	2007年 5月 10日
		2007年 5月 11日	2007年 5月 14日
		2007年 5月 14日	2007年 5月 15日